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The Discriminative Validity of "Nociceptive," "Peripheral Neuropathic," and "Central Sensitization" as Mechanisms-based Classifications of Musculoskeletal Pain

Keith M. Smart, PhD, Catherine Blake, PhD,† Anthony Staines, PhD,‡ and Catherine Doody, PhD†*

Objectives: Empirical evidence of discriminative validity is required to justify the use of mechanisms-based classifications of musculoskeletal pain in clinical practice. The purpose of this study was to evaluate the discriminative validity of mechanisms-based classifications of pain by identifying discriminatory clusters of clinical criteria predictive of "nociceptive," "peripheral neuropathic," and "central sensitization" pain in patients with low back (± leg) pain disorders.

Methods: This study was a cross-sectional, between-patients design using the extreme-groups method. Four hundred sixty-four patients with low back (± leg) pain were assessed using a standardized assessment protocol. After each assessment, patients' pain was assigned a mechanisms-based classification. Clinicians then completed a clinical criteria checklist indicating the presence/absence of various clinical criteria.

Results: Multivariate analyses using binary logistic regression with Bayesian model averaging identified a discriminative cluster of 7, 3, and 4 symptoms and signs predictive of a dominance of "nociceptive," "peripheral neuropathic," and "central sensitization" pain, respectively. Each cluster was found to have high levels of classification accuracy (sensitivity, specificity, positive/negative predictive values, positive/negative likelihood ratios).

Discussion: By identifying a discriminatory cluster of symptoms and signs predictive of "nociceptive," "peripheral neuropathic," and "central" pain, this study provides some preliminary discriminative validity evidence for mechanisms-based classifications of musculoskeletal pain. Classification system validation requires the accumulation of validity evidence before their use in clinical practice can be recommended. Further studies are required to evaluate the construct and criterion validity of mechanisms-based classifications of musculoskeletal pain.

Key Words: classification, pain mechanisms, validity

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Mechanisms-based pain classification refers to the classification of pain based on assumptions as to the underlying neurophysiological mechanisms responsible for its generation and maintenance.[1,2] Mechanisms-based classifications of pain have been advocated in clinical practice on the grounds that they may help explain observed variations in the nature and severity of many clinical presentations of musculoskeletal pain [eg, low back pain (LBP) disorders] (1) in which pain is reported in the absence of or disproportionate to any clearly identifiable pathology, (2) in which pain is reported to persist after the resolution of injury or pathology, (3) in which the severity of pain reported by patients with similar injuries and pathologies differs greatly, and paradoxically (4) in which pain does not exist despite evidence of injury or pathology.[3–5] In addition, it has been suggested that mechanisms-based approaches could improve the treatment of pain and optimize patients' outcomes by facilitating the selection of clinical interventions known or hypothesized to target the dominant underlying neurophysiological mechanisms responsible for its generation and maintenance.[6]

Nociceptive pain (NP), peripheral neuropathic pain (PNP), and central sensitization pain (CSP) (ie, "central hyper-excitability"/"functional" pain) have been suggested as clinically meaningful mechanisms-based classifications of musculoskeletal pain,[7–10] whereby each classification refers to a clinical presentation of pain assumed to reflect a dominance of nociceptive, peripheral neuropathic, or central pain mechanisms, respectively.

In the absence of a diagnostic gold standard, it has been hypothesized that mechanisms-based classifications of patients' pain may be undertaken clinically on the basis of patterns of symptoms and signs assumed to reflect its underlying neurophysiology.[11] In this regard, attempts have been made to develop a 3-category classification system for musculoskeletal pain. Using a judgemental approach toward classification system development, a Delphi survey was undertaken to generate expert, consensus-derived lists of clinical criteria associated with a dominance of "nociceptive," "peripheral neuropathic," and "central" mechanisms of musculoskeletal pain.[12]

Empirical evidence of discriminative validity is required to justify the use of mechanisms-based classifications of musculoskeletal pain in clinical practice.[13] For the purpose of this study, discriminative validity was defined as the extent to which the categories of a classification system are able to differentiate between those with and without the disorder.[14] The discriminative validity of a classification system is supported if it can be shown that the presence or absence of specific clinical criteria can be used to differentiate between and predict membership of the categories that make up the classification system. To continue the development of mechanisms-based classifications of musculoskeletal pain, the aim of this study was to

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evaluate the discriminative validity of NP, PNP, and CSP as mechanisms-based classifications of pain in patients with low back (± leg) pain disorders by testing for and identifying a discriminatory cluster of clinical indicators associated with each category of pain.

MATERIALS AND METHODS

Study Design

This study was a cross-sectional, between-patients design using the validation by extreme-groups method.[14]

Setting

This discriminative validity study was carried out at 6 separate locations including 4 hospital sites, (1) the Back Pain Screening Clinic of the Adelaide and Meath Hospital, Dublin, (2) the Back Care Programme of Waterford Regional Hospital, Waterford, (3) the Physiotherapy Department of St Vincent's University Hospital, Dublin (all Ireland), and (4) the Physiotherapy Department of Guy's and St Thomas' NHS Foundation Trust, London (United Kingdom); and 2 private physiotherapy practices; (1) Portobello Physiotherapy Clinic, Dublin and (2) Milltown Physiotherapy Clinic, Dublin. This study was conducted according to the principles outlined in the Declaration of Helsinki. Ethical approval for this study was granted by the Ethics and Medical Research Committees of each Irish institution and the National Research Ethics Service (UK).

Participants

Fifteen physiotherapists participated in data collection, including 13 public hospital-based clinicians, 1 of whom was the primary investigator (K.M.S.) and 2 private practitioners. All of the clinicians had specialized in general or specific fields of musculoskeletal physiotherapy. The mean number of years since qualification and spent working within the speciality of musculoskeletal physiotherapy was 12 (SD 5.2; range, 5 to 21) and 9.2 years (SD 4.38; range, 3 to 18), respectively. Thirteen clinicians possessed "masters" level qualifications in physiotherapy and 1 clinician had a postgraduate diploma.

Patients of 18 years of age or older referred with low back (± leg) pain were eligible for inclusion. Exclusion criteria included patients with a history of diabetes or central nervous system injury, pregnancy, or nonmusculoskeletal LBP. Patients were recruited from the outpatient waiting lists of each back pain screening clinic/physiotherapy service. All patients gave signed informed consent before their participation. A flowchart detailing patient recruitment is presented in Figure 1.

Instrumentation and Procedures

Patient demographics were collected using a standardized form. Each patient was assessed using a standardized clinical interview and examination procedure based on accepted clinical practice.[15] During the clinical interview, patients were encouraged to disclose details of their LBP history, current symptomology, and its behavior. Patients were also screened for "red" and "yellow" flags associated with serious spinal pathology and psychosocial mediators, respectively in accordance with clinical practice guidelines.[16] The clinical examination included postural, movement, and neurological-based assessments. To complete the clinical criteria checklist (CCC), a number of additional symptoms (eg, spontaneous, paroxysmal pain, and dysesthesias) and signs (eg, allodynia, hyperalgesia, hyperpathia, and nerve palpation) were assessed.

After each patient examination, clinicians were required to complete a CCC consisting of 2 parts. "Part 1" required examiners to classify each patient's pain presentation. Patients were classified in to 1 of 3 categories of pain mechanism (ie, NP, PNP, CSP) or 1 of 4 possible "mixed" pain states derived from a combination of the original 3 categories (ie, Mixed: NP/PNP; Mixed: NP/CSP; Mixed: PNP/CSP; Mixed: NP/PNP/CSP) on the basis of experienced clinical judgement with regard to the likely dominant mechanisms assumed to underlie each patient's pain. Discriminative validity designs require the identification of the "extreme groups" (ie, pain type) and in the absence of a diagnostic gold standard the best alternative "reference standard"—defined as, "…the best available method for establishing the presence or absence of a condition of

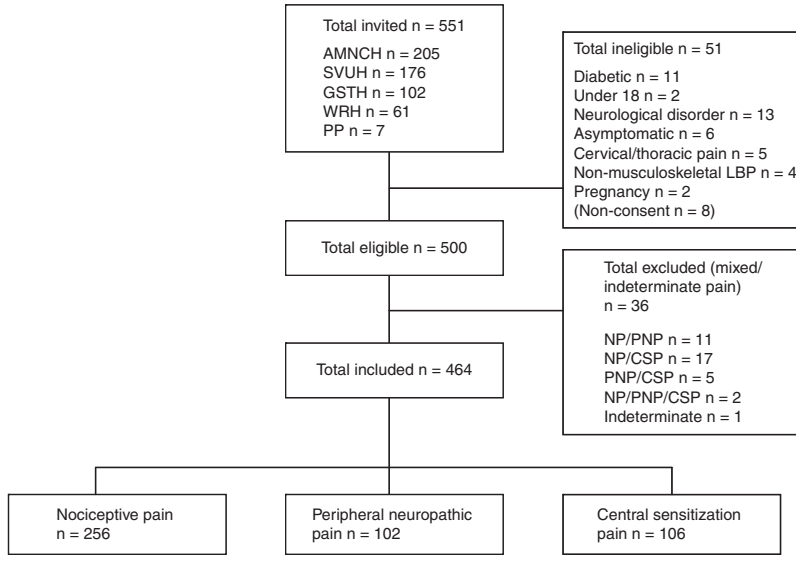

FIGURE 1. Flowchart of patient recruitment.

interest,"[17] may be expert clinical judgement.[14] "Under this assumption the development of classification criteria becomes an exercise in determining which history [and] physical examination…findings match the impression of an experienced clinician."[18]

"Part 2" required examiners to complete a 38-item CCC, consisting of 26 symptoms and 12 signs (Table 1), based on an expert consensus-derived list of clinical criteria assumed to reflect a dominance of NP, PNP, and CSP.[12] Response options for each criterion included "Present," "Absent," or "Don't know." To ensure that symptoms and signs were assessed consistently, clinicians were provided with practical training together with an "Assessment Manual" containing written instructions on how to undertake each patient examination, and interpret and document findings.

Sample Size Requirements

The minimum sample size required for this study was based on a recommended minimum of 10 patients per predictor variable.[19] The number of predictor variables evaluated in this study was 40, corresponding to the 38 items on the CCC plus the variables "age" and "sex," thus necessitating a minimum sample of 400 patients.

Data Analysis

Univariate analyses, using a χ^2 test for independence, were carried out initially as a means of item reduction by identifying and excluding nondiscriminatory criteria.[19] Multivariate analyses using binary logistic regression (BLR) with Bayesian model averaging were then undertaken to test for and identify discriminatory clusters of

TABLE 1. Individual Items Included on the 38-item Clinical Criteria Checklist

Criterion	Description
1.	Pain of recent onset
2.	Pain associated with and in proportion to trauma, a pathologic process or movement/postural dysfunction
3.	History of nerve injury, pathology, or mechanical compromise
4.	Pain disproportionate to the nature and extent of injury or pathology
5.	Usually intermittent and sharp with movement/mechanical provocation; may be a more constant dull ache or throb at rest
6.	More constant/unremitting pain
7.	Pain variously described as burning, shooting, sharp, or electric-shock-like
8.	Pain localized to the area of injury/dysfunction (with/without some somatic referral)
9.	Pain referred in a dermatomal or cutaneous distribution
10.	Widespread, nonanatomic distribution of pain
11.	Clear, proportionate mechanical/anatomic nature to aggravating and easing factors
12.	Mechanical pattern to aggravating and easing factors involving activities/postures associated with movement, loading, or compression of neural tissue
13.	Disproportionate, nonmechanical, unpredictable pattern of pain provocation in response to multiple/nonspecific aggravating/easing factors
14.	Reports of spontaneous (ie, stimulus-independent) pain and/or paroxysmal pain (ie, sudden recurrences and intensification of pain)
15.	Pain in association with other dysesthesias (eg, crawling, electrical, heaviness)
16.	Pain of high severity and irritability (ie, easily provoked, taking longer to settle)
17.	Pain in association with other symptoms of inflammation (ie, swelling, redness, heat)
18.	Pain in association with other neurological symptoms (eg, pins and needles, numbness, weakness)
19.	Night pain/disturbed sleep
20.	Responsive to simple analgesia/NSAIDs
21.	Less responsive to simple analgesia/NSAIDs and/or more responsive to antiepileptic (eg, Lyrica)/antidepression (eg, Amitriptyline) medication
22.	Usually rapidly resolving or resolving in accordance with expected tissue healing/pathology recovery times
23.	Pain persisting beyond expected tissue healing/pathology recovery times
24.	History of failed interventions (medical/surgical/therapeutic)
25.	Strong association with maladaptive psychosocial factors (eg, negative emotions, poor self-efficacy, maladaptive beliefs, and pain behaviors, altered family/work/social life, medical conflict)
26.	Pain in association with high levels of functional disability
27.	Antalgic (ie, pain relieving) postures/movement patterns
28.	Clear, consistent, and proportionate mechanical/anatomic pattern of pain reproduction on movement/mechanical testing of target tissues
29.	Pain/symptom provocation with mechanical/movement tests (eg, Active/Passive, Neurodynamic, ie, SLR) that move/load/compress neural tissue
30.	Disproportionate, inconsistent, nonmechanical/nonanatomic pattern of pain provocation in response to movement/mechanical testing
31.	Positive neurological findings (altered reflexes, sensation, and muscle power in a dermatomal/myotomal or cutaneous nerve distribution)
32.	Localized pain on palpation
33.	Diffuse/nonanatomic areas of pain/tenderness on palpation
34.	Positive findings of allodynia within the distribution of pain
35.	Positive findings of hyperalgesia (primary and/or secondary) within the distribution of pain
36.	Positive findings of hyperpathia within the distribution of pain
37.	Pain/symptom provocation on palpation of relevant neural tissues
38.	Positive identification of various psychosocial factors (eg, catastrophization, fear-avoidance behavior, distress)

NSAIDs indicates nonsteroidal anti-inflammatory drugs; SLR, straight leg raise.

symptoms and signs associated with a clinical classification of NP, PNP, and CSP. Three BLR models were evaluated, 1 for each category of pain. Modeling for each pain category, using NP versus non-NP as an example, was undertaken sequentially in the following way:

1. With NP as the designated "reference category," patients with NP were coded as "1" (equivalent to presence of the trait), and patients with non-NP (ie, those patients classified with a dominance of PNP and CSP) were coded as "0" (equivalent to "absence" of the trait). Clinical criteria were coded according to an identical interpretation (ie, "1" = present, "0" = absent). "Don't know" responses were treated as missing values.
2. Consensus-based Delphi-derived criteria associated with a dominance of NP were initially selected as candidate criteria for inclusion into the BLR model.[12]
3. Additional clinical criteria with potential discriminative value were identified and included, when on the basis of a univariate analysis, the "absence" of specific criterion seemed to be associated with a dominance of NP.
4. Any criteria identified as "nondiscriminatory" from the univariate analyses were excluded.
5. All remaining candidate criteria were entered into the initial model, which was labeled as "Model 1."
6. Model parameters, for each criterion, were examined. Criteria with a low "posterior probability" (eg, < 5%) were identified and excluded. Remaining criteria were retained and reentered into a subsequent model ("Model 2").
7. The posterior probabilities of each criterion were reevaluated. The criterion with the lowest "posterior probability" was identified and excluded. Remaining

TABLE 2. Patient Demographics by Pain Classification (n=464)

Variable	Nociceptive (n = 256)	Peripheral Neuropathic (n = 102)	Central Sensitization (n = 106)
Sex (Female)	150 (59%)	53 (52%)	57 (54%)
Age (y), Mean (SD, Range)	44 (14.5, 19-85)	44 (13.1, 20-76)	43 (12.3, 20-80)
Source of referral			
GP	144 (56%)	68 (67%)	44 (42)
Orthopedics	41 (16%)	12 (12%)	11 (10)
ED	25 (10%)	14 (14%)	5 (5%)
Pain clinic	6 (2%)	3 (3%)	38 (36%)
Occ Health	25 (10%)	2 (2%)	2 (2%)
Rheumatologist	4 (2%)	0	1 (1%)
Other	11 (4%)	3 (3%)	5 (5%)
Assessment setting			
BPSC	128 (50%)	68 (67%)	24 (23%)
Physio Dept	119 (47%)	33 (32%)	39 (37%)
Pain Clinic	2 (1%)	1 (1%)	43 (41%)
Private Practice	7 (3%)	0	0
Predominant pain location			
Back	209 (82%)	9 (9%)	65 (61%)
Back/Thigh	37 (15%)	19 (19%)	17 (16%)
Uni Leg BK	3 (1%)	60 (59%)	4 (4%)
Back/Uni leg BK	7 (3%)	11 (11%)	10 (9%)
Bilat Leg BK	0	1 (1%)	1 (1%)
Back/Bilat leg BK	0	2 (2%)	9 (9%)
Duration current episode			
0-3 wk	17 (7%)	2 (2%)	2 (2%)
4-6 wk	33 (13%)	14 (14%)	2 (2%)
7-12 wk	33 (13%)	18 (18%)	2 (2%)
4-6 mo	36 (14%)	23 (22%)	2 (2%)
7-12 mo	27 (11%)	21 (21%)	10 (9%)
> 1 y	110 (43%)	24 (23%)	88 (83%)
[Mean duration (y), SD, range]	(6.8, 6.9, 1-40)	(3.4, 3.3, 1-14)	(7.1, 7.2, 1.5-40)
Work status			
Full time	111 (43%)	35 (34%)	12 (11%)
Part time	23 (9%)	10 (10%)	7 (6%)
Homemaker	23 (9%)	8 (8%)	9 (9%)
Off work (2nd LBP)	33 (13%)	27 (27%)	22 (21%)
Off work (2nd Other)	13 (5%)	6 (6%)	9 (9%)
U/E	13 (5%)	2 (2%)	6 (6%)
Retired	28 (11%)	11 (11%)	9 (9%)
Student	7 (3%)	1 (1%)	2 (2%)
Reg Disabled (2nd LBP)	2 (1%)	0	28 (26%)
Reg Disabled (2nd Other)	1 (0%)	2 (2%)	1 (1%)
Unknown	0	0	1 (1%)
Medico-legal case pending	10 (4%)	3 (3%)	26 (25%)

Bilat Leg BK indicates bilateral leg pain below knee; BPSC, back pain screening clinic, Physio Dept, Physiotherapy Department; ED, Emergency Department; GP, General Practitioner; LBP, low back pain; Occ Health, Occupational Health Department; Reg Disabled, Registered Disabled; U/E, unemployed; Uni Leg BK, unilateral leg pain below knee.

TABLE 3. Model Parameters for Criteria in the Final "Nociceptive," "Peripheral Neuropathic," and "Central Sensitization" Pain Models

Criteria	Regression Coefficient	SD	95% CI Lower	95% CI Upper	OR	OR 95% CI Lower	OR 95% CI Upper
Nociceptive							
5 Intermittent	1.45	0.74	−0.00	2.89	4.25	0.99	18.25
7 Burning	−1.28	0.37	−2.00	−0.56	0.28	0.14	0.57
8 Localized	4.25	0.52	3.22	5.27	69.79	25.13	193.81
11 Clear aggravating/easing	2.91	0.58	1.78	4.05	18.41	5.91	57.37
15 Dysesthesias	−1.89	0.46	−2.79	−1.00	0.15	0.06	0.37
19 Night pain	−1.51	0.38	−2.25	−0.77	0.22	0.11	0.46
27 Antalgic	−1.41	0.40	−2.19	−0.63	0.24	0.11	0.53
Peripheral neuropathic							
3 History of nerve injury	2.54	0.64	1.29	3.80	12.64	3.59	44.49
9 Dermatomal	3.19	0.69	1.85	4.53	24.29	6.33	93.18
29 Nerve movement tests	2.68	0.49	1.72	3.65	14.64	5.59	38.37
Central							
4 Pain disproportionate to injury	2.72	0.63	1.48	3.96	15.19	4.39	52.48
13 Disproportionate aggravating/easing	3.42	0.66	2.13	4.72	30.69	8.41	112.03
25 Psycho social symptoms	2.03	0.79	0.49	3.58	7.65	1.64	35.79
33 Diffuse palpation	3.32	0.75	1.84	4.80	27.57	6.28	121.09

95% CI indicates 95% confidence interval; OR, odds ratio.

criteria were retained and reentered into a subsequent model ("Model 3").

8. This process continued, with successive models labeled consecutively as "Model 4," "Model 5," and so on, until only criteria with a "posterior probability" of $\geq 50\%$ remained. These models were considered candidate "final models."

The aim of each logistic regression was to produce an optimum model guided by considerations of classification accuracy and parsimony, that is to produce a discriminatory cluster of symptoms and signs for each category of pain, comprising the fewest clinical criteria while preserving classification accuracy.[19]

Indices of classification accuracy [sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios] with 2-sided 95% confidence intervals (CIs) were calculated to assess the classification accuracy of each final model. Univariate analyses were carried out using SPSS (SPSS for windows, version 15). Multivariate analyses were carried out in "R" (2009, version 2.9.2).

RESULTS

A convenience sample of 551 patients with musculoskeletal low back (± leg) pain disorders was invited to participate in this study. Fifty-one patients were ineligible according to the exclusion criteria, and 36 patients with a mixed (n = 35) or indeterminate (n = 1) pain state were excluded. Patient demographics for the final sample (n = 464) are presented in Table 2.

Univariate

A χ^2 test for independence indicated that "Criterion 17" [χ^2 (2, n = 464) = 2.30, $P = 0.32$] and "sex" [χ^2 (2, n = 464) = 1.59, $P = 0.45$] were not significantly associated with pain classification, and a one-way between-groups analysis of variance [Browne-Forsythe F-ratio 0.23 (df 2, 463), $P = 0.80$] indicated that there was no statistically significant differences in the mean age of patients across pain classifications. These variables were, therefore, excluded from the multivariate analyses.

Multivariate

Missing values were identified for 12 cases, thus reducing the valid sample size from n = 464 to n = 452 (NP n = 252, PNP n = 102, CSP n = 98). Model parameters [regression coefficients and odds ratios (ORs) with 95% CI] for each criterion in the final NP, PNP, and CSP models are presented in Table 3 (where shortened criterion descriptions are given; full descriptions are presented in Table 1).

Cross tabulations from which the indices of classification accuracy were calculated for each final cluster are presented in Tables 4 to 6.[20] Indices of classification accuracy, with 95% CIs, for each final model are presented in Table 7.

Nociceptive

A dominance of NP was predicted by 7 criteria, including the presence of 3 symptoms (criteria 5, 8, 11), the "absence" of 3 symptoms (criteria 7, 15, 19), and 1 sign (criterion 27). According to the NP model, the strongest predictor of NP was criterion 8 (OR = 69.79; 95% CI, 25.13-193.81] suggesting that patients with "pain localized 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 with those with non-NP, controlling for all other variables in the model. The OR of 0.15 for criterion 15 was < 1, indicating that patients with "pain in association with other

TABLE 4. Classification Accuracy of the Final "Nociceptive" Pain Model

	Reference Standard Positive	Reference Standard Negative
Cluster positive	229 patients	18
Cluster negative	23	182

TABLE 5. Classification Accuracy of the Final "Peripheral Neuropathic" Pain Model

	Reference Standard Positive	Reference Standard Negative
Cluster positive	88 patients	14
Cluster negative	14	336

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, that is the presence of dysesthesias decreased the odds of being classified with NP by 85%.

A sensitivity of 90.9% indicates that this cluster of clinical criteria correctly predicted a dominance of NP in 90.9% of those patients classified with NP according to the reference standard of "experienced" clinical judgement, but incorrectly predicted 9.1% of these patients as having non-NP. The diagnostic OR of 100.67 indicates that that the cluster is 100 times more likely to accurately than inaccurately predict a dominance of NP in patients with a dominance of NP.

Peripheral Neuropathic

Three criteria (criteria 3, 9, 29) were found to be predictive of PNP. According to the final model, the strongest predictor 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 than non-PNP, controlling for all other variables in the model.

A positive predictive value of 86.3% indicates that a patient with the cluster of clinical criteria outlined by the model is likely to have a dominance of PNP with an 86.3% level of probability. The negative predictive value indicates that the probability of a patient without the cluster having non-PNP is 96.0%.

Central Sensitization

A dominance of CSP was predicted by the presence of 3 symptoms (criteria 4, 13, 25) and 1 sign (criterion 33). The strongest predictor of CSP was criterion 13 (OR = 30.69; 95% CI, 8.41-112.03) suggesting that patients with "disproportionate, nonmechanical, unpredictable pattern of pain provocation in response to multiple/nonspecific aggravating/easing factors," were over 30 times more likely to be classified with a dominance of CSP than non-CSP.

The LR+ of 40.64 suggests that the CSP cluster is over 40 times more likely to be found in a patient with a dominance of CSP than non-CP. The LR− indicates that the likelihood of the cluster being absent in patients with a dominance of CSP compared with non-CSP is 0.08. A summary of the mechanisms-based classification system for musculoskeletal pain based on the results of this study is presented in Figure 2.

TABLE 6. Classification Accuracy of the Final "Central Sensitization" Pain Model

	Reference Standard Positive	Reference Standard Negative
Cluster positive	90 patients	8
Cluster negative	8	346

TABLE 7. Indices of Classification Accuracy for the "Final," "Nociceptive," "Peripheral Neuropathic," and "Central Sensitization" Pain Models

	Value	95% CI Lower	95% CI Upper
Nociceptive			
CA	90.9	87.9	93.4
Sensitivity	90.9	86.6	94.1
Specificity	91.0	86.1	94.6
PPV	92.7	88.7	95.6
NPV	88.9	83.6	92.8
LR+	10.10	6.49	15.72
LR−	0.10	0.07	0.15
DOR	100.67	52.72	192.22
Peripheral Neuropathic			
CA	93.8	91.2	95.8
Sensitivity	86.3	78.0	92.3
Specificity	96.0	93.4	97.8
PPV	86.3	78.0	92.3
NPV	96.0	93.4	97.8
LR+	21.57	12.84	36.24
LR−	0.14	0.09	0.23
DOR	150.86	69.36	328.13
Central			
CA	96.5	94.3	98.0
Sensitivity	91.8	84.5	96.4
Specificity	97.7	95.6	99.0
PPV	91.8	84.5	96.4
NPV	97.7	95.6	99.0
LR+	40.64	20.43	80.83
LR−	0.08	0.04	0.16
DOR	486.56	177.74	1331.97

CA indicates classification accuracy; DOR, diagnostic odds ratio; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

Using a statistical approach toward classification development, discriminatory clusters of symptoms and signs associated with a clinically determined dominance of NP, PNP, and CSP were identified from an original Delphi-derived consensus of clinical indicators. In doing so, this study provides some preliminary discriminative validity evidence for NP, PNP, and CSP as mechanisms-based classifications of low back (± leg) pain.

A common mechanisms-based approach toward the classification of pain has been to dichotomize pain as being either predominantly "neuropathic" or "nociceptive,"[11,21,22] and a number of screening instruments have been developed to facilitate this distinction clinically.[23] However, a fundamental attribute of any classification system is that its categories should be exhaustive,[24] meaning that all patients should be classifiable into one category. A dichotomized model of pain may be problematic for those patients hypothesized to have pain arising from or maintained by a dominance of dysfunctional central pain processes, whereby pain occurs or persists in the absence of, or disproportionate to, trauma/inflammation (ie, NP) or a peripheral nerve lesion (ie, PNP)[25] such as those with "fibromyalgia," whiplash-associated disorders, and some forms of chronic

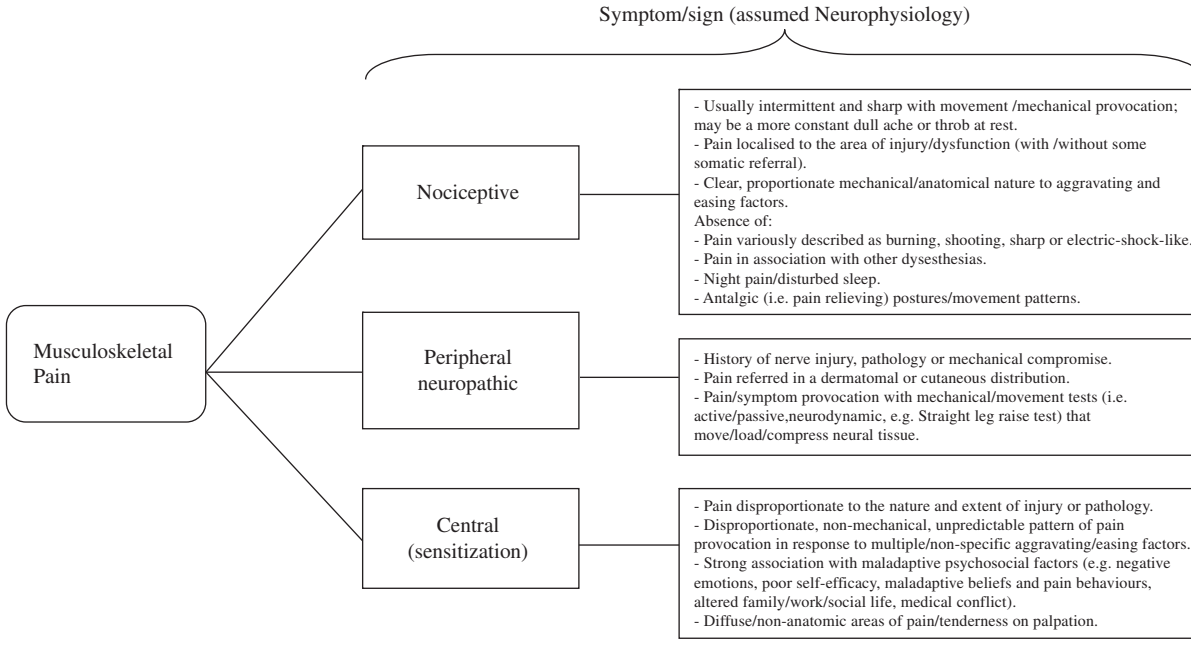

FIGURE 2. A summary of the mechanisms-based classification system for musculoskeletal pain.

LBP.[9] A mechanisms-based classification system for pain comprising 3 categories may allow for the classification of broader populations of patients and be more useful clinically.

Although the classification system proposed in this study was comprised of three categories it is acknowledged that other "categories" of pain mechanisms may exist, such as "autonomic," "neuroendocrine," and "neuroimmune" pain. A number of investigators and mechanisms-based clinical reasoning strategies for pain have described the potential influence of autonomic, neuroendocrine, and neuroimmune mechanisms on pain transmission and modulation.[26–28] However, it has been suggested that activity from within these systems may not be so readily identifiable from clusters of symptoms and signs, and that they operate simultaneously and synergistically more as response and background systems in association with activity in the peripheral and central nervous systems.[10] Further elucidation of the role of these systems and the recognition of clinical markers may facilitate their inclusion into an expanded mechanisms-based classification system for pain.

A further consideration concerns the homogeneity of categorizations such as NP, PNP, and CSP, that is the extent to which patients classified with a given dominant pain state have pain attributable to common pathophysiological mechanisms. Categorical labels for constructs such as NP, PNP, and CSP, essentially describe and compartmentalize the highly complex and numerous pathophysiological processes associated with each construct together under a single umbrella term. For example, a patient with a dominance of NP could have pain secondary to inflammatory (tissue injury) or ischemic (tissue loading) mechanisms.[10] A patient with a dominance of PNP may have pain arising from the formation of "abnormal impulse generating sites," which may themselves be variously mechanosensitive, ischemic-sensitive, or chemo-sensitive, or from "cross-excitation" of injured axons from neighboring uninjured neurons.[29] And a patient with a dominance of CSP may have pain secondary to one or more of the following pathophysiological processes, such as "classic dorsal horn-mediated central sensitization," loss of spinal cord inhibitory interneurones, or forebrain-mediated descending facilitation.[30–32] The manner in which these different processes manifest, and the extent to which they may be identified and distinguished clinically is not known. Furthermore, neurobiological research currently allows for more mechanistic possibilities than can be distinguished clinically.[33]

A more pragmatic perspective suggests that the validity and usefulness of any classification system is ultimately dependent on the extent to which it fulfills the purposes for which it was designed.[34] If categorical designations such as NP, PNP, and CSP can be shown to (1) help clinicians make sense of a patient's pain presentation, (2) facilitate an appropriate assessment, (3) predict an outcome (whether in response to natural history or treatment), and (4) facilitate the selection of appropriate interventions and/or discourage the selection of inappropriate ones, thus optimizing clinical outcomes and the use of healthcare resources, then arguably the classification system has fulfilled its function regardless of the extent to which its constituent categories can be said to exactly reflect homogenous pathophysiological mechanisms. Therefore, precise knowledge of the underlying pathophysiology of the disorder, although desirable to enhance the specificity of treatment selection, may not be an essential requirement for clinical validity.[35]

Consistent with the findings of Scholz et al,[11] who developed a clinical tool for distinguishing neuropathic from non-neuropathic pain, the findings from this study suggest that relatively few symptoms and signs may be required to distinguish between pain types. Differentiating between the dominant mechanisms assumed to underlie

patients' pain may be important clinically as it may have a direct impact on clinical decision making.[36] However, the predictive and prescriptive validity of mechanisms-based classifications of pain requires further empirical evaluation. The findings from this study should be interpreted in light of a number of methodological limitations.

In the absence of a "diagnostic" gold standard by which to determine mechanisms-based classifications of pain, patients were necessarily classified on the basis of a "reference standard" of "experienced" clinical judgement.[18] The robustness of the reference standard may have been improved if patients' pain had been classified on the basis of a unanimous agreement after independent assessments by 2 (or more clinicians). Validation by "extreme groups" on the basis of agreement by 2 clinicians (specialist pain consultants) has been used during the development and preliminary validation of a number of screening instruments designed for the purpose of identifying patients with neuropathic pain, such as the "painDETECT"[22] and "Douleur Neuropathique 4."[37] Other neuropathic screening instruments, however, such as the "ID-Pain,"[38] "Neuropathic Pain Questionnaire,"[39] and "Leeds Assessment of Neuropathic Symptoms and Signs,"[40] have been developed on the basis of a single expert clinical judgement suggesting this could be an acceptable approach.

The assessment protocol used in this study required each clinician to both classify each patient's pain presentation and complete the CCC. This procedure could render the findings subject to a type of "clinical review bias,"[41] whereby a clinician's preconceived ideas about the clinical criteria associated with each category of pain may have biased their responses during completion of the CCC. Ideally, the assignment of patients to each reference category and the completion of the CCC should be undertaken independently by 2 separate clinicians. In this way, the potential for a clinician's earlier classification to influence (ie, bias) their subsequent responses is eliminated. The resources available for this study did not allow for patient assessments by 2 clinicians.

Statistical approaches toward classification system development have inherent limitations. With logistic regression, the inclusion/exclusion of a criterion within a model can be dependent to some extent on statistical variation during the modeling process.[42] Therefore, any statistically derived model is characterized by a degree of uncertainty in that logistic regression will generate "a" model from a potential pool of other similar competing models. Determination of a "definitive" single model by means of logistic regression is, therefore, not possible. In light of this, regression modeling on a different data set from a different sample of patients would likely produce different, albeit similar, models (ie, clusters of clinical criteria) for each category of pain.

In addition, it has been shown that studies using logistic regression with small-to-moderate sample sizes tend to overestimate the OR of predictor variables as a consequence of a systematic mathematical bias inherent with logistic regression.[43] It is accepted that the sample included in this study may have led to inflated model estimates, and that a larger sample size with increased numbers of patients within each reference category may have produced more accurate estimates of model parameters and classification accuracy.

Development methodologies also tend to produce inflated estimates of model parameters and predictive accuracies because the model fitting process optimizes the model parameters to make the model fit the data as closely as possible.[42] It is this phenomenon that necessitates cross-validation in an independent sample to obtain more accurate estimates of the "true" model parameters. As the methodology used in this study was developmental, it is likely that estimates concerning the relative contributions of criteria to each model (ie, regression coefficients and ORs) and the indices of classification accuracy (sensitivity, specificity etc) are inflated. Therefore, the values of these parameters should be interpreted with this caveat in mind.

The clusters of clinical criteria identified in this study were derived from a population of patients with LBP disorders. Evaluation of the same CCC on patient populations with other musculoskeletal disorders may have yielded different clusters. For example, it could be argued that the criterion, "pain in association with other symptoms of inflammation" was unlikely ever to be a potential predictor of NP because such symptoms (swelling, redness, heat), arguably, are rarely if ever identifiable in patients with LBP. However, it is possible that this criterion may have emerged as a significant predictor of NP in a patient population with ankle or knee injuries. Therefore, the clusters identified may not generalize to other musculoskeletal disorders.

By identifying a discriminatory cluster of symptoms and signs predictive of "nociceptive," "peripheral neuropathic," and "central sensitization" pain, this study provides some preliminary discriminative validity evidence for mechanisms-based classifications of musculoskeletal pain. Classification system validation requires the accumulation of validity evidence before their use in clinical practice can be recommended. As such, further studies are required to evaluate the construct and criterion validity of mechanisms-based classifications of musculoskeletal pain.

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REFERENCES

1. Woolf CJ, Bennett GJ, Doherty M, et al. Towards a mechanism-based classification of pain? *Pain*. 1998;77:227–229.
2. Portenoy RK. Mechanisms of clinical pain: observations and speculations. *Neurol Clin North Am*. 1989;7:205–230.
3. Quintner JL, Cohen ML, Buchanan D, et al. Pain medicine and its models: helping or hindering. *Pain Med*. 2008;9:824–834.
4. Main CJ, Spanswick CC. Models of pain. In: Main CJ, Spanswick CC, eds. *Pain Management. An Interdisciplinary Approach*. Edinburgh: Churchill Livingstone; 2000:3–18.
5. Haldeman S. Presidential address, North American Spine Society: failure of the pathology model to predict back pain. *Spine*. 1990;15:718–724.

6. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep*. 2009; 13:185–190.
7. Yunus MB. The concept of central sensitivity syndromes. In: Wallace DJ, Clauw DJ, eds. *Fibromyalgia and Other Central Pain Syndromes*. Philadelphia: Lippincott Williams and Watkins; 2005:29–44.
8. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140:441–451.
9. Lidbeck J. Central hyperexcitability in chronic musculoskeletal pain: a conceptual breakthrough with multiple clinical implications. *Pain Res Manag*. 2002;7:81–92.
10. Butler DS. *The Sensitive Nervous System*. Adelaide: Noigroup Publications; 2000.
11. Scholz J, Mannion RJ, Hord DE, et al. A novel tool for the assessment of pain: validation in low back pain. *PLoS Med*. 2009;6:e1000047. doi: 10.1371/journal.pmed.1000047.
12. Smart KM, Blake C, Staines A, et al. Clinical indicators of "nociceptive", "peripheral neuropathic" and "central" mechanisms of musculoskeletal pain: a Delphi survey of expert clinicians. *Man Ther*. 2010;15:80–87.
13. Ford J, Story I, O'Sullivan P, et al. Classification systems for low back pain: a review of the methodology for development and validation. *Phys Ther Rev*. 2007;12:33–42.
14. Streiner DL, Norman GR. *Health Measurement Scales: A Practical Guide to Their Development and Use*. 3rd ed. Oxford: Oxford University Press; 2003.
15. Petty NJ, Moore AP. *Neuromusculoskeletal Examination and Assessment. A Handbook for Therapists*. Edinburgh: Churchill Livingstone; 2001.
16. Koes BW, van Tulder MW, Ostelo R, et al. Clinical guidelines for the management of low back pain in primary care: an international comparison. *Spine*. 2001;26:2504–2513.
17. Bachman LM, Jüni P, Reichenbach S, et al. Consequences of different diagnostic "gold standards" in test accuracy research: Carpal tunnel syndrome as an example. *Int J Epidemiol*. 2005;34:953–955.
18. Katz JN, Stock SR, Evanoff BA, et al. Classification criteria and severity assessment in work-associated upper extremity disorders: methods matter. *Am J Ind Med*. 2000;38:369–372.
19. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd ed. New York: John Wiley & Sons; 2000.
20. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem*. 2003;49:7–18.
21. Bennett MI, Smith BH, Torrance N, et al. Can pain be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain*. 2006;122:289–294.
22. Freynhagen R, Baron R, Gockel U, et al. Pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911–1920.
23. Bennett MI, Attal N, Backonja MM, et al. Using screening tools to identify neuropathic pain. *Pain*. 2007;127:199–203.
24. Merskey H, Bogduk N. *Classification of Chronic Pain*. 2nd ed. Seattle: IASP Press; 1994.
25. Loeser JD, Treede R-D. The Kyoto protocol of IASP basic terminology. *Pain*. 2008;137:473–477.
26. Jänig W, Levine JD. Autonomic-endocrine-immune interactions in acute and chronic pain. In: McMahon SB, Koltzenburg M, eds. *Textbook of Pain*. 5th ed. Amsterdam: Elsevier; 2006:205–218.
27. Moalem G, Tracey DJ. Immune and Inflammatory mechanisms in neuropathic pain. *Brain Res Rev*. 2006;51: 240–264.
28. Lutgendorf SK, Costanzo ES. Psychoneuroimmunology and health psychology: an integrative model. *Brain Behav Immun*. 2003;17:225–232.
29. Devor M. Response of nerves to injury in relation to neuropathic pain. In: McMahon SB, Koltzenburg M, eds. *Textbook of Pain*. 5th ed. Amsterdam: Elsevier; 2006: 905–927.
30. Finnerup NB, Sindrup S, Jensen TS. Chronic neuropathic pain: mechanisms, drug targets and measurement. *Fundam Clin Pharmacol*. 2007;21:129–136.
31. Craig KD. Emotions and psychobiology. In: McMahon SB, Koltzenburg M, eds. *Textbook of Pain*. 5th ed. Amsterdam: Elsevier; 2006:231–239.
32. Fields HL, Basbaum AI, Heinricher MM. Central nervous system mechanisms of pain modulation. In: McMahon SB, Koltzenburg M, eds. *Textbook of Pain*. 5th ed. Amsterdam: Elsevier; 2006:125–142.
33. Woolf CJ, Max MB. Mechanisms-based pain diagnosis. *Anesthesiol*. 2001;95:241–249.
34. Turk DC, Okifuji A. Pain terms and taxonomies of pain. In: Loeser JD, ed. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2001:17–25.
35. Coggan D, Martyn C, Palmer KT, et al. Assessing case definitions in the absence of a diagnostic gold standard. *Int J Epidemiol*. 2005;34:949–952.
36. Smart K, Doody C. Mechanisms-based clinical reasoning of pain by experienced musculoskeletal physiotherapists. *Physiother*. 2006;92:171–178.
37. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114:29–36.
38. Portenoy R. Development and testing of a neuropathic pain screening questionnaire: ID pain. *Curr Med Res Opin*. 2006; 22:1555–1565.
39. Krause SJ, Backonja M. Development of a neuropathic pain questionnaire. *Clin J Pain*. 2003;19:306–314.
40. Bennett M. The LANSS pain scale: the leeds assessment of neuropathic symptoms and signs. *Pain*. 2001;92:147–157.
41. Scott IA, Greenberg PB, Poole PJ. Cautionary tales in the clinical interpretation of studies of diagnostic tests. *Intern Med J*. 2008;38:120–129.
42. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. 5th ed. Boston: Allyn and Bacon; 2007.
43. Nemes S, Jonasson JM, Genell A, et al. Bias in odds ratios by logistic regression modelling and sample size. *BMC Med Res Methodol*. 2009;9:56. doi: 10.1186/1471-2288-9-56.