

## Title page

### **Title:**

Mechanisms-based classifications of musculoskeletal pain: Part 2 of 3: Symptoms and signs of peripheral neuropathic pain in patients with low back ( $\pm$  leg) pain.

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### **Manuscript**

## **1. Introduction**

Peripheral neuropathic pain (PNP) refers to pain attributable to a lesion or dysfunction in a peripheral nerve, dorsal root ganglion or dorsal root arising from trauma, compression, inflammation or ischemia (Woolf, 2004a; Devor, 2006). Entrapment neuropathies of spinal roots, dorsal root ganglia or their peripheral branches are a likely common cause of PNP encountered by physiotherapists (Scadding and Koltzenberg, 2006).

As a mechanisms-based classification of pain, where pain is classified according to the dominant neurophysiological mechanisms responsible for its generation and/or maintenance (Woolf et al. 1998; Portenoy, 1989) PNP has been proposed as a category of pain distinct from other mechanisms-based classifications of pain, such as ‘nociceptive’ pain (NP) and ‘central sensitisation’ pain (CSP) (Butler, 2000; Smart et al. 2008; Costigan et al. 2009;). Whilst many clinical presentations of pain may be attributable to a mix of nociceptive, peripheral neuropathic and central mechanisms, the concept of pain arising from a relative dominance of PNP mechanisms has been proposed (Bennett et al. 2006; Schäfer et al. 2009).

Estimates suggest that between 20-35% of patients with low back pain (LBP) may have an underlying neuropathic component; and that the costs associated with managing such patients are around 70% higher compared to those with ‘nociceptive’ LBP (Freyenhagen and Baron 2009). Importantly, patients with a dominance of neuropathic pain are known to report more severe pain, greater functional impairments and poorer health related quality of life compared to those with nociceptive/non-neuropathic pain (Smith et al. 2007; Bouhassira et al. 2008; Smart et

al. 2012). The incidence, costs and consequences associated with PNP in patients with low back ( $\pm$  leg) pain suggest they represent an important clinical cohort.

PNP is not a single mechanism but the product of a number of complex pathophysiological processes that variously alter the structure and function of peripheral nerves and their central terminals in response to injury (Callin and Bennett, 2008). Key pathophysiological mechanisms underlying PNP may include (Devor, 2006; Nee and Butler, 2006; Thacker et al. 2007; Costigan et al. 2009):

1. Sensitisation of neural connective tissue nociceptors: Impaired intraneural circulation and hypoxia in response to nerve injury may elicit an inflammatory response within neural connective tissues. As a consequence, nociceptors within the nervi nervorum and sinu-vertebral nerves may become sensitised to chemical and mechanical stimuli, thus contributing to an increase in nociceptive drive.
2. Ectopic excitability: The upregulation of ion channels at sites of nerve injury leading to the formation of abnormal impulse generating sites (AIGS) which may fire spontaneously and independently of a peripheral stimulus (i.e. stimulus-independent pain). Alternatively, these sites may become thermo-, mechano-, or chemo-sensitive causing injured nerves to become abnormally reactive to thermal, mechanical or chemical stimuli (i.e. stimulus-dependent pain). For example, AIGS may also become reactive to the chemical mediators of inflammation (e.g. cytokine signalling), and/or to catecholamines (adrenaline and noradrenaline) of the autonomic nervous system, such that inflammatory processes and sympathetic-sensory neurone coupling may also enhance PNP mechanisms.

3. 'Cross-excitation': i.e. electrically or chemically-mediated excitation between adjacent injured and uninjured neurons which may amplify nociceptive signalling.
4. Structural changes: Axonal sprouting of non-nociceptive A $\beta$  fibres into dorsal horn laminae receiving nociceptive inputs, such that non-nociceptive peripheral input (i.e. touch, movement) may enhance onward nociceptive signalling in ascending tracts.
5. Neuro-immune interactions: The activation of immune cells in both the peripheral and central nervous systems, such as microglia in the dorsal horn, in response to nerve injury stimulates the release additional chemical modulators that may contribute to the development and persistence of PNP.

Far from occurring in isolation, peripheral neuropathic mechanisms are subject to modulation from the simultaneous descending facilitatory and inhibitory influences of the central nervous system (CNS) (Finnerup et al. 2007; Costigan et al. 2009). The diversity of pathophysiological mechanisms underlying PNP reflects a high degree of heterogeneous peripheral and central nervous system plasticity although the extent to which they occur clinically is difficult to determine (Zusman, 2008).

Interestingly, only a proportion of individuals with injuries capable of causing PNP go on to develop it. For example, imaging studies reveal evidence of spinal nerve root compression/displacement in 4-17% of adults without any history of pain (Boos et al. 1995; Weishaupt et al. 1998). Mogil and Max (2006 p.159) suggest that, '*As with all biological phenomena, this variability is produced by some combination of as yet undetermined genetic and environmental factors*'. Clinicians are therefore reminded

of the complex biopsychosocial influences that mediate the transition of pathology into pain, and of people into patients.

In the absence of an available gold standard test with which to diagnose or classify patients' pain as being 'peripheral neuropathic' its presence clinically must be inferred indirectly on the basis of pattern recognition of various pain-related symptoms and signs thought to reflect a dominance of PNP mechanisms (Finnerup et al. 2006). Symptoms and signs assumed to reflect a dominance of PNP in patients with musculoskeletal/LBP disorders, include: pain with a burning or electric-shock-like quality, pain in a dermatomal or cutaneous distribution, spontaneous pain, paroxysmal pain, dysesthesias, allodynia and hyperalgesia (Smart et al. 2008; Freynhagen and Baron, 2009); all of which should occur in a neuroanatomically plausible distribution consistent with the site of nerve lesion (Cruccu et al. 2004).

A number of screening tools have been developed to help distinguish neuropathic from non-neuropathic/nociceptive pain in patient populations with a broad range of neuropathic pain disorders (Bennett 2007). The 'painDETECT' (Freynhagen et al. 2006) and the 'Standardized Evaluation of Pain (StEP)' (Scholz et al. 2009) have been developed and preliminarily validated specifically in patient populations with low back pain disorders. These tools generally distinguish neuropathic from non-neuropathic pain on the basis of verbal symptom descriptors with or without a limited clinical examination (see Table 1).

A recent Delphi-type survey of pain consultants and musculoskeletal physiotherapists identified a consensus-derived list of nine symptoms and five signs suggestive of a dominance of PNP (see Figure 1) (Smart et al. 2010).

The symptoms and signs associated with a clinical classification, i.e. an assumed dominance, of PNP in patients with low back ( $\pm$  leg) pain presenting to physiotherapists have not been widely studied. The purpose of this study was to identify a cluster of symptoms and signs associated with a clinical classification of PNP in patients with low back ( $\pm$  leg) pain presenting for physiotherapy assessment. Data related to the identification of symptoms and signs associated with PNP have previously been reported in the wider context of the discriminative validity of mechanisms-based classifications of pain (Smart et al. 2011). The following paper, derived from the same study, provides an expanded analysis and allows for the presentation of additional results as well as a more detailed discussion of the underlying biological plausibility of those symptoms and signs associated with a clinical classification of PNP.

## **2. Methods**

The design, setting, participants, instrumentation/procedures, sample size requirements and methods of analysis employed for this study have been reported elsewhere in this issue (Smart et al. \*\*\*\*).

Delphi-derived consensus-based symptoms and signs associated with a dominance of PNP were initially selected as candidate criteria for inclusion into the model (Smart et al. 2010) (Criteria: 3, 7, 9, 12, 14, 15, 16, 18, 27, 29, 31, 34, 35, 36, 37; see Table 1; Smart et al. \*\*\*\*).

### **3. Results**

The characteristics of the patient sample ( $n = 464$ ) were reported earlier in this issue (Smart et al. \*\*\*\*).

#### **3.1 Data screening and Univariate analyses**

The variables 'age' and 'gender' were excluded from the multivariate analyses as previously reported (Smart et al. \*\*\*\*).

#### **3.2 Multivariate analyses**

Missing values were identified for 12 cases, thus reducing the valid sample size from  $n = 464$  to  $n = 452$  (PNP  $n = 102$ , Non-PNP  $n = 350$ ). Model parameters (posterior probabilities, expected values of the regression coefficients) and indices of classification accuracy for successive models are presented in Tables 2 and 3 respectively. 'Model 9' was selected as the 'final' PNP model on the grounds that i) the symptoms and signs within the model appeared reasonable clinically, and ii) all had posterior probabilities of 100.0% and iii) the model appeared to reflect a reasonable balance between predictive accuracy and parsimony. Model parameters for each criterion in the final PNP model are presented in Table 4 (where shortened criterion descriptions are given; full descriptions are presented in Table 1, see Smart et al. \*\*\*\*).

A clinical classification of PNP was predicted by the presence of two symptoms (Criteria 3 and 9) and one sign (Criterion 29). The strongest predictor of PNP was Criterion 9 (OR: 24.29; 95% CI: 6.33-93.18) suggesting that patients with '*Pain referred in a dermatomal or cutaneous distribution*', were over 24 times more likely

to be classified with a dominance of PNP compared to those with non-PNP, controlling for all other variables in the model. Patients with *'Pain/symptom provocation with mechanical/movement tests (e.g. Active/Passive, Neurodynamic, i.e. SLR) that move/load/compress neural tissue'* and a *'History of nerve injury, pathology or mechanical compromise'* were over 14 and 12 times more likely, respectively, to have been classified with a dominance of PNP compared to those with non-PNP.

### **3.3 Classification accuracy**

The cross tabulation from which the indices of classification accuracy were calculated are presented in Table 5. Indices of classification accuracy, with 95% confidence intervals, for the final PNP model are presented in Table 6.

The final model had a sensitivity of 86.3% (95% CI: 78.0-92.3%) suggesting that the cluster of two symptoms and one sign correctly predicted a clinical classification of PNP in 86.3% of patients classified with PNP according to the reference standard of 'expert' clinical judgement, but incorrectly predicted 13.7% of these patients as having Non-PNP. A specificity of 96.0% (95% CI: 93.4-97.8%) suggests that the final model correctly predicted 96% of patients with Non-PNP, but incorrectly predicted 4.0% of patients as having PNP.

The PPV of 86.3% (95% CI: 78.0-92.3%) indicates that a patient with the cluster of symptoms and signs outlined by the model was likely to have been classified with PNP with an 86.3% level of probability. The NPV indicates that the probability of a patient without the cluster having Non-PNP is 96.0% (95% CI: 93.4-97.8%).

The LR+ of 21.57 (95% CI: 12.84-36.24) suggests that the specified cluster of symptoms and signs is over 21 times more likely to be found in patients classified with PNP than Non-PNP. The LR- indicates that the likelihood of the cluster being absent in patients classified with PNP is 0.14 (95% CI: 0.09-0.23). According to the cut point of  $\leq 0.1$  specified by Jaeschke et al. (1994), an absence of this cluster of symptoms and signs may not be sufficiently accurate for ruling out PNP clinically.

The diagnostic odds ratio of 150.86 (95% CI: 69.36-328.13) indicates that that the cluster is 150 times more likely to accurately than inaccurately predict a clinical classification of PNP in patients classified with PNP.

A graphical representation of discriminatory properties of the model is demonstrated by the scatter plot presented in Figure 2. In Figure 2 (left), the clusters in the top right and bottom left quadrant of the graphic represent those patients correctly ‘observed’ (i.e. classified) and predicted by the model to have a dominance of PNP and Non-PNP respectively. Those clusters in the top left and bottom right represent those patients misclassified by the model with PNP and Non-PNP respectively. The scatter plot depicted in Figure 2 (right) shows the spread of predictive probabilities from the model, which suggest that the model is predicting very well.

#### **4. Discussion**

This study identified a cluster of two symptoms and one sign associated with a clinical classification of PNP in patients with low back ( $\pm$  leg) pain presenting for physiotherapy assessment.

Two of the initial eight symptoms and one of the original seven signs entered into the first model were retained as predictors of PNP suggesting the presence of a few symptoms and signs may be adequate to identify patients with an assumed dominance of PNP. We speculate that each symptom and sign in the cluster is underpinned by a degree of clinical and biological plausibility.

According to the final model, '*Pain referred in a dermatomal or cutaneous distribution*', was the strongest predictor of PNP. Pathophysiologically, dermatomal/radicular pain is thought to arise from ectopic discharges from the dorsal root or its ganglion (Bogduk, 2009), a mechanism entirely consistent with those thought to underlie PNP (Costigan et al. 2009).

Existing data, either directly or indirectly, supports the presence of leg pain as an indicator of PNP in patients with lumbar spine disorders. During the development and preliminary validation of the painDETECT (Freynhagen et al. 2006) 'radiating pain' emerged as an important predictor of PNP. A systematic review evaluating the diagnostic value of the history and physical examination in patients suspected of sciatica secondary to disc herniation, from which we infer the presence if not dominance of PNP, found pain extending below the knee to be the only useful diagnostic item from the clinical history (Vroomen et al. 1999). A subsequent study

investigating the diagnostic value of the history and physical examination in 274 patients suspected of lumbosacral nerve root compression found further evidence supporting a 'dermatomal distribution' of pain as a predictor of nerve root compression, as determined against a 'gold' standard of magnetic resonance imaging (adjusted DOR 3.2; 95% CI 2.2-4.7) (Vroomen et al. 2002).

However, the validity of strictly dermatomal distributions of pain as a predictor of nerve root pain/PNP could be undermined by variations in dermatomal maps and the geography of dermatomes between individuals (Dubuisson, 2006). Consistent with this assertion, some recent evidence has suggested that nerve root pain may not necessarily present according to accepted dermatomal pain patterns (Murphy et al. 2009). Despite the variability it seems that, at the very least, pain referred into the leg extending below the knee, if not in a strictly dermatomal distribution, is a useful predictor of nerve root compression and by extension PNP. Whilst further studies are required to evaluate and quantify the extent of its predictive accuracy its inclusion as an item within clinical history taking of patients with low back pain disorders has been recommended (Chou et al. 2007).

*'Pain/symptom provocation with mechanical/movement tests (e.g. Active/Passive, Neurodynamic, i.e. SLR) that move/load/compress neural tissue'* was the second strongest predictor of PNP. Pain and symptom provocation in response to neurodynamic tests, such as the Straight leg raise (SLR) test, as a predictor of PNP is in keeping with some of the known pathophysiological consequences associated with nerve injury in general and spinal nerve root irritation or compression in particular. Mechanical compression of nerve roots or the action of inflammatory mediators in

response to intervertebral disc injury or degeneration may alter nerve root sensitivity such that mechanical loads or stresses, such as those accompanying spinal movement or neurodynamic tests which are known to impart mechanical deformation of lumbar nerve roots, may initiate or exacerbate pain (Devor, 2006; Nee and Butler, 2006).

Additional clinical evidence supports the SLR test as an indicator of radicular LBP (Scholz et al. 2009) and as a diagnostic test for lumbar disc herniation and radiculopathy, and again by extension we assume PNP, in predominantly surgical populations (Devillé et al. 2000; Vroomen et al. 1999) and its inclusion within the clinical examination of LBP has been similarly recommended (Chou et al. 2007).

A recent Cochrane systematic review of physical examination tests for lumbar radiculopathy due to disc herniation in patients with LBP however has challenged this assertion. Its findings suggest that there is as yet insufficient evidence supporting the usefulness of the SLR as a test for a disorder that might reasonably assumed to generate a significant element, if not dominance of PNP (van der Windt et al. 2010). The authors cite the test's lack of generalisability across different clinical settings (e.g. primary versus secondary care) and patient cohorts (i.e. non-surgical) as some of its main shortcomings.

Data supporting of the validity of a subjective clinical judgement such as '*History of nerve injury, pathology or mechanical compromise*' as a specific indicator of PNP is sparse. The presence/absence of this criterion was determined by a general clinical judgement as to whether the patients' history of low back ( $\pm$  leg) pain (i.e. its onset) suggested nerve injury/pathology etc. The presence of this criterion as an indicator of

PNP is presumably based on logic, i.e. that a history suggestive of and consistent with nerve injury/pathology/mechanical compromise would account for the development of the neurophysiological processes underlying, and therefore be a predictor of, PNP. A history suggestive of a lesion to the peripheral somatosensory system has been suggested by others as a necessary prerequisite for determining the presence of peripheral neuropathic pain (Treede et al. 2008).

Interestingly, the cluster of clinical criteria associated with PNP identified in this study differs notably from those criteria contained in many of the existing screening instruments for neuropathic pain, which nearly all contain items related to qualitative pain/symptom descriptors and/or behaviours, including i) Pricking/tingling, ii) electric shocks/shooting and hot/burning and iii) numbness and iv) pain evoked by light touching (Bennett et al. 2007). The cluster identified in this study contained no such criteria. The reasons for this are not known but could reflect a spectrum effect (Scott et al. 2008), whereby the cluster presented in our study was derived from patients with PNP assessed mainly in physiotherapy/back clinic settings, which may reflect patients with less severe presentations of PNP whereas the criteria contained in most existing neuropathic screening instruments were derived from pain clinic settings which may reflect more severe presentations of PNP.

Other symptoms and signs commonly associated with PNP such as allodynia, hyperalgesia, hyperpathia, paroxysmal pain and pain on nerve palpation (Baron, 2005; Nee and Butler, 2006; Walsh and Hall, 2009) did not emerge as strong predictors of PNP according to the findings of our study. The reasons for this are not known.

Pattern recognition of a cluster of symptoms and signs associated with an assumed dominance of PNP mechanisms could be useful clinically for informing subsequent clinical decision-making associated with the treatment and prognosis of patients' pain. For example, pain characterised by a dominance of PNP may invite clinicians to consider recommending/prescribing appropriate pharmacological agents, such as anti-convulsants (Finnerup et al. 2005). A classification of PNP might similarly invite clinicians to employ physiotherapeutic interventions comprising neurodynamic /neurobiological education and/or neurodynamic mobilisation techniques (Nee and Butler, 2006). Employing treatment strategies known or hypothesised to target the underlying mechanisms of PNP may help improve clinical outcomes in a patient population known to experience significant suffering; however the prescriptive validity and efficacy of this approach requires evaluation.

The findings from this study should be interpreted in light those methodological limitations described earlier in this issue (Smart et al. \*\*\*\*).

## **5. Conclusion**

This study identified a cluster of two symptoms and one sign associated with a clinical classification of PNP in patients with low back ( $\pm$  leg) pain. This cluster was found to have high levels of classification accuracy suggesting it might be helpful for identifying pain arising from an assumed dominance of PNP mechanisms. Subsequent validation studies of clinical criteria associated with PNP in larger samples with a range of neuromusculoskeletal disorders are desirable in order to provide more robust estimates of classification accuracy as well as identify other potential symptoms and signs.

**Conflicts of interest:** None declared.

## References

Baron R. Mechanisms of disease: neuropathic pain-a clinical perspective. *Nature Clinical Practice Neurology* 2005; 2: 95-106.

Bennett MI, Smith BH, Torrance N, Lee AJ. Can pain be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain* 2006; 122: 289-94.

Bennett MI, Attal N, Backonja MM et al. Using screening tools to identify neuropathic pain. *Pain* 2007; 127: 199-203.

Bogduk N. On the definition and physiology of back pain, referred pain and radicular pain. *Pain* 2009; 147: 17-19.

Boos N, Rieder R, Schade V, Spratt KF, Semmer N, Aebi M. 1995 Volvo award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception and psychosocial factors in identifying symptomatic disc herniations. *Spine* 1995; 20: 2613-25.

Bossuyt PM, Reitsma JB, Bruns DE et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clinical Chemistry* 2003; 49: 7-18.

Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008; 136: 380-7.

Butler DS. *The Sensitive Nervous System*. Adelaide: Noigroup Publications; 2000.

Callin S, Bennett MI. Assessment of neuropathic pain. *Continuing Education in Anesthesia, Critical Care and Pain* 2008; 8: 210-13.

Chou R, Qaseem A, Snow V et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Annals of Internal Medicine* 2007; 147: 478-91.

Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual Review of Neuroscience* 2009; 32: 1-32.

Cruccu G, Anand P, Attal N et al. EFNS guidelines on neuropathic pain assessment. *European Journal of Neurology* 2004; 11: 153-62.

Devillé WLJM, van der Windt DAWM, Džaferragić A, Bezemer PD, Bouter LM. The test of Lasègue. Systematic review of the accuracy in diagnosing herniated discs. *Spine* 2000; 25: 1140-7.

Devor M. Response of nerves to injury in relation to neuropathic pain. In: McMahon SB, Koltzenburg M, editors. Textbook of Pain. 5<sup>th</sup> ed. Elsevier: Churchill Livingstone; 2006. p. 905-27.

Dubuisson D. Root disorders and arachnoiditis. In: McMahon SB and Koltzenburg M, editors. Textbook of Pain. 5<sup>th</sup> ed. Elsevier: Churchill Livingstone; 2006. p. 1029-42.

Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289-304.

Finnerup NB, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain – a critical analysis. Nature Clinical Practice Neurology 2006; 2: 107-15.

Finnerup NB, Sindrup SH, Jensen TS. Chronic neuropathic pain: mechanisms, drug targets, measurement. Fundamental and Clinical Pharmacology 2007; 21: 129-36.

Freyenhagen R, Baron R, Gockel U, Tölle TR. Pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Current Medical Research and Opinion 2006; 22: 1911-20.

Freyenhagen R, Baron R. The evaluation of neuropathic components in low back pain. Current Pain and Headache Reports 2009; 13: 185-90.

Jaeschke R, Guyatt GH, Sackett DL. Users' guide to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients. *JAMA* 1994; 271: 703-7.

Krause SJ, Backonja M. Development of a neuropathic pain questionnaire. *Clinical Journal of Pain* 2003; 19: 306-14.

Mogil JS, Max MB. The genetics of pain. In: McMahon SB, Koltzenburg M, editors. *Textbook of Pain*. 5<sup>th</sup> ed. Elsevier: Churchill Livingstone; 2006. p. 159-74.

Murphy DR, Hurwitz EL, Gerrard JK, Clary R. Pain patterns and descriptions in patients with radicular pain: does the pain necessarily follow a specific dermatome. *Chiropractic and Osteopathy* 2009; 17: 9 doi: 10.1186/1746-1340-17-9.

Nee RJ, Butler D. Management of peripheral neuropathic pain: integrating neurobiology, neurodynamics, and clinical evidence. *Physical Therapy in Sport* 2006; 7: 36-49.

Portenoy RK. Mechanisms of clinical pain. Observations and speculations. *Neurologic Clinics of North America* 1989; 7: 205-30.

Scadding JW, Koltzenberg M. Painful peripheral neuropathies. In: McMahon SB and Koltzenburg M, editors. *Textbook of Pain*. 5<sup>th</sup> ed. Elsevier: Churchill Livingstone; 2006. p. 973-99.

Schäfer A, Hall T, Briffa K. Classification of low back-related leg pain – A proposed patho-mechanism-based approach. *Manual Therapy* 2009; 14: 222-30.

Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. *Nature Neuroscience* 2007; 10: 1361-68.

Scholz J, Mannion RJ, Hord DE, Griffin RS, Rawal B, Zheng H, Scoffings D, Phillips A, Guo J, Laing RJC, Abdi S, Decosterd I, Woolf CJ. A novel tool for the assessment of pain: validation in low back pain. *PLoS Medicine* 2009; 6(4): e1000047.doi: 10.1371/journal.pmed.1000047.

Smart KM, O'Connell NE, Doody C. Towards a mechanisms-based classification of pain in musculoskeletal physiotherapy? *Physical Therapy Reviews* 2008; 13: 1-10.

Smart KM, Blake C, Staines A, Doody C. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. *Manual Therapy* 2010; 15: 80-87.

Smart KM, Blake C, Staines A, Doody C. Self-reported pain severity, quality of life, disability, anxiety and depression in patients classified with 'nociceptive', 'peripheral neuropathic' and 'central sensitisation' pain. The discriminant validity of mechanisms-based classifications of low back ( $\pm$  leg) pain. *Manual Therapy* 2012 (in press).

Smart KM, Blake C, Staines A, Thacker, Doody C. Mechanisms-based classifications of musculoskeletal pain: Part 1 of 3: Symptoms and signs of central sensitisation in patients with low back ( $\pm$  leg) pain. *Manual Therapy* \*\*\*\*; \*\*: \*\*\*-\*\*\*\*. [If series accepted]

Smith BH, Torrance N, Bennett MI, Lee AJ. Health and Quality of Life Associated With Chronic Pain of Predominantly Neuropathic Origin in the Community. *Clinical Journal of Pain* 2007; 23: 143-49.

Thacker MA, Clark AK, Marchand F, McMahon SB. Pathophysiology of peripheral neuropathic pain: immune cells and molecules. *Anesthesia & Analgesia* 2007; 105: 838-47.

Treede RD, Jensen TS, Campbell JN et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008; 70: 1630-5.

van der Windt DAWN, Riphagen SE, Verhagen AC et al. Physical examination for lumbar radiculopathy due to disc herniation in patients with low back pain. *Cochrane database of systematic reviews* 2010, Issue 2, Art. No.: CD007431. DOI: 10.1002/14651858.CD007431.pub2.

Vroomen PCAJ, de Krom MCTFM, Knottnerus JA. Diagnostic value of the history and physical examination in patients suspected of sciatica due to disc herniation: a systematic review. *Journal of Neurology* 1999; 46: 899-906.

Vroomen PCAJ, de Krom MCTFM, Wilmlink JT, Kester ADM, Knottnerus JA. Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression. *Journal of Neurology, Neurosurgery and Psychiatry* 2002; 72: 630-4.

Walsh J, Hall T. Reliability, validity and diagnostic accuracy of palpation of the sciatic, tibial and common peroneal nerves in the examination of low back related leg pain. *Manual Therapy* 2009; 14: 623-9.

Weishaupt D, Zanetti M, Hodler J, Boos N. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. *Radiology* 1998; 209: 661-6.

Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. *Life Sciences* 2004a; 74: 2605-10.

Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine* 2004b; 140: 441-51.

Woolf CJ, Bennett GJ, Doherty M et al. Towards a mechanism-based classification of pain? *Pain* 1998; 77: 227-9.

Zusman M. Mechanisms of peripheral neuropathic pain: implications for musculoskeletal physiotherapy. *Physical Therapy Reviews* 2008; 13: 313-23.

## Legends for illustrations:

Figure 1. Delphi-derived clinical indicators of ‘peripheral neuropathic’ pain.

<p><b>Subjective:</b> Pain variously described as burning, shooting, sharp, aching or electric-shock-like. History of nerve injury, pathology or mechanical compromise. Pain in association with other neurological symptoms (e.g. pins and needles, numbness, weakness). Pain referred in a dermatomal or cutaneous distribution. Less responsive to simple analgesia/NSAIDS* and/or more responsive to anti-epileptic (e.g. Neurontin, Lyrica)/anti-depression (e.g. Amitriptyline) medication. Pain of high severity and irritability (i.e. easily provoked, taking longer to settle). Mechanical pattern to aggravating and easing factors involving activities/postures associated with movement, loading or compression of neural tissue. Pain in association with other dysesthesias (e.g. crawling, electrical, heaviness). Reports of spontaneous (i.e. stimulus-independent) pain and/or paroxysmal pain (i.e. sudden recurrences and intensification of pain).</p> <p><b>Clinical examination:</b> Pain/symptom provocation with mechanical/movement tests (e.g. Active/Passive, Neurodynamic, i.e. SLR<sup>#</sup>, Brachial plexus tension test) that move/load/compress neural tissue. Pain/symptom provocation on palpation of relevant neural tissues. Positive neurological findings (including altered reflexes, sensation and muscle power in a dermatomal/myotomal or cutaneous nerve distribution). Antalgic posturing of the affected limb/body part. Positive findings of hyperalgesia (primary or secondary) and/or allodynia and/or hyperpathia within the distribution of pain.</p>
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\* Non-steroidal anti-inflammatory drugs.

<sup>#</sup>Straight leg raise.

Figure 1. Delphi-derived clinical indicators of ‘peripheral neuropathic’ pain (Smart et al. 2010b).

Figure 2. A graphical representation of the discriminatory properties of the final ‘peripheral neuropathic’ pain model.

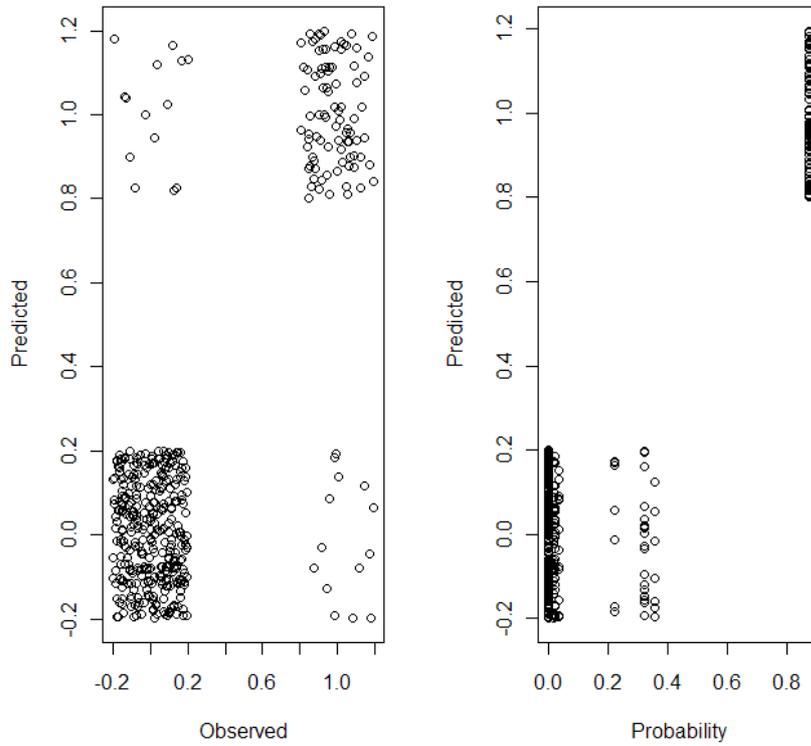


Figure 2. A graphical representation of the discriminatory properties of the ‘final’ peripheral neuropathic pain model.