
Authors:

Keith M Smart PhD: Physiotherapy Department, St Vincent’s University Hospital, Elm Park, Dublin 4, Ireland.

Catherine Blake PhD: UCD School of Public Health, Physiotherapy and Population Science, University College Dublin, Belfield, Dublin 4, Ireland.

Anthony Staines PhD: Professor of Health Systems Research, School of Nursing, Dublin City University, Dublin 9, Ireland.

Mick Thacker PhD: Centre of Human and Aerospace Physiological Sciences & Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College London, London, United Kingdom.

Catherine Doody PhD: UCD School of Public Health, Physiotherapy and Population Science, University College Dublin, Belfield, Dublin 4, Ireland.

Corresponding author: Keith M Smart. Physiotherapy Department, St Vincent’s University Hospital, Elm Park, Dublin 4, Ireland. Tel: +353 1 221 4467. Fax: +353 1 221 4001. Email: k.smart@svuh.ie.

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1. Introduction

As a mechanisms-based classification of pain, where pain is classified according to the dominant neurophysiological mechanisms responsible for its generation and/or maintenance (Portenoy, 1989; Woolf et al. 1998) nociceptive pain (NP) has been proposed as a category of pain distinct, but not inseparable, from other mechanisms-based classifications of pain, such as ‘peripheral neuropathic’ pain (PNP) and ‘central sensitisation’ pain (CSP) (Gifford, 1998; Smart et al. 2008).

Nociceptive pain refers to pain conditions assumed to be predominantly driven by the activation of peripheral nociceptive sensory fibres (Scholz and Woolf, 2002). Specifically, NP refers to pain attributable to those pathophysiological processes associated with activation of the peripheral receptive terminals of primary afferent neurones (Aδ and C fibres) in response to noxious chemical (inflammatory), mechanical or thermal stimuli (Ekman and Koman, 2004; Julius and McCleskey, 2006). Chemically mediated nociception arising from the activation of nociceptors by pro-inflammatory chemicals released in response to injury or pathology (McMahon et al. 2006) or by a lowering of tissue pH in response to tissue ischaemia from static mechanical (postural) tissue loading or compression (Butler, 2000) represent some of the peripheral mechanisms that might underlie many clinical presentations of musculoskeletal pain including low back pain (LBP).

In the absence of a gold standard method with which to diagnose or classify patients’ pain as being predominantly ‘nocieptive’ such clinical impressions must inevitably be determined clinically. Advocates of mechanisms-based classifications of pain have proposed a number of pain-related symptoms and signs assumed to reflect a
dominance of NP, including; the cardinal signs of inflammation (heat, redness, swelling), pain of aching quality that may be shaper on movement, predictable and proportionate pain provocation on mechanical testing, all of which are usually associated with natural recovery along a timeline in accordance with tissue healing or resolution of pathology (Butler, 2000; Smart et al. 2008).

A recent Delphi-type survey of pain consultants and musculoskeletal physiotherapists identified a consensus-derived list of eight symptoms and four signs suggestive of a dominance of NP (see Figure 1) (Smart et al. 2010). However the clinical features of NP as a mechanisms-based classification of pain have not been extensively studied in patient populations with musculoskeletal pain conditions. The purpose of this study was to identify a cluster of symptoms and signs associated with a clinical classification of NP in a cohort of patients with low back (± leg) pain presenting for physiotherapy assessment. Data related to the identification of symptoms and signs associated with NP 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 NP.
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 NP were initially selected as candidate criteria for inclusion into the model (Smart et al. 2010) (Criteria: 1, 2, 5, 8, 11, 22, 27, 28, 32; see Table 1; Smart et al. ****). An additional five symptoms and one sign were included when data screening and univariate analyses suggested their ‘absence’ might also be associated with a dominance of NP (Criteria: 7, 14, 15, 16, 19, 36; see Table 1; Smart et al. ****).
3. Results

The characteristics of the patient sample \((n = 464)\) were as previously reported earlier in this issue (see Table 2, 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. ****). Bayesian model averaging performed in ‘R’ (2009, version 2.9.2) is unable to process missing values. In order to preserve the maximum possible sample size available for the regression analysis Criterion 20: ‘Responsive to simple analgesia/NSAIDs’, which had over 20 missing values was also excluded.

3.2 Multivariate analyses

Missing values were identified for 12 cases, thus reducing the valid sample size from \(n = 464\) to \(n = 452\) (NP \(n = 252\), Non-NP \(n = 200\)). Model parameters (posterior probabilities, expected values of the regression coefficients) and indices of classification accuracy for successive models are presented in Tables 1 and 2 respectively. After a review of model estimates and indices of classification associated with each model, ‘Model 6’ was selected as the ‘final’ NP model on the grounds that i) the criteria within the model appeared reasonable clinically, ii) the model contained criteria with high posterior probabilities (range: 87.4 to 100.0%), and iii) a subsequent model (Model 7) demonstrated some loss of classification accuracy. Model parameters for each criterion in the final NP model are presented in Table 3 (where shortened criterion descriptions are given; full descriptions are presented in Table 1, see Smart et al. ****).
According to the final model a clinical classification of NP was predicted by the presence of three symptoms (Criteria 5, 8, 11) and the ‘absence’ of three symptoms (Criteria 7, 15, 19) and one sign (Criterion 27). Of those symptoms ‘present’, the strongest predictor of NP was Criterion 8 (OR: 69.79; 95% CI: 25.13-193.81) suggesting that patients with ‘Pain localised to the area of injury/dysfunction (with/without some somatic referral)’ were over 69 times more likely to be classified with a dominance of NP compared to those with non-NP, controlling for all other variables in the model. Patients who presented with a ‘Clear, proportionate mechanical/anatomical nature to aggravating and easing factors’, and whose pain was ‘Usually intermittent and sharp with movement/mechanical provocation; may be a more constant dull ache or throb at rest’, were over 18 and 4 times more likely to be classified with a dominance of NP, respectively.

The odds ratio of 0.15 for Criterion 15 was less than 1, indicating that patients with ‘Pain in association with other dysesthesias’, were 0.15 times less likely to be classified with NP than patients with non-NP (OR: 0.15; 95% CI: 0.06-0.37), controlling for all other factors in the model, i.e. the presence of dysesthesias decreased the odds of being classified with NP by 85%. Similarly, the presence of ‘Night pain/disturbed sleep’, ‘Antalgic (i.e. pain relieving) postures/movement patterns’ and ‘Pain variously described as burning, shooting, sharp or electric-shock-like’ decreased the odds of being classified with NP by 78%, 76% and 72% respectively.

3.3 Classification accuracy
The cross tabulation from which the indices of classification accuracy were calculated for the final cluster are presented in Table 4. Indices of classification accuracy, with 95% confidence intervals, for the final NP model are presented in Table 5.

The final model had a sensitivity of 90.9% suggesting that this cluster of symptoms and signs correctly predicted a clinical classification of NP in 90.9% of patients classified with NP according to the reference standard of ‘expert’ clinical judgement, but incorrectly predicted 9.1% of these patients as having Non-NP. A specificity of 91.0% suggests that the final model correctly predicted 91.0% of patients with Non-NP, but incorrectly predicted 9.0% of patients as having NP.

The positive predictive value (PPV) of 92.7% indicates that a patient with the cluster of symptoms and signs outlined by the model was likely to have been classified with NP with a 92.7% level of probability. The negative predictive value indicates that the probability of a patient without the cluster having Non-NP is 88.9%.

The positive likelihood ratio (LR+) of 10.10 suggests that the specified cluster of symptoms and signs is over 10 times more likely to be found in patients classified with NP than Non-NP. The negative likelihood ratio LR− indicates that the likelihood of the cluster being absent in patients classified with NP is 0.10. According to the cut point of ≤ 0.1 specified by Jaeschke et al. (1994), the absence of this cluster of symptoms and signs may be useful for ruling out NP clinically.
The diagnostic odds ratio of 100.7 indicates that the cluster is 100 times more likely to accurately than inaccurately predict a clinical classification of NP in patients classified with NP.

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 NP and Non-NP respectively. Those clusters in the top left and bottom right represent those patients misclassified by the model with NP and Non-NP 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 well.
4. Discussion

This study identified a cluster of six symptoms and one sign associated with a clinical classification (i.e. an assumed dominance) of NP in patients with LBP disorders. The indices of classification accuracy associated with this cluster suggest that NP may be predicted with high levels of accuracy. For example the PPV, a clinically useful index since it answers the question, ‘How likely is it that a patient has a dominance of NP if they have this cluster of clinical criteria’ was high (92.7%, 95% CI: 88.7-95.6) (Lalkhen and McCluskey, 2008). The LR+ and LR− of 10.10 and 0.10, according to the cut-points described by Jaeschke et al. (1994), also suggest that the cluster could be useful clinically for discriminating between patients with and without an assumed dominance of NP.

Of the 11 symptoms and four signs entered into the first model, six and one respectively were retained as predictors of NP, suggesting that symptomatic features rather than clinical signs may be relatively more useful for identifying an assumed dominance of NP. Whilst additional data supporting the validity of clinical criteria associated with NP is often lacking, we speculate that each criterion in the cluster is underpinned by a degree of clinical and biological plausibility.

According to our findings, ‘Pain localised to the area of injury/dysfunction (with/without some somatic referral)’, was the strongest predictor of NP. It has been suggested that a dominance of NP mechanisms could underlie much simple back pain (Butler, 2000). The presence of more localised LBP as a predictor of NP could be associated with pain attributable to inflammatory, mechanical or ischaemic processes within more anatomically defined non-neural sources (e.g. disc, ligament etc) which
in turn could invoke specific nociceptive processes involving the preferential activation of the somatosensory cortices associated with the sensory-discriminative dimension of pain and thus the perception of more localised symptoms (Bushnell and Apkarian, 2006).

A ‘Clear, proportionate mechanical/anatomical nature to aggravating and easing factors’, associated with pain was the second strongest predictor of NP.

Neurophysiologically, the proportionate and mechanical nature to patients’ aggravating and easing factors could reflect the preservation of a close stimulus-response relationship (Woolf, 2004), meaning that pain provocation (or relief) appears proportionate to the intensity (or withdrawal) of the initiating stimulus. A preserved stimulus-response relationship could also imply the absence of those neurophysiological processes associated with the development and dominance of ‘central sensitisation’ which might otherwise distort this relationship (Woolf, 2011).

Patients’ whose pain was, ‘Usually intermittent and sharp with movement/mechanical provocation; may be a more constant dull ache or throb at rest’ could reflect the preferential activation of A-fibre afferent neurones which, it has been suggested, could be responsible for both sharp and/or aching-type qualities of pain (Meyer et al. 2006). Alternatively, it is possible that the intermittent and sharp nature of NP could reflect the periodic activation of primary nociceptors in response to mechanical (movement, touch, pressure) stimuli, as mediated by Aδ-fibre transmission (Butler, 2000), whereas the more constant aching/throbbing quality could reflect nociception associated with more inflammatory-mediated pain and the activation of ‘silent nociceptors’ (Gifford and Butler, 1997).
Classifying patients’ pain may be supported by the ‘absence’ as well as the presence of symptoms and signs (Helliwell et al. 2003). Of the four criteria whose absence appeared predictive of an assumed dominance of NP, the absence of ‘Pain in association with other dysesthesias’ was the strongest predictor. In effect, the presence of dysesthesias decreased the odds of being classified with NP by 85%.

Dysesthetic symptoms i.e. unpleasant abnormal sensations (e.g. crawling, electrical, heaviness, coldness, burning) have been linked to PNP states in response to some degree of axonal damage and altered function (Hall and Elvey, 2004; Quintner, 1990), such as C-fibre sensitisation (Jensen et al. 2001). Therefore the absence of dysesthesias as a predictor of NP may logically reflect the absence of peripheral nerve damage and associated changes in nerve function as necessary antecedents for its development. Dysesthetic symptoms and have been included as a feature in a number of neuropathic screening instruments, including the ‘Standardised Evaluation of Pain’ (StEP) (Scholz et al. 2009), ‘painDETECT’ (Freynhagen et al. 2006), ‘Douleur Neuropathique 4’ (Bouhassira et al. 2005), ‘Neuropathic Pain Questionnaire’ (Krause and Backonja, 2003) and the ‘Leeds Assessment of Neuropathic Symptoms and Signs’ (Bennett, 2001). Since these instruments tend to dichotomise pain as being either neuropathic or nociceptive, the relative absence of dysesthesias as a predictor of NP is consistent with this approach.

The absence of ‘Night pain/sleep disturbance’ in patients classified with NP could be linked to the severity and/or affective dimensions of pain and may reflect potential differences in the neurobiology underlying NP and non-NP pain states.
A number of potential neurobiological explanations underlying the relationship between pain and sleep disturbance have been proposed. Briefly, the serotonergic and cholinergic systems, the hypothalamic-pituitary-adrenal cortex and cytokine-mediated neuroimmune interactions all have the potential to modulate pain and sleep via their actions throughout a widely distributed central nervous system (Menefee et al. 2000). Whilst entirely speculative, the reduced odds of sleep disturbance in patients classified with NP could reflect the relative absence of neurobiological dysfunction in these systems.

Similarly, and hypothetically, the absence of ‘Antalgic (i.e. pain relieving) postures/movement patterns’ as a feature of NP could reflect an absence of those motor responses i) designed to protect against the consequences of neural tissue mechanosensitivity in patients with PNP (Hall and Elvey, 2004) or ii) that might occur as an indirect result of elevated fear, attention and stress or more directly as a result of altered CNS processes involved in motor planning (e.g. in the anterior cingulate cortex) in patients with more centrally-mediated pain (Hodges and Moseley, 2003).

‘Pain variously described as burning, shooting, sharp or electric-shock-like’ reduced the odds of a patient being classified with NP by 72%. Its absence as a predictor of NP is consistent with number of existing screening instruments which use such descriptors to identify and distinguish peripheral neuropathic from nociceptive pain (Bennett et al. 2007).
A more general consideration concerns the homogeneity and validity of NP (and PNP/CSP) as a mechanisms-based classification of pain. Mechanisms-based categorisations such as NP essentially group patients together based on an assumption that their pain is attributable to a similar, clinically meaningful and relatively homogenous set of pathophysiological mechanisms. However, a patient with an assumed dominance of NP could have pain arising from inflammatory (tissue injury) or ischaemic (tissue loading) mechanisms (Butler, 2000). The heterogeneity of pathophysiological mechanisms underlying NP may invite the delineation of subcategories in an attempt to describe increasingly more homogenous patient subgroups. However, validity evidence for such sub-categories of NP is sparse.

During the development and preliminary validity of the StEP tool (Scholz et al. 2009) for distinguishing neuropathic from non-neuropathic pain in patients with radicular and axial LBP, evidence was found for 2 statistically-derived subgroups of patients with axial (i.e. NP) LBP although the precise discriminatory symptoms and signs require further elucidation.

In addition, a recent survey of 105 specialist musculoskeletal clinicians, comprising spinal surgeons, rheumatologists, physiotherapists and chiropractors, was unable to identify specific symptoms and signs with which to discriminate between ‘inflammatory’ and ‘mechanical’ non-specific LBP (Walker and Williamson, 2009). A subsequent pilot discriminative validity study involving 50 patients presenting for chiropractic treatment similarly found no evidence for a symptom profile with which to distinguish ‘inflammatory’ from ‘mechanical’ LBP (Riksman et al. 2011).

Evidently, further research is required to test for and validate sub-categories of NP.
Identification of a cluster of symptoms and signs with which to distinguish an assumed dominance of NP from PNP/CSP in patients with musculoskeletal pain conditions could be useful clinically for informing decision-making associated with the i) treatment of patients’ pain, by inviting the selection of therapeutic interventions either known or hypothesised to target the dominant neurophysiological mechanisms underlying NP and ii) and predicting outcomes. For example clinicians might recommend peripherally acting anti-inflammatory or analgesic medications as part of an intervention (Kidd et al. 2007). And pain judged to be predominantly ‘nociceptive’ has been associated with more favourable prognoses in the clinical reasoning of experienced physiotherapists (Smart and Doody, 2006). However suitably designed longitudinal studies supporting the prescriptive and predictive validity of NP as a mechanisms-based classification of pain are required as proof of its clinical usefulness (Ford et al. 2007).

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 seven symptoms and signs associated with a clinical classification of NP in patients with low back (± leg) pain. The cluster was found to have high levels of classification accuracy suggesting it might be useful clinically. Further studies involving larger patient samples with a range of musculoskeletal disorders are required in order to provide more robust model estimates as well as identify other potential symptoms and signs associated with NP.
Conflicts of interest: None declared.
References


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Legends for illustrations:

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

- Non-steroidal anti-inflammatory drugs.

Subjective:
Clear, proportionate mechanical/anatomical nature to aggravating and easing factors.
Pain associated with and in proportion to trauma or a pathological process or movement/postural dysfunction.
Pain localised to the area of injury/dysfunction (with/without some somatic referral).
Usually rapidly resolving or resolving in accordance with expected tissue healing/pathology recovery times.
Responsive to simple analgesia/NSAIDs*.
Usually intermittent and sharp with movement/mechanical provocation; may be a more constant dull ache or throb at rest.
Pain in association with other symptoms of inflammation (i.e. swelling, redness, heat).
Pain of recent onset.

Clinical examination:
Clear, consistent and proportionate mechanical/anatomical pattern of pain reproduction on movement/mechanical testing of target tissues.
Localised pain on palpation.
Absence of or expected/proportionate findings of (primary and/or secondary) hyperalgesia and/or allodynia.
Antalgic (i.e. pain relieving) postures/movement patterns.

*Non-steroidal anti-inflammatory drugs.

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

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