Systematic Review and Synthesis of Mechanism-based Classification Systems for Pain Experienced in the Musculoskeletal System

Muath A. Shraim, BPhty (Hons), Hugo Massé-Alarie, PhD,*† Leanne M. Hall, PhD,* and Paul W. Hodges, PhD**

Objectives: Improvements in pain management might be achieved by matching treatment to underlying mechanisms for pain persistence. Many authors argue for a mechanism-based classification of pain, but the field is challenged by the wide variation in the proposed terminology, definitions, and typical characteristics. This study aimed to (1) systematically review mechanism-based classifications of pain experienced in the musculoskeletal system; (2) synthesize and thematically analyze classifications, using the International Association for the Study of Pain categories of nociceptive, neuropathic, and nociplastic as an initial foundation; and (3) identify convergence and divergence between categories, terminology, and descriptions of each mechanism-based pain classification.

Materials and Methods: Databases were searched for papers that discussed a mechanism-based classification of pain experienced in the musculoskeletal system. Terminology, definitions, underlying neurobiology/pathophysiology, aggravating/easing factors/response to treatment, and pain characteristics were extracted and synthesized on the basis of thematic analysis.

Results: From 224 papers, 174 terms referred to pain mechanisms categories. Data synthesis agreed with the broad classification on the basis of ongoing nociceptive input, neuropathic mechanisms, and nociplastic mechanisms (eg, central sensitization). "Mixed," "other," and the disputed categories of "sympathetic" and "psychogenic" pain were also identified. Thematic analysis revealed convergence and divergence of opinion on the definitions, underlying neurobiology, and characteristics.

Discussion: Some pain categories were defined consistently, and despite the extensive efforts to develop global consensus on pain definitions, disagreement still exists on how each could be defined, subdivided, and their characteristic features that could aid differentiation. These data form a foundation for reaching consensus on classification.

Key Words: pain, mechanisms-based, classification, musculoskeletal, systematic review

(*Clin J Pain* 2020;36:793–812)

Received for publication February 10, 2020; revised May 16, 2020; accepted June 8, 2020.
From the *NHMRC Centre of Clinical Research Excellence in Spinal Pain, Injury & Health, School of Health & Rehabilitation Sciences, The University of Queensland, St Lucia, QLD, Australia; and †Center for Interdisciplinary Research in Rehabilitation and Social Integration (CIRRIS), Laval University, Québec City, QC, Canada.
Supported by a Program Grant (APP1091302) from the National Health and Medical Research Council (NHMRC) in Canberra, ACT, Australia. P.W.H. was supported by a Fellowship (APP1102905) from the NHMRC, and H.M.-A. was supported by a Fellowship from the Canadian Institute of Health Research (358797) in Ottawa, ON, Canada. M.A.S. was supported by a postgraduate scholarship from the University of Queensland in Brisbane, QLD, Australia. L.M.H. declares no conflicts of interest.
Reprints: Paul W. Hodges, PhD, NHMRC Centre of Clinical Research Excellence in Spinal Pain, Injury & Health, School of Health & Rehabilitation Sciences, The University of Queensland, St Lucia 4072, QLD, Australia (e-mail: p.hodges@uq.edu.au).
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.clinicalpain.com.

DOI: 10.1097/AJP.0000000000000860

There is no doubt that pain is a major issue. Approximately 10% to 20% of individuals in Western societies experience persistent pain.[1–3] Despite substantial research and developments in management, pain outcomes have improved little.[4–6] An important consideration is that not all pain is the same, and there is growing discussion that pain outcomes might improve if the mechanisms underlying maintenance of pain were considered when tailoring interventions for individuals.[7–10] "Mechanisms" could reflect a vast group of processes within the body. For clarity, we define pain "mechanisms" as the general groupings of neurobiological processes involved in and dominating the pain experience. There is not yet agreement on how different pain mechanisms can be classified and discriminated.[8,11] This is particularly problematic for pain associated with the musculoskeletal system, where definitive identification of underlying mechanisms for persistence of pain can be difficult because of limitations of diagnostic tests,[10,11] lack of consensus on the possible mechanisms of pain,[11] and the interaction between biological, psychological, and social features.[12,13] A first step toward the classification and discrimination of pain mechanisms in pain associated with the musculoskeletal system is to understand the diversity of current opinion.

It is well recognized that the experience of pain does not simply involve transmission of input via a pain pathway.[7,13,14] Instead, it involves an array of potential inputs and outputs, with the involvement of diverse biological systems and regions of the nervous system, that are influenced by many factors including emotions and cognitions.[7,13,14] Although activation of nociceptive neurons provides one input, particularly in an acute context, many other inputs and mechanisms can interplay to shape the pain experience, and these will differ between individuals.[15] The notion that different mechanisms might respond to different treatments is not new.[15–17] It has been broadly discussed that identification of mechanism and subsequent classification of patients to a pain mechanism category (PMC) may be based on the characteristics of their presentation.[18–21] On this basis, many different groupings have been proposed with a diversity of terminology and proposed features.[11,15,18]

The expansive research on this issue has resulted in considerable confusion. First, different terminologies are used,[11,15,18] and it is often unclear which terms are interchangeable. For

TABLE 1. International Association for the Study of Pain (IASP) Pain Mechanism Definitions

Pain Mechanism	Definition
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system
Nociplastic pain	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain

Definitions of pain mechanism categories as proposed by the IASP.[22] Note that neuropathic pain can be further subdivided into peripheral and central neuropathic pain.

instance, the International Association for the Study of Pain (IASP) suggests 3 main PMCs: nociceptive, neuropathic, and the recently proposed nociplastic mechanisms (Table 1).[22] Although the IASP has provided definitions for these 3 groups, multiple other classifications have been proposed that have used different terminology, different definitions, and a variety of presenting features.[23–26] Second, the understanding of underlying mechanisms continues to evolve and some early terminology and groupings that were included in early summaries of terminology appear to have become redundant and are not included in the most recent IASP terminology (eg, sympathetic pain[22]). Third, some work has focused on specific conditions and developed unique language and interpretation rather than an overarching and generalizable conceptualization (eg, dystonic pain in Parkinson disease[27]). Fourth, because many aspects of the underlying mechanisms are difficult, if not impossible, to directly assess in vivo,[10,28] validation of methods to differentiate categories has been limited. Fifth, some confusion with interpretation of outcomes is likely to have led to overidentification of some categories (eg, identification of features of sensitivity in some musculoskeletal conditions has been interpreted as evidence of neuropathic pain,[29,30] when it might be explained by nociplastic mechanisms rather than nerve damage/dysfunction). Finally, mechanisms that underlie pain in an individual can change over time, and multiple mechanisms can occur simultaneously.[16,31]

OBJECTIVES

This study aimed to (1) systematically review mechanism-based classifications that have been proposed to differentiate pain experienced in the musculoskeletal system; (2) synthesize and thematically analyze proposed classifications, using the IASP categories of nociceptive, neuropathic, and nociplastic pain as an initial foundation; and (3) and identify convergence and divergence between categories, terminology, and descriptions of each mechanism-based pain classification as described by opinions presented in the literature, which could aid differentiation of mechanisms.

MATERIALS AND METHODS

Study Design

The literature describing mechanism-based pain classification for pain experienced in the musculoskeletal system was systematically reviewed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[32] A protocol of this systematic review was registered with PROSPERO (ID: CRD42018115452). The review was undertaken by 4 reviewers with backgrounds in physiotherapy research and clinical practice (years of experience: M.A.S.—4; H.M.-A.—10; L.M.H.—13; and P.W.H.—28).

Search Strategy and Screening

As the primary objective was to document the breadth of systems used to classify pain experienced in the musculoskeletal system by mechanisms and the opinions on classifications presented in the literature, lenient eligibility criteria were used. Papers of any type were considered and there were no restrictions by publication date or by patient population other than the fact that the pain must be considered to be primarily experienced in the musculoskeletal system and not related to cancer.

The strategy to identify relevant papers included a search of (1) PubMed, EMBASE, and CINAHL databases, (2) reference lists of included papers and relevant previously published reviews, and (3) resources provided by the IASP. A comprehensive search was conducted on November 11, 2018 and updated on December 6, 2019 before the final analyses. A similar search strategy was used for all 3 databases, but was modified where necessary. Search strategies for all databases are presented in Supplemental Digital Content 1 (http://links.lww.com/CJP/A657).

Papers were included if they fulfilled the following criteria: (1) the paper describes a classification of pain, primarily experienced in the musculoskeletal system, on the basis of different underlying mechanisms (eg, physiological/neurobiological processes), (2) the classification system must acknowledge >1 category or mechanism of pain, (3) the classification system could be either complete (accounting for every possible presentation of pain) or partial (accounting for some but not all possible presentations of pain) within a single condition or multiple conditions, (4) the paper must include a definition and/or characterization of at least 2 pain categories or mechanisms, (5) the pain could have any time-course (eg, acute, chronic) and can be either clinical or experimental, (6) human studies or reviews of pain mechanisms based on animal studies, or (7) papers or abstracts in English.

Papers were excluded if they (1) described a classification system that was related to pain not primarily experienced in the musculoskeletal system (eg, visceral pain, vascular pain) or pain related to cancer or surgery, (2) described a classification system that was not related to pain mechanisms (eg, differentiation of groups on the basis of treatment response without consideration of mechanisms; differentiation by disease mechanism rather than pain mechanism; and differentiation between separate clinical conditions, without explicit reference to pain mechanism such as back pain vs. fibromyalgia), (3) were primary intervention studies (except interventions that include differentiation of pain on the basis of mechanism), (4) were studies or reviews that refer to a mechanism-based system presented by other authors without provision of information in addition to that provided in the primary sources, (5) were studies that simply translated questionnaires that aimed to differentiate pain into a second language, or (6) were primary non-human animal studies.

Data Extraction

All titles and abstracts yielded by the search were screened for eligibility by 1 reviewer (M.A.S.). To control for potential

bias, a second reviewer (H.M.-A.) screened a random sample of the papers (3% ~300 papers), and a comparison of included papers was used to test for agreement between the 2 reviewers. Any discrepancies were noted and discussed with a third reviewer (P.W.H.). Once all potential discrepancies were identified and there was minimal disagreement, 1 reviewer (M.A.S.) continued the screening process.

The full-text review and inclusion/exclusion of screened papers was undertaken by 1 reviewer (M.A.S.). The third reviewer (P.W.H.) evaluated a random selection of papers (~30 to 40 papers) to evaluate the accuracy of inclusion and discussed any papers that the first reviewer highlighted as uncertain for inclusion.

All data extraction was undertaken by 1 reviewer (M.A.S.). The third reviewer (P.W.H.) evaluated a random selection of papers (~30 to 40 papers) to evaluate the accuracy of data extraction and discussed any papers highlighted by the first reviewer as requiring clarification for data extraction.

A piloted form was used to extract the following data: participant group, paper type, or method used to derive the definition for the mechanism-based pain classification (eg, systematic review, expert consensus), the group or individuals who contributed to the development/proposal of the pain classification system (data included whether the papers involved a single or multiple authors, and whether a consensus approach was used), the primary purpose of the paper, the categories or mechanisms of pain (this was the terminology used by the authors if a title for the category was provided or keywords from the description if no title was provided), the definition/description of each category or mechanism of pain, and the presenting characteristics/features of each category or mechanism of pain.

No paper was excluded on the basis of assessment of quality as the purpose of the review was to gain a comprehensive view of the mechanism-based classifications proposed to differentiate pain experienced in the musculoskeletal system. An adapted version of Critical Appraisal of Classification Systems[33] was used to document the comprehensiveness and utility of the proposed classification methods via assessing the following criteria: purpose, content validity, face validity, feasibility, construct validity, and reliability. The Critical Appraisal of Classification Systems was modified where appropriate to fit the purpose of this review. The rubric and scoring system are presented as tables, along with modifications to the tool and the justification for these modifications, in Supplemental Digital Content 2 (http://links.lww.com/CJP/A658).

Data Synthesis and Analysis

The primary purpose of this systematic review was to synthesize the definitions and characteristics of different PMCs presented by different authors or groups. The extracted data were qualitatively synthesized via thematic analysis and convergence of terminology.

The first step involved allocation of PMC into groups with similar meaning. Two reviewers (M.A.S. and H.M.-A.) independently allocated all proposed PMC into groups. First, PMCs that used descriptions that were aligned with the current consensus of pain definitions proposed by the IASP as either nociceptive, neuropathic, or nociplastic (Table 1)[22] were allocated to those major categories. Convergence of PMCs into these categories despite different terminology was based on the term, its definition, and the described characteristics or features of the PMC. Subtypes of the 3 major categories, if mentioned by papers, were also allocated. Second, PMCs that could not be categorized to the 3 major categories were allocated to additional groups as follows: PMCs that described "sympathetic pain" and "psychogenic pain" mechanisms were allocated to a "disputed" category. PMCs were allocated to a "mixed" category if it clearly described a mix of separate mechanisms (eg, nociceptive and central mechanisms), without identification of a predominant PMC, and thus could not provide information that would aid differentiation between PMCs. Any individual PMC that did not share similarities with any of the nominated PMC groups was categorized to an "other" category, which included PMCs referring to "idiopathic/unknown" mechanisms, specific diseases or conditions, and "unclear" if insufficient information was provided for allocation. The mixed and other categories were not included in the subsequent thematic analysis (see below).

After independent allocation of PMCs by M.A.S. and H.M.-A., a third reviewer (L.M.H.) compared the allocations and identified differences. Any differences in allocation to groups between reviewers were resolved by discussion with a fourth reviewer (P.W.H.). A table was generated with the diversity of terms used for presentations with a specific PMC. Terms with alternative spelling or prefixes/suffixes (eg, nociceptive and nocioceptive, physiologic, and physiological) were combined. For this step, analysis involved calculation of the number of times that a term was mentioned across papers (frequency) and percentage of papers that used a term relative to all terms used for each PMC.

The second step involved thematic analysis to evaluate the features proposed, by authors of the identified classification systems, to characterize each PMC. After reading through the extracted data, 3 reviewers (M.A.S., H.M.-A., P.W.H.) proposed possible themes that would capture concepts of similar meaning and account for the majority of the extracted data. After discussion, 3 main topics for organization of the thematic data were proposed: (1) underlying neurobiology/pathology, (2) aggravating factors, easing factors, and response to treatment, and (3) pain characteristics. Data extracted for each PMC were first organized into major themes within the main topic areas. For instance, within the main topic "underlying neurobiology/pathology," extracted data were allocated to major themes such as "tissue damage or input," "nervous system damage," etc. Once this broad allocation was agreed by the reviewers, data allocated to each major theme was further subdivided into subthemes. For example, the theme "Pain location" was divided into subthemes such as "localized pain," "diffuse, widespread, generalized pain," etc. Allocation to subthemes was undertaken by M.A.S. and reviewed by P.W.H. and H.M.-A. Once all reviewers agreed with the allocation, the subthemes were analyzed to evaluate those that converged within a specific PMC (eg, what are the most commonly reported "pain characteristics" associated with a specific PMC, as reported by authors) and subthemes that diverged (eg, where authors propose contrasting characteristics of pain within a PMC). For this step, analysis involved quantification of the proportion of papers that included a specific subtheme. Tables were generated for each major topic to highlight convergent features that were unique to a PMC, those that overlapped with other PMCs, and features that diverged. Using this thematic analysis, the description of each PMC category was summarized. In description of the analysis, standard terms are used throughout the text to describe the frequency of reporting of a specific subtheme: "most" discussed by 75% or more

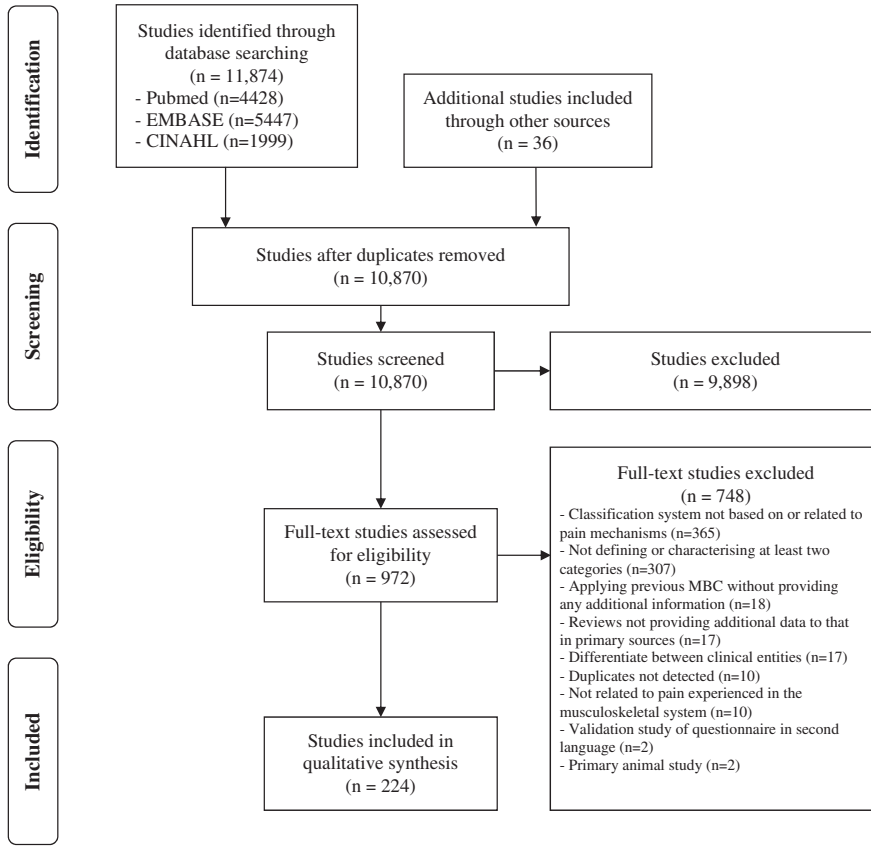

FIGURE 1. Inclusion Tree. Inclusion flow diagram based on the 2009 PRISMA statement.[32] MBC indicates mechanism-based classification.

papers, "many" for 25% to 74%; "several" for 10% to 24%; "some" for 3% to 10%; and "few" for <3% of papers.

Note that it was originally indicated in the registered study protocol "to propose an overarching mechanism-based classification that takes into account the diverse opinions presented in the literature." However, as most classifications could be included within the framework proposed by IASP, rather than creating a new classification, we addressed the intention of this aim by focusing the analysis on detailed evaluation of areas of convergence and divergence.

RESULTS

Paper Characteristics and Quality

The search strategy yielded 11,874 papers from the 3 databases. After removal of duplicates and ineligible papers, and searching the references for eligible papers, 224 papers were included. The number of papers at each step and the reasons for exclusion are presented in Figure 1. A summary of the methods used in each paper to develop the proposed mechanism-based classifications is presented in Table 2.

The evaluation of the included papers according to the Critical Appraisal of Classification Systems is presented as a table in Supplemental Digital Content 3 (http://links.lww.com/CJP/A659). The critical appraisal tool identified that for content and face validity, many did not address mixed categories (criterion 3a), lacked consensus and/or validation in development of classification (criterion 4), did not propose clear criteria for inclusion into PMCs (criterion 7), and/or did not discuss the validity/reliability of the criteria (criterion 7b). For feasibility, most classifications were not simple to perform in a clinical setting (criteria 11 to 12) because of the requirement for extra resources (eg, skills, training, equipment; criterion 13). For validation and reliability, most papers could

TABLE 2. Method Used to Develop Mechanism-based Classification

Method	No. Papers (%)	References
Systematic review	6 (2.7)	34–39
Narrative review	145 (64.7)	7–11,15–17,23,27,28, 40–173
Experimental study	39 (17.4)	174–212
Delphi consensus approach	7 (3.1)	18–21,24,25,213
Expert panel	3 (1.3)	214–216
Opinion of author: Editorial	15 (6.7)	217–231
Opinion of author: Letter	2 (0.9)	232,233
Opinion of author: Commentary	3 (1.3)	234–236
Opinion of author: no reference to other literature	4 (1.8)	26,237–239

The method used by author(s) to report, propose, or develop the mechanism-based classification with number of papers for each method and percentage as a total of all identified papers.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

not be scored as this was not addressed (criterion 15, 17 to 18). Some of the most developed and highest-scoring classification systems across criteria are those developed by Smart and colleagues,[19–21,174] Schafer and colleagues,[40–42] and Dewitte and colleagues.[24,25]

Allocation to Pain Mechanism-based Classification Categories

A total of 174 different terms were used to identify PMCs (Table 3). Consensus was reached to converge PMCs to the 6 a priori defined categories (Fig. 2). This included the 3 major categories of Nociceptive, Neuropathic, and Nociplastic with 8 subtypes, a Disputed category that included the debated terms of sympathetic and psychogenic pain, and categories that clustered PMCs that were Mixed or Other.

Nociceptive Pain

Of the 224 included papers, 198 papers included 264 PMCs that were identified in the papers to involve nociceptive input from the tissues. Many of these PMCs (44.7%) use the term "nociceptive pain" to describe this mechanism (Table 3). Other terms used to describe nociceptive pain include somatic pain (6.5%) or musculoskeletal pain (8.7%) (Table 3).

Many of the PMCs (72.4%) in this category described nociceptive pain as a single type; others defined subtypes. The 27.6% of PMCs that described subtypes of nociceptive pain used the rationale that these subtypes can be differentiated clinically.[23,175] Nociceptive mechanical pain was described in 13 PMCs as a subtype. The term used most frequently for this subtype of nociceptive pain was "mechanical pain" (2.7%) (Table 3). Nociceptive ischemic pain was described in 4 PMCs as nociceptive pain induced by ischemia. Nociceptive inflammatory pain was described in 55 PMCs and considered to involve inflammation as the stimulus for nociceptive input. The terms used were "inflammatory" (11.7%), "peripheral sensitization" (1.1%), or "peripheral nerve sensitization" (1.9%). A key area of divergence between papers was some papers consider that the term "nociceptive pain" should be used only for a transient pain that reflects the normal function of the nociceptive pathway; whereas others consider that nociceptive input can be maintained by mechanisms such as inflammation.

Neuropathic Pain

Of the 224 included papers, 182 papers included 242 PMCs that were considered by the authors to involve damage, lesion, or disease to the nervous system as the mechanism to drive or maintain the pain experience. Many papers (42.1%) used the term "neuropathic pain" to describe the single category; few used the terms "neurologic" (0.4%) or "neurogenic pain" (1.2%), but most used terms that identify a specific element of the nervous system (Table 3).

Although many PMCs (43.0%) described neuropathic pain as a single category, others described subtypes (57.0%). Peripheral neuropathic pain was identified in 97 PMCs as pain involving damage, lesion, or disease to the peripheral nervous system. Several PMCs (15.3%) use the term "peripheral neuropathic pain," whereas several others (10.3%) use this definition for all neuropathic pain. Other terms used are "peripheral neurogenic pain" (5.0%), "deafferentation" (0.8%), "denervation" (2.5%), or "radicular" (2.9%) (Table 3). Central neuropathic pain was identified in 41 PMCs and was considered to involve damage, lesion, or disease to the central nervous system (CNS). Some PMCs

TABLE 3. Mechanism-based Pain Categories and Terminology Frequencies

Terminology	No. PMCs (% of Term Within PMC)
Nociceptive pain	264 (100)
Nociceptive (general)	191
Nociceptive pain	118 (44.7)
Musculoskeletal pain	23 (8.7)
Nociceptive somatic pain	10 (3.8)
Somatic pain	7 (2.7)
Physiological pain	6 (2.3)
Acute physiological nociceptive pain	1 (0.4)
Physiological nociceptive pain	1 (0.4)
Transient pain	1 (0.4)
Peripheral nociceptive pain	6 (2.3)
Peripherally mediated pain	2 (0.8)
Peripheral non-neurogenic pain	1 (0.4)
Mechanical pain	2 (0.8)
Bone-soft tissue pain	2 (0.8)
Muscle tension pain	1 (0.4)
Articular pain	1 (0.4)
Articular dysfunction pattern	2 (0.8)
Myofascial dysfunction pattern	2 (0.8)
Sensorimotor control dysfunction pattern	2 (0.8)
Local stimulation	1 (0.4)
Localized pain	1 (0.4)
Referred pain	1 (0.4)
Tissue injury pain—primary afferent	1 (0.4)
Inflammatory pain	5 (1.9)
Antinociception	1 (0.4)
Nociceptive—mechanical	13
Mechanical pain	7 (2.7)
Nociceptive mechanical pain	2 (0.8)
Nociceptive pain	6 (2.3)
Compressive pain	2 (0.8)
Nociceptive compressive pain	2 (0.8)
Muscular pain	1 (0.4)
Peripheral nociceptive mechanism	1 (0.4)
Peripheral non-neurogenic pain	1 (0.4)
Inflammatory pain	1 (0.4)
Nociceptive—ischemic	4
Nociceptive ischemic pain	4 (1.5)
Nociceptive—inflammatory	55
Inflammatory pain	31 (11.7)
Nociceptive inflammatory pain	6 (2.3)
Pathologic pain—inflammatory pain	1 (0.4)
Inflammatory and infection pain	1 (0.4)
Peripheral nerve sensitization	5 (1.9)
Peripheral sensitization	3 (1.1)
Nociceptive pain	5 (1.9)
Pathophysiological nociceptive pain	2 (0.8)
Peripheral nociceptive pain	2 (0.8)
Peripheral non-neurogenic pain	1 (0.4)
Mechanical pain	1 (0.4)
Nociceptive/nerve pain	1
Nociceptive nerve pain	1 (0.4)
Neuropathic pain	242 (100)
Neuropathic (general)	104
Neuropathic pain	102 (42.1)
Neuropathic-like pain	1 (0.4)
Pathologic—neuropathic pain	2 (0.8)
Clinical pain—neuropathic pain	1 (0.4)
Neurogenic pain	3 (1.2)
Neurogenic pain syndrome	1 (0.4)
Neurological pain	1 (0.4)
Peripheral neuropathic	97
Peripheral neuropathic pain	37 (15.3)

(*Continued*)

TABLE 3. (*continued*)

Terminology	No. PMCs (% of Term Within PMC)
Peripheral neuropathic pain mechanism	1 (0.4)
Peripherally generated neuropathic pain	1 (0.4)
Pathologic—peripheral neuropathic pain	1 (0.4)
Nervous system injury pain—primary afferent	1 (0.4)
Neuropathic pain	25 (10.3)
Peripheral neurogenic pain	12 (5.0)
Peripherally evoked neurogenic pain	1 (0.4)
Denervation pain	6 (2.5)
Deafferentation pain	2 (0.8)
Radicular pain	7 (2.9)
Radicular neuropathic pain	4 (1.7)
Segmental nerve pain	1 (0.4)
Peripheral sensitization	3 (1.2)
Neuropathic sensitization pain	2 (0.8)
Neural dysfunction pattern	2 (0.8)
Neurodysfunctional/dysfunctional peripheral pain	1 (0.4)
Central neuropathic	41
Central neuropathic pain	22 (9.1)
Central pain	9 (3.7)
Centrally generated neuropathic pain	1 (0.4)
Pathologic—central neuropathic pain	1 (0.4)
Centralized neuropathic pain	1 (0.4)
Neuropathic pain	2 (0.8)
Neuropathic pain—ongoing extremity pain	1 (0.4)
Neurogenic pain	2 (0.8)
Central neurogenic pain	1 (0.4)
Primary pain	2 (0.8)
Central sensitization	1 (0.4)
Spinal cord pain	1 (0.4)
Central parkinsonian pain	2 (0.8)
Nociplastic pain	111 (100)
Central sensitization	42 (37.8)
Central sensitivity syndrome	3 (2.7)
Sensory hypersensitivity	3 (2.7)
Central hypersensitivity	3 (2.7)
Generalized hypersensitivity	1 (0.9)
Generalized pain	2 (1.8)
Widespread pain	2 (1.8)
Regional pain	1 (0.9)
Central amplification	1 (0.9)
Functional pain	18 (16.2)
Dysfunctional pain	12 (10.8)
Pathologic—dysfunctional pain	3 (2.7)
Central dysfunction pattern	2 (1.8)
Dysfunctional pain syndrome	1 (0.9)
Functional pain syndrome	2 (1.8)
Functional neurogenic pain	1 (0.9)
Central pain	16 (14.4)
Centralized pain	8 (7.2)
Nociplastic pain	10 (9.0)
Nocipathic pain	1 (0.9)
Neuroplastic pain	1 (0.9)
Algopathic pain	1 (0.9)
Centrally evoked pain	1 (0.9)
Tissue injury pain—central nervous system mediated	1 (0.9)
Central modulation	1 (0.9)
Central neuropathic pain	4 (3.6)
Central neurogenic mechanism	3 (2.7)
Centrally generated neuropathic pain	1 (0.9)
Central nociceptive mechanism	3 (2.7)
Central parkinsonian pain	3 (2.7)
Supraspinal pain	1 (0.9)
Pathologic pain—chronic pain	1 (0.9)
Pronociception pain	1 (0.9)
Idiopathic pain	3 (2.7)
Nonmechanical pain	1 (0.9)
Sympathetic pain	21 (100)
Sympathetically maintained pain	9 (42.9)
Sympathetic pain	8 (38.1)
Sympathetically dependent pain mechanism	3 (14.3)
Autonomic pain	6 (28.6)
Dysautonomic pain	1 (4.8)
Motor pain	1 (4.8)
Causalgia	1 (4.8)
Psychogenic pain	29 (100)
Psychogenic pain	17 (58.6)
Psychogenic pain syndrome	1 (3.4)
Psychophysiological pain	1 (3.4)
Psychological pain	2 (6.9)
Psychosomatic pain	1 (3.4)
Psychic pain	1 (3.4)
Cognitive-affective (psychosocial) mechanism	4 (13.8)
Affective pain	4 (13.8)
Cognitive pain	2 (6.9)
Emotional pain	1 (3.4)
Supratentorial pain	1 (3.4)
Idiopathic pain	1 (3.4)
Mixed pain	42 (100)
Mixed nociceptive and neuropathic	22
Mixed pain	12 (28.6)
Mixed nociceptive and neuropathic pain	6 (14.3)
Nociceptive/neuropathic pain	1 (2.4)
Mixed neuropathic and non-neuropathic pain	1 (2.4)
Combined nociceptive and neuropathic pain	1 (2.4)
Mixed nociceptive and nociplastic	6
Mixed pain—peripheral and central sensitization	1 (2.4)
Mixed pain—nociceptive+central sensitization	1 (2.4)
Central sensitization linked to nociception	1 (2.4)
Mixed central sensitization	1 (2.4)
Combination of peripheral and central mechanisms	1 (2.4)
Nociceptive central pain	1 (2.4)
Mixed neuropathic and nociplastic	3
Neuropathic pain	2 (4.8)
Mixed pain—neuropathic + central sensitization	1 (2.4)
Mixed central neuropathic and nociplastic	6
Central pain	2 (4.8)
Central neuropathic pain	2 (4.8)
Central sensitization	1 (2.4)
Neurodysfunctional/dysfunctional central pain	1 (2.4)
Nervous system injury pain—central nervous system mediated	1 (2.4)
Mixed general (multiple mechanisms)	5
Mixed pain—nociceptive+neuropathic+central sensitization	1 (2.4)
Mixed mechanisms	1 (2.4)
Mixed pain	2 (4.8)
Other pain	1 (2.4)
Other pain	86
Idiopathic/unknown/unspecified pain	29 (100.0)
Other pain	6 (20.7)
Unknown pain	15 (51.7)
Unclear pain	1 (3.4)
Pain of unknown origin	1 (3.4)
Idiopathic pain	7 (24.1)
Pain related to specific condition/symptom	48 (100.0)
Phantom limb pain	1 (2.1)
Dystonia-related pain	3 (6.3)

(*Continued*)

TABLE 3. (*continued*)

Terminology	No. PMCs (% of Term Within PMC)
Dystonic pain	6 (12.5)
Akathitic discomfort/pain	4 (8.3)
Regional influences	1 (2.1)
Regional and remission	1 (2.1)
Migrainous pain	1 (2.1)
Inflammation	2 (4.2)
Motor pain	2 (4.2)
Mixed pain—painful tonic spasms	1 (2.1)
Mixed pain—spasticity pain	1 (2.1)
Neuropathic pain—ongoing extremity pain	1 (2.1)
Neuropathic pain—trigeminal neuralgia	3 (6.3)
Neuropathic pain—Lhermitte phenomenon	3 (6.3)
Miscellaneous pain	1 (2.1)
Chronic primary pain	1 (2.1)
Nociceptive pain (other)	1 (2.1)
Joint pain	1 (2.1)
Thalamic pain	1 (2.1)
Other pain	1 (2.1)
Psychosocial pain	1 (2.1)
Persistent pain	1 (2.1)
Nociceptive pain—autonomic dysreflexia headache	1 (2.1)
Neuropathic pain—complex regional pain syndrome	2 (4.2)
Neuropathic pain—ongoing neuropathic pain	1 (2.1)
Neuropathic pain—central extremity pain	1 (2.1)
Nociceptive pain (autonomic depression/ dysreflexia headache)	1 (2.1)
Somatic sensory-mediated pain	1 (2.1)
Unclear	9 (100.0)
Nociceptive pain—treatment-induced pains	1 (11.1)
Myofascial pain	1 (11.1)
Non-neuropathic pain	1 (11.1)
Cancer-associated neuropathic pain	1 (11.1)
Not central sensitization	1 (11.1)
Fibromyalgia	1 (11.1)
Group 1 (spontaneous pain, marked dynamic allodynia, thermal hyperalgesia)	1 (11.1)
Group 2 (spontaneous pain, variable dynamic allodynia, thermal hypoalgesia)	1 (11.1)
Group 3 (spontaneous pain, analgesia, anesthesia)	1 (11.1)

Each major mechanism-based pain category heading shows the total number of pain mechanism categories (PMCs), and the percentage of PMCs that use a specific term. Terms are repeated from the general category in subtypes if an author defined the term in a manner that was specific for that subtype.

(9.1%) use the term "central neuropathic pain," whereas some (3.7%) used the term "central pain," which can be confusing, as this term is also used to describe pain that is predominantly maintained by altered nociceptive processing (see next section, Nociplastic Pain).

Nociplastic Pain

Of the 224 included papers, 106 papers included 127 PMCs that were considered by the authors to involve a pain maintained by altered nociceptive processing.[22] Many (37.8%) PMCs use the term "central sensitization" (Table 3). Some (3.6%) PMCs classify this category under neuropathic pain originating from the CNS and use the term "central neuropathic pain," as they consider that this represents a dysfunction of the nervous system. Other terms used are "central pain" (14.4%), "centralized pain" (7.2%), "functional pain" (16.2%), and "dysfunctional pain" (10.8%). The term "nociplastic pain" was adopted in 2016 by the IASP[11] and has been used by some (9.0%) authors since that recommendation.

Disputed Pain Categories

Sympathetic pain was identified by 21 papers and described in 21 PMCs as involving the autonomic nervous system. Although originally described as a separate category of pain, some authors recommend it as a subtype of neuropathic pain.[43,240–242] Although not all agree, aspects of this PMC are now commonly referred to as complex regional pain syndrome (CRPS; type 1 without nerve damage and type 2 with nerve damage).[240] The absence of nerve damage as a criterion for CRPS type 1 differs from the general definition of neuropathic pain, except that several authors highlight evidence for dysfunction of the nervous system[7,240] and has been argued to involve the nervous system at later stages.[214,243] Others consider CRPS type 1 to fall under nociplastic pain.[244] Hence, this pain category remains controversial. The most commonly used terms to describe this PMC are "sympathetic pain" (38.1%) or "sympathetically maintained pain" (42.9%; Table 3).

Psychogenic pain was described in 28 papers and included 29 PMCs that were considered by authors to involve pain caused or driven by psychological factors. The mechanism through which psychological issues are believed to mediate the pain experience is generally regarded to involve altered processing of nociception, that is, nociplastic mechanisms.[12,13] Thus, psychogenic pain might be considered to converge with nociplastic pain. Many (58.6%) PMCs used the term "psychogenic pain" to describe this category, whereas others used "affective pain" (13.8%) and "cognitive pain" (6.9%; Table 3).

Mixed and Other Categories

After classification, 137 PMCs, using 61 unique terms, could not be allocated to the major or disputed categories. Forty-two PMCs used 21 terms to describe mixed pain subtypes (Table 3). As these subtypes refer to a combination of PMCs, they could not be attributed to any 1 of the 3 major categories. They were separately grouped under a mixed pain category (Fig. 2). As expected, by definition, mixed pain subtypes are described to share features or characteristics of 2 or more PMCs. The mixed pain subtypes category was not included in the thematic analysis because this term was generally used without clarification of the specific features that underpin the dual categorization and it does not permit interpretation of features that characterize/distinguish the main PMC.

Eighty-six PMCs used 41 terms (Table 3) that were identified as other if they referred to pain that was clearly stated to have unknown/idiopathic mechanisms (n = 29), related to a specific disease, and could not be generalized (n = 48; eg, Parkinson disease, multiple sclerosis, spinal cord injury, and orofacial pain), or unclear (n = 9) if the paper did not provide sufficient description to be allocated. PMCs allocated to the other category were not included in the thematic analysis because most failed to provide details of features of the grouping, and consideration of the condition-specific PMCs did not serve the overall goal of this review.

Thematic Analysis of PMCs

The thematic analyses of the data extracted from each paper for the 3 *major* pain categories and the 2 *disputed* pain categories were evaluated according to the 3 main topics of (1) underlying neurobiology/pathology, (2) aggravating factors, easing factors, and response to treatment, and (3) pain characteristics. Summary data are presented in Tables 4–6 and

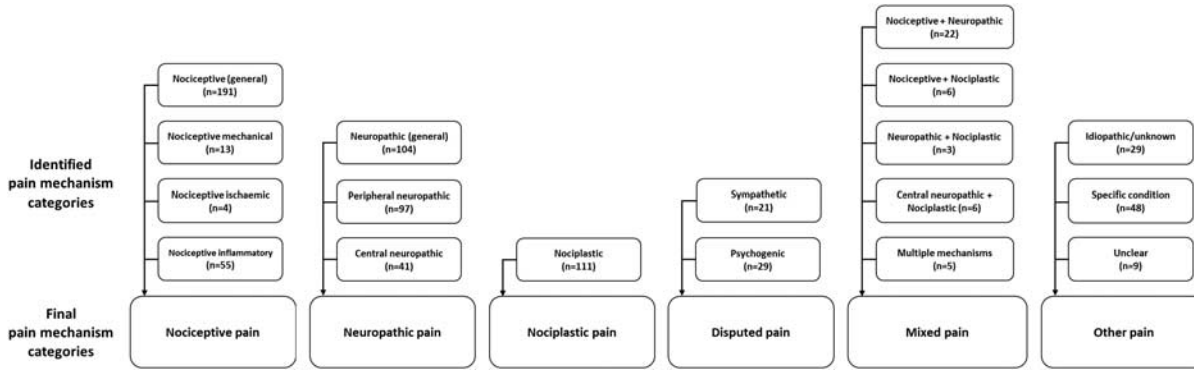

FIGURE 2. Distribution of major pain mechanism categories and subtypes. Number of papers (n) that include description of each is identified.

complete data are presented as extensive tables for each of the 3 main topics in Supplemental Digital Contents 4 to 6 (http://links.lww.com/CJP/A660, http://links.lww.com/CJP/A661, http://links.lww.com/CJP/A662). Key findings are summarized below to define and characterize how each major/other PMC and subtype is described in the literature.

Nociceptive Pain

The thematic analysis was carried out on 264 PMCs that were considered by the authors to involve nociceptive input from the tissues. Table 4 summarizes this pain type on the basis of thematic analysis and the main topic areas. Key convergent characteristics of this PMC include pain in response to peripheral noxious stimuli, involves damage to non-neural tissue, is provoked by movement and postures, and is localized. Some areas of divergence were identified. Some authors consider inflammatory and nociceptive pain to be different categories, whereas others consider them to be subtypes of an overarching nociceptive mechanism. Some authors consider that all nociceptive pain is invoked by or involves inflammation.[44,45] Although most consider nociceptive pain to be characterized by its localization, some describe it as diffuse and hard to localize pain.[46] Many (26.7%) consider this pain to be provoked by movements, postures, etc., but it has also been described as continuous in nature.[237]

Subtypes of Nociceptive Pain. Nociceptive mechanical pain was considered by authors to involve a mechanical source of nociceptive input. Nociceptive mechanical pain is characterized, as described by authors, by all features of nociceptive pain described in Table 4, but with an emphasis on mechanical stimuli. Themes described by authors include mechanical peripheral noxious stimulus (30.8%); provoked by movement (30.8%), activity (23.1%), postures (7.7%), or pressure (15.4%); and can be relieved by rest (15.4%).

Nociceptive ischemic pain, as described by authors, is characterized by all features of nociceptive pain, but with evidence or suggestion of a response/nociceptive input secondary to constricted blood flow to the tissue. Nociceptive ischemic pain is believed to be provoked by postures, especially if sustained, and relieved when the provoking posture is changed (75.0%), and unresponsive to anti-inflammatory drugs or application of ice (25.0%).

Nociceptive inflammatory pain, as described by authors, is characterized by all features of nociceptive pain, but the focus is that this subtype is driven by an inflammatory stimulus. Few papers (3.0%) considered all nociceptive pain to involve inflammation and reserved the term "nociceptive pain" for the transient physiological process of nociception,[9,15,47–49,217] with one paper considering all pain to be driven by inflammatory processes.[50,51] Many (29.1%) suggest that it may involve hyperalgesia/hypersensitivity, or even mechanical and thermal allodynia (10.9%[52–55]). Nociceptive inflammatory pain is described to be provoked by movements (21.8%) and pressures (7.3%) and responsive to anti-inflammatory drugs (12.7%). Signs of inflammation (redness, heat/warmth, and swelling) are highlighted by several papers as a key feature of this PMC (21.8%). An area of divergence is that one author states that inflammatory pain involves diffuse hyperalgesia and/or allodynia,[53] which others would consider to be a feature of nociplastic pain. Several (14.5%) papers suggest that it may involve spontaneous or stimulus-independent pain, which again may not infer nociceptor involvement, whereas others (7.3%) consider it to be stimulus dependent.

Neuropathic Pain

The thematic analysis was carried out on the 242 PMCs that were considered to involve neuropathic mechanisms defined as involving damage, lesion, or disease to the nervous system that is driving or maintaining the pain experience. Table 5 summarizes this pain type on the basis of thematic analysis and the main topic areas. Key characteristics of this PMC, as described by authors, include history or evidence of damage or disease of somatosensory system; pain following a neuroanatomically plausible distribution; with burning or electric-shock-like quality; and associated with paresthesias/sensory deficits. There were some areas of divergence. Several authors considered neuropathic pain to be due to dysfunction or maladaptive processing within the nervous system (18.1%), which is more commonly considered to be a characteristic of nociplastic pain. One author (2.4%) suggests that it can involve permanent and irreversible changes within the CNS.[218] Further, one author exclusively stated that central neuropathic pain is caused by "central sensitization" mechanisms.[232] Another author states that neuropathic pain does not adhere to nerve distributions,[56] which again suggests blurring between neuropathic and nociplastic mechanisms.

Subtypes of Neuropathic Pain. Peripheral neuropathic pain is described by authors to be characterized by most features of neuropathic pain, with a history or evidence of damage or lesion to the peripheral nervous system (eg, nerve root) (71.1%). One author suggests Peripheral neuropathic pain

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 4. Nociceptive Pain: Summary of Thematic Analysis

Main Topic	Thematic Analysis	%
Underlying neurobiology/pathology	Response to a peripheral noxious stimulus that activates nociceptors (stimulus can be mechanical, thermal, or chemical [inflammatory or ischemic])	44.5
	Involves actual injury or damage to non-neural tissue	42.4
	Involves potential injury or damage to non-neural tissue	18.3
	Can include local peripheral sensitization or primary hyperalgesia	8.4
	Some signs of central sensitization may be present but not as the predominant driver of the experience of pain	2.1
	Nociceptive input provoked by inflammation	3.1
	Triggered more specifically by a mechanical stimulus	0.5
	Conflicting observations	
	Purely involves the acute transient/physiological pain that acts as a warning system for potential tissue damage, hence using other terms such as "inflammatory" pain to describe the above processes	3.0
Aggravating/easing factors and response to treatment	Provoked by movement (self-reported or clinical test)	17.8
	Can be aggravated by postures	6.8
	Can be aggravated by pressures such as palpation	7.3
	Aggravated by *all* activity/movement	4.2
	Clear and proportional relationship to the aggravating and easing factors	9.4
	Usually responsive to anti-inflammatory drugs	5.8
	Usually responsive to tissue-based treatments (active or passive)	7.3
	Can be relieved by rest	2.6
	Follows a predictable healing time based on tissue healing guidelines	3.1
Pain characteristics	*Pain location*	
	Generally localized to the area of injury	21.5
	May be referred to other body regions	7.9
	Does not involve generalized hypersensitivity	2.1
	Pain quality	
	Described as dull	10.5
	Constant ache at rest	17.8
	A sharp intermittent pain with movement	7.3
	Other descriptions used are throbbing, cramping, lacerating, stinging, heavy, suffocating, sore, tender, crushing, knife-like, piercing, and pricking (refer to Supplemental Digital Content 6, http://links.lww.com/CJP/A662, for all descriptors)	—
	Evoked or stimulus-dependent	1.0
	Associated symptoms	
	Abnormal muscle contractions (ie, spasms, spasticity)	5.2
	Limited/reduced range of motion	4.2
	May involve motor deficits such muscle as weakness and/or atrophy	1.0
	Conflicting observations	
	Pain location	
	Can involve diffuse[46] or generalized pain due to secondary hyperalgesia[76]	2.1
	Pain quality	
	Continuous or constant in nature[237]	3.7
	May present with allodynia[43]	1.0
	Associated symptoms	
	Involves signs that indicate inflammation such as tenderness, warmth, and swelling[44,45]	2.6
	May be associated with significant cognitive factors such fear-avoidance behaviors.	0.5
Features of specific conditions	In Parkinson disease, nociceptive pain is associated with other symptoms such as fatigue, abnormal muscle contractions/spasms, bradykinesia, and rigidity/immobility	1.0
	In Parkinson disease, nociceptive pain is usually responsive to disease-specific drugs, specifically levodopa	1.6

A summary of the thematic analysis for the 3 main topics describing nociceptive pain, which are divided into subthemes along with the percentage of pain mechanism categories describing that subtheme.

can be differentiated from Nociceptive inflammatory pain by the presence of mechanical and/or cold allodynia and/or paresthesias/dysesthesias.[57] Unlike other neuropathic pain, peripheral neuropathic pain is thought to be aggravated by movement and activity that loads the peripheral neural tissue (16.5%).

The authors suggest that Central neuropathic pain is characterized by features similar to the general neuropathic pain category, but involves evidence or history of damage, lesion, or disease to the CNS (68.3%). The authors suggest that the feature that could distinguish central from peripheral neuropathic pain is that the former is continuous/constant (24.4%) and spontaneous/stimulus independent (19.5%),[58] whereas the latter is intermittent/transient (5.2%) and evoked/stimulus dependent (9.3%)[58] (although this diverges from others, who argue that neuropathic pain in general is

TABLE 5. Neuropathic Pain: Summary of Thematic Analysis

Main Topic	Thematic Analysis	%
Underlying neurobiology/pathology	Involves damage or disease of the somatosensory nervous system, or more broadly the nervous system	67.6
	Can be due to dysfunction or maladaptive processing within the nervous system	18.1
	May be no evidence for tissue damage or inflammation	3.8
	May be associated with allodynia	30.5
	May be associated with hyperalgesia	33.3
	A noxious stimulus is no longer required to generate pain, or that pain is generated without adequate stimulation of peripheral nociceptors	2.9
	May involve central sensitization	12.4
	Conflicting observations	
	Sensitization is absent in general	1.0
Aggravating/easing factors and response to treatment	Aggravated by movement and activity that stresses the neural tissue	3.8
	Aggravated by cold and damp weather and may be worse at night	1.0
	Responsive to nerve blocks	1.0
	Conflicting observations	
	Not affected by movement, activity, or postures/positions	2.9
Pain characteristics	*Pain location*	
	Generally follows a dermatomal distribution or "a neuroanatomically plausible distribution" of pain	21.9
	May involve referred pain that can be distal	5.7
	Can be well localized	1.9
	Can be either superficial or deep	4.8
	May have a unilateral distribution	2.9
	May have a symmetrical/bilateral distribution	3.8
	Pain quality	
	Burning	44.8
	Electric-shock-like	23.8
	Shooting	22.9
	Sharp	9.5
	Sudden paroxysmal attacks	13.3
	Stinging, throbbing/pulsating, or tender/sore/hurting (refer to Supplemental Digital Content 6, http://links.lww.com/CJP/A662, for all descriptors)	8.6
	Can be stimulus independent or spontaneous	18.1
	Can be stimulus dependent or evoked	13.3
	Can involve wind-up pain or hyperpathia where there is a latent onset to a provoking stimulus	4.8
	Can have sensory after-effects	4.8
	Can be continuous or constant in nature	5.7
	Can be intermittent or transient in nature	2.9
	Associated symptoms	
	Associated with sensory deficits (numbness or loss of sensation)	34.3
	Associated with paresthesias or dysesthesias (abnormal sensations such as pins and needles, tingling, prickling, or itchiness)	41.0
	The presence of sensory deficits and paresthesias/dysesthesias are features that differentiate neuropathic pain from other pain types[87]	1.0
	Associated with motor deficits (weakness and reduced reflexes)	4.8
	Associated with autonomic symptoms or signs (sweating, nausea, skin temperature changes, and skin color changes)	7.6
	Can be associated with hyperesthesia	6.7
	Can be associated with hypoesthesia	9.5
	Can be associated with hypoalgesia	4.8
	Conflicting observations	
	Pain location	
	Does not strictly follow a dermatomal distribution	3.8
Features of specific conditions	Different features distinguish neuropathic pain within people with spinal cord injury (SCI), based on the location of the pain (above-level, at-level, below-level)	5.8
	In lower back pain, referral below the knee is considered a discriminating feature of neuropathic pain[74]	1.0

A summary of the thematic analysis for the 3 main topics describing neuropathic pain, which are divided into subthemes along with the percentage of pain mechanism categories describing that subtheme.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 6. Nociplastic Pain: Summary of Thematic Analysis

Main Topic	Thematic Analysis	%
Underlying neurobiology/pathology	A state where there is amplification/increased excitability or signaling within the central nervous system, especially in response to normal or subthreshold afferent input	50.5
	A state where there is alteration or dysfunction in the normal sensory processing or signaling within the central nervous system	40.5
	Involves maladaptive processing or neuroplasticity that contributes to the persistence of pain	14.4
	Can involve reduced or disrupted inhibition of the descending pain pathways	27.0
	Pain is disproportionate to the nature of the pathologic changes or extent of injury	18.9
	No evidence or signs of tissue (neural or non-neural) damage, inflammation, pathology, or even psychiatric illnesses	18.9
	Hyperalgesia can be present	29.7
	Allodynia can be present	21.6
	Specifically involves secondary hyperalgesia (generalized or widespread)	27.0
	Specifically involves secondary allodynia (generalized or widespread)	12.6
	Coexists with primary (local) or peripheral sensitization	4.5
	Involves specific mechanisms: temporal summation (wind-up)	16.2
	Involves specific mechanisms: ectopic discharge	2.7
	Involves specific mechanisms: phenotypic switching	0.9
	Involves specific mechanisms: Aβ fiber sprouting	0.9
	Pain is of unknown origin	4.5
	Considered a subgroup of neuropathic pain	0.9
	Can be mixed with nociceptive pain	1.8
	Can co-occur in other pain states over a continuum/spectrum rather than being a "yes" or "no" pain state	1.8
	Discriminatory features	
	Secondary or generalized hyperalgesia can be used to discriminate nociplastic pain	3.6
	Allodynia and hyperalgesia can infer central sensitization	2.7
	Conflicting observations	
	Due to not only dysfunction of the central nervous system but can also be due to damage or a lesion to the central nervous system[219]	0.9
Aggravating/easing factors and response to treatment	Follows a disproportionate, nonmechanical, unpredictable pattern of pain provocation in response to multiple, nonspecific aggravating, and easing factors	17.1
	All activities and movements aggravate pain	2.7
	Triggered by physical and emotional stressors	7.2
	Variable and/or unpredictable response to passive treatments and medications (ie, therapeutics, surgery, exercise)	9.0
	Persists beyond the expected tissue or pathology healing time (if it exists)	14.4
	Worse at night and can involve disrupted sleep	5.4
	Previous experiences including trauma, illness and diseases, poor general health, and genetic predisposition can predispose to pain	7.2
	Responds to centrally acting drugs	2.7
	Responds to antidepressants	3.6
	Responds to cognitive behavioral therapy	1.8
	Responds to active treatments (eg, exercise)	0.9
Pain characteristics	*Pain location*	
	Follows a diffuse, widespread, generalized, poorly localized, or nonanatomic pain distribution	43.2
	Follows a nondermatomal pattern	4.5
	Can manifest bilaterally	7.2
	Can involve referred pain	2.7
	Pain quality	
	Few papers describe specific subjective descriptors that characterize nociplastic pain. For papers that do, they are similar to those that describe neuropathic pain (refer to Supplemental Digital Content 6, http://links.lww.com/CJP/A662, for all descriptors)	—
	Constant or unremitting even at rest	13.5
	Pain is of moderate to high severity	10.8
	Has a latent onset	5.4
	Involves spontaneous (stimulus-independent) pain	10.8
	Involves stimulus-dependent (evoked) pain	2.7
	Involves paroxysmal pain	4.5
	Involves wind-up pain/hyperpathia	3.6
	May have sensory after-effects	2.7
	Shows a nonlinear relationship between nociception and pain intensity (stimulus and response)	6.3
	Has no clear relationship between pain and movement behaviors	0.9

(*Continued*)

TABLE 6. (*continued*)

Main Topic	Thematic Analysis	%
	Associated symptoms	
	Generalized hypersensitivity or abnormal response to other nonpainful stimuli (ie, mechanical, thermal, olfactory, auditory, and visual stimuli) can exist	18.0
	Somatic symptoms such as fatigue, memory difficulties, concentration difficulties, sleep, and mood disturbance may coexist	10.8
	Can be associated with motor deficits	3.6
	Can be associated with sensory deficits	4.5
	Can be associated with paresthesias/dysesthesias	9.0
	Can be associated with autonomic signs and symptoms	3.6
	Can be associated with high levels of functional disability	6.3
	Muscle spasms/spasticity can exist	1.8
	Limited range of motion can exist	0.9

A summary of the thematic analysis for the 3 main topics describing nociplastic pain, which are divided into subthemes along with the percentage of pain mechanism categories describing that subtheme.

continuous), and central neuropathic pain is unresponsive to a peripheral nerve block (4.9%[59]). In Parkinson disease, a CNS disease, central neuropathic pain is described as fluctuating and is relieved by levodopa, has qualities *described as* formication, scalding, relentless bizarre quality, boring, and ineffable, and involves an urge to move.[60]

Nociplastic Pain

The thematic analysis was carried out on the 111 PMCs that were presumed to be maintained by altered nociceptive processing and generally consistent with the IASP definition for nociplastic pain (Table 1).[22] Table 6 summarizes this pain type on the basis of thematic analysis and the main topic areas. Key characteristics of this PMC, as described by authors, include a state of amplified/increased excitability or neural signaling within the CNS in response to normal or subthreshold afferent input; pain that is disproportionate to the nature of pathologic changes or injury; presence of hyperalgesia, allodynia, and temporal summation; a disproportionate, nonmechanical, unpredictable pattern of pain provocation in response to multiple, nonspecific aggravating, and easing factors; persists beyond the expected tissue or pathology healing time; follows a diffuse, widespread, generalized, poorly localized, or nonanatomic pain distribution; and is constant or unremitting even at rest. This category has been heavily debated in the literature. As mentioned above, some authors consider some of the features of nociplastic pain to infer neuropathic pain. A major divergence is that some consider altered nociceptive processing to potentially have underlying disease or lesion of the CNS and therefore consider it as central neuropathic pain,[232] and others consider "central pain" to be caused by not only dysfunction but also damage or disease of the CNS[219]; however, this is before the redefinition of neuropathic pain.[245,246]

Disputed Pain Categories

Some authors describe sympathetic pain to be characterized by features that reflect those of neuropathic pain but relate to the autonomic component of the nervous system (38.1%). Many state that a sympathetic block can provide complete or near complete pain relief (33.3%); few (4.8%) state that sympathetic pain can be worsened by cold weather or psychological factors (eg, stress),[61] is independent of movement or position,[44] can be deep,[44] or even initially be confined to a nerve distribution but can spread beyond these confines.[62] Several (19.0%) state that sympathetic pain can involve allodynia or hyperalgesia/hypersensitivity. Some (9.5%) state that it can be boring, ongoing, or persistent, and can involve wind-up pain or hyperpathia (an abnormally painful reaction to a stimulus, especially a repetitive stimulus, and an increased threshold[22]). Others state that the pain can be burning (14.3%), throbbing (4.8%), or like a lightning/shock (4.8%). Others state that sympathetic pain may involve vasomotor changes such as temperature (28.6%) and skin color changes (38.1%), sudomotor changes such as swelling (28.6%) and sweating (33.3%), motor/trophic changes (33.3%) such as decreased range of movement, weakness, dystonia, tremor, and skin/hair/nail changes. Paresthesias or dysesthesias (eg, pins and needles, tingling; 9.5%) or hypoalgesia (4.8%) can be present. As previously mentioned, the new terminology of CRPS 1 and 2 highlights divergence of opinion, with features that overlap with different major pain categories.[244]

Psychogenic pain was characterized, as described by authors, by many features of nociplastic pain, but many argue that the primary cause is a psychiatric disease or significant psychological features or turmoil (33.3%). There may have been an initial injury (13.3%) or organic pathology (3.3%). Some consider that the autonomic nervous system may be involved (3.3%). Psychogenic pain, as described by authors, presents with features of acute anxiety (3.3%), affective factors such as emotions and feelings (6.7%), concerns for bodily function (6.7%), and cognitive factors (13.3%; eg, maladaptive behaviors and understanding of pain, and fear-avoidance behaviors). Also, it may be aggravated by significant psychological features such as emotion, anxiety, or depression (16.7%). The authors argue that psychogenic pain does not respond to removal of tissue pathology, if it exists, or to modifying input to CNS (3.3%), but placebo (isotonic saline injection) can lead to complete or long-lasting relief (13.3%). Many features described by authors overlap with nociplastic pain, but with the abnormal processing of pain mediated by primary psychological/psychiatric features.

DISCUSSION

This systematic review aimed to synthesize and summarize the vast literature on descriptions of mechanism-based classifications for pain experienced in the musculoskeletal system as described by authors. On the basis of the definitions and features published in a variety of formats, most PMCs could be broadly aligned with the 3 major groupings proposed

by the IASP: nociceptive, neuropathic, and nociplastic (Table 1).[22] We also identified classification on the basis of the disputed pain categories of sympathetic and psychogenic pain, and mixed or other categories. The categories encompassed a multitude of terms and characteristics. Although there was substantial convergence, some important areas of divergence of opinion were identified.

Methods to Develop Mechanism-based Classifications for Pain

A range of methods has been used to develop or propose classifications on the basis of mechanisms. Although consensus is considered important for controversial topics with divergent opinions,[247,248] a limited number of papers (4.4%) involved a consensus approach (eg, Delphi, expert panel).[8,18,24,63] Few (2.7%) were systematic reviews, which aim to limit bias and consider consistency and heterogeneity to produce robust conclusions.[249,250] Instead, many classifications were proposed or stated in narrative reviews (64.7%), which are limited by potential bias from selective reporting of the literature, variation in critical appraisal and syntheses, and author opinion.[251] We judged the quality of process undertaken to develop the classifications according to a scale devised to assess classification systems. When assessed in this manner, most classifications received a partial score on the method of development (criterion 4) as they did not involve consensus and/or validation processes (see Table, Supplemental Digital Content 3, http://links.lww.com/CJP/A659), which is unsurprising as many were in the form of narrative review (64.7%).

The present study provides the first comprehensive systematic review of mechanism-based classifications of pain experienced in the musculoskeletal system, presenting the vast convergent and divergent views presented in the literature, which provides a foundation to progress to a consensus approach to refine the clinical classification.

Major Mechanism-based Classification Categories and Areas of Conflict

Nociceptive Pain

Nociceptive pain was agreed by most authors to refer to pain that is evoked and/or maintained by nociceptive input from tissues, which agrees with the IASP definition (Table 1).[22] Some subdivide this classification on the basis of the presumed nociceptive stimulus (eg, mechanical, ischemic, inflammatory).

Some challenges arise for identification of this pain mechanism. First, clinical proof of ongoing nociception is difficult to obtain. Nociceptive neuron discharge can be detected with specialized techniques such as microneurography,[252,253] but this is not easily implemented and cannot be used for all situations. Although some argue that involvement of nociceptive input has been supported using blinded anesthetic blocks[254]; in some specific cases, this method requires careful control of potential placebo effects. In most cases, clinical identification depends on history, pain characteristics, and aggravating and relieving factors.

Second, opinions diverge on what pain presentations should be included under the umbrella term of nociceptive pain. Some argue that inflammatory pain is distinct to nociceptive pain,[15] whereas others consider it a subtype[255] in which nociceptive input is maintained by an inflammatory process (eg, peripheral sensitization[64]). Others use the term "inflammatory pain" to refer to any noxious input from tissue *damage*, irrespective of the noxious modality.[9,15,47–49] Further, some limit nociceptive pain to reflect the normal transient physiological response to a noxious stimulus (eg, pin-prick) without tissue damage,[9,15,47–49,217] whereas others exclude this transient response from the clinical entity of nociceptive pain.[52,54,65,220] On the basis that nociceptive pain is an experience of pain that is evoked and/or maintained in response to activity of nociceptive neurons, we included both transient pain and pain associated with tissue damage as nociceptive pain. It is noteworthy that many of the mixed pain categories include nociceptive plus either neuropathic or nociplastic mechanisms. This highlights the view of many authors that once persistent, nociceptive pain will be accompanied by other mechanisms. Whether pain can be primarily maintained by nociceptive input is an issue that requires clarification.[256,257]

Neuropathic Pain

Consistent with the IASP definition (Table 1),[22] neuropathic pain is generally considered by authors to involve damage or dysfunction/disease of the nervous system. Some divide this on the basis of the region of the nervous system (ie, peripheral and central). Whether neuropathic pain should be considered a pain related to the musculoskeletal system requires consideration. Neuropathic pain was included in this review as it is often experienced in the musculoskeletal system and requires differentiation from the other pain mechanisms.

There is disagreement on reference to damage or dysfunction. Some argue that damage must be present[245,246]; others challenge the definition of dysfunction,[258] which has been removed from the definition in 2011.[245,246] However, what constitutes dysfunction is sometimes unclear,[24,66,67] and in some cases considered to include abnormal processing leading to confusion with nociplastic mechanisms. Divergence of opinion is demonstrated by some who consider that neuropathic pain requires evidence of nerve injury, whereas others consider neural inflammation and sensory changes (eg, paresthesias, allodynia) sufficient.[176,221] This creates confusion as sensory changes can also be present in other pain types (eg, nociplastic). Compounding this divergence of opinion, others consider that the neuropathophysiological process of central sensitization (defined by the IASP as increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input[22]) dominates[68] or exclusively causes[221,232] neuropathic pain, and is, thus, an example of dysfunction of the nervous system on the basis of their definition, again creating overlap with nociplastic pain. Interestingly, some papers have used the term "peripheral sensitization" to describe neuropathic pain,[44,69] where it has also been used to describe nociceptive pain (Table 3). This term reflects a neurophysiological process defined as the increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields,[22] and we recommend that it should be reserved for describing this process rather than a PMC.

There has been specific debate on fibromyalgia; some describe it as neuropathic pain, because it involves nerve damage[68,70,232] and changes in the density of small diameter afferents,[259] whereas others refer to nociplastic mechanisms as a basis for this condition, because symptoms are explained by central sensitization.[11] The use of dysfunction in the definition[24,66,71,232,260] and the fibromyalgia debate suggest that some literature still deviate from the 2011 definition of neuropathic pain,[245,246] and do not yet consider the recent definition of nociplastic pain.[22]

Nociplastic Pain

Nociplastic pain has recently been defined by the IASP as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain."[22] In this case, pain has been generally considered by authors as being maintained by the altered central processing including central sensitization, hence the alternate terms of "central pain" or "central sensitization pain."

There has been considerable debate on terminology and characteristics.[11,22,261,262] First, as highlighted in the preceding section, some consider this pain mechanism a subgroup or subset of neuropathic pain as it could be considered to represent dysfunction of the CNS.[68,232]

Second, some argue against using the term "central sensitization,"[263] as it refers to a neurophysiological mechanism that is inferred from clinical measures (eg, allodynia and hyperalgesia[22]) and cannot generally be measured directly. Central sensitization is also involved in other pain mechanisms (eg, neuropathic pain) as was identified in the numerous references to mixed pain types. Third, others argue that because the cause is unknown, terms such as "unknown pain" and "idiopathic pain" should be used,[11,72,73] which suggests overlap between nociplastic and some of the groups that we allocated in the group Other. As these terms provide no insight into the putative underlying mechanisms, there is concern that using such terms may stigmatize many patients,[264,265] and provides limited guidance for management.[11] The term nociplastic was developed to resolve these and other issues and is derived from "nociceptive plasticity," which reflects change in the function of nociceptive pathways.[11]

Some challenge the term "nociplastic pain" as there is no specific structural pathology,[11] the term is imprecise and vague,[261,262] and because most, if not all, cases of persistent pain involve altered central processing and plastic changes.[261] Others argue that commonly used terms that suggest pain origin (eg, centralized pain, central sensitization, central hypersensitivity) should be used.[262] The definition provided by the IASP is also somewhat confusing as it includes reference to "no clear evidence of … threatened tissue damage." This implies pain without tissue damage and concurs with features described for nociplastic pain. The present review provides a comprehensive summary of the varied terminology, the clinical features that authors attribute to this PMC, and features that may differentiate this PMC from others as described by authors. Although there is some divergence of opinion, we found a high degree of consistency, which should provide a strong foundation to further consider this debate.

Disputed Pain Categories

The allocation of sympathetic pain is not without question as it has been argued that its signs and symptoms are generated by the sympathetic nervous system in response to sensitized input,[7] which implies dysfunction rather than damage to the nervous system. As an alternative to the term, expert consensus developed the term CRPS to describe aspects of this presentation, with 2 types—type 1, which involves no nerve damage (which some consider to be nociplastic),[244] and type 2, which involves nerve damage (which would fit into neuropathic pain by definition).[214,240] Further discussion is required to resolve whether this presentation of pain should be considered a subclass of neuropathic pain,[43,240–242] nociplastic pain,[244] a mixed pain state,[266–268] or as a separate entity.[44,61,222]

Psychogenic pain is considered to be an outdated term by some[244] and no longer listed in pain terminology by IASP, whereas others argue for it as a unique pain mechanism group.[26,74,75] On the basis of the premise that, in psychogenic pain, perhaps psychological and cognitive factors are likely to maintain pain by an impact on nociceptive/pain processing in the CNS[12] and sensitization,[13] it is plausible to consider possible convergence of Psychogenic with the nociplastic pain category. This may not be universally accepted, and the present summary should form a basis for ongoing discussion.

Limitations of Mechanism-based Classifications

Overlap among underlying neurobiological mechanisms is common. Although one mechanism may predominantly contribute to the pain experience, multiple mechanisms will be present for many. Many authors agree that individuals with ongoing nociceptive input will also have central sensitization.[65,76,77,217] Some authors created mixed categories,[71,78] whereas others advocate attempts to discriminate a predominant/primary mechanism.[7,8,23,24,63,177]

The 3 major PMCs proposed by IASP and reinforced by this review provide a general framework to consider differentiation of patients to guide management[8,220] and prediction of prognosis, etc. As highlighted here, these can be further subdivided, which would be expected to further refine decision-making. However, although the IASP provides definitions for these PMCs, a lack of consensus-driven criteria is a major issue for nociceptive and nociplastic pain. Development of criteria to determine the presence of nociplastic pain is a challenge as it relies, by definition, on the exclusion of nociceptive pain, for which criteria do not exist.

A major objective of this review was to summarize the features proposed by authors (neurobiological features, pain characteristics, aggravating, and easing factors) that characterize each PMC and consider the convergence or divergence of opinion. For each PMC, some features were largely consistent. However, many of these features also overlap among most PMCs, which is expected, as mechanisms could overlap. For this reason, some authors state that pain characteristic features cannot identify mechanisms as they are not specific.[16] Further, many diagnostic tools have poor validity and reliability.[10] A combination of measures is likely to be required and might include objective measures and response to pharmacological agents that target specific neurobiological mechanisms.[16,17] A major challenge is validation as there is no objective gold standard against which they can be compared. This review provides an overview of potential factors that can inform future work.

Study Limitations

Several limitations required consideration when interpreting the findings of this review. First, defining the term "mechanism" was sometimes challenging. We considered mechanism to refer to the general groupings of neurobiological processes involved in the pain experience and all screened papers were considered with respect to this definition. Some papers that did not express this explicitly may have been excluded. It is important to consider that within the 3 main PMCs, a range of specific neurobiological processes are possible and not yet completely understood.

Second, we aimed to consider "pain experienced in the musculoskeletal system," but excluded pain related to the viscera, surgery, and cancer. Although these pain groups can be experienced in the musculoskeletal system, they

present specific stimuli/pathologies that were beyond the scope of this review.

Third, we only considered studies in English, which may have excluded classifications and opinions in other languages. Fourth, we included studies across a broad range of types that would vary in quality of control of bias. We considered this to be appropriate for this review as we considered it a priority to identify the breadth of views presented in the literature. Quality was difficult to judge with this diversity of methods, and we adapted the Critical Appraisal of Classification Systems tool to provide quantification of key quality aspects that could be used across the diversity of included studies. Fifth, screening and data extraction were undertaken by one reviewer, which may allow potential bias. However, according to the principles expressed in AMSTAR 2,[269] a second reviewer undertook screening and data extraction for a sample of papers and achieved acceptable agreement (> 80%) before completion of the task. Sixth, convergence of PMCs was based on interpretation of descriptions provided by authors. We acknowledge that some ambiguity may have been misinterpreted. All data are presented in the Supplemental Digital Contents 4 to 6 (http://links.lww.com/CJP/A660, http://links.lww.com/CJP/A661, http://links.lww.com/CJP/A662) for readers to consider.

Finally, we did not include details of methods that could be used to discriminate between PMCs (eg, questionnaires—PainDETECT,[270] Central Sensitisation Inventory[178]; clinical tests—quantitative sensory testing[271]). This review aimed to consider the features of each pain group, and separate work should carry out detailed analysis of identification and discrimination of those features.

CONCLUSIONS

This paper describes an extensive systematic review and synthesis of mechanism-based classifications of pain experienced in the musculoskeletal system. We report a convergence, and divergence, of diverse nomenclature, descriptions of neurobiology, pain characteristics, and aggravating/easing factors. There was considerable agreement, but some inconsistency and evolution of terminology. A next step is clarification of models and methods to differentiate PMCs and reach expert consensus. This review provides a summary of the current state of the literature that can support that process.

ACKNOWLEDGMENT

The authors acknowledge the valuable contribution of Nathalia da Costa, BSc (Hons), School of Health & Rehabilitation Sciences, The University of Queensland, QLD, Australia, for her assistance in the development of the search strategy.

REFERENCES

1. Magni G, Caldieron C, Rigatti-Luchini S, et al. Chronic musculoskeletal pain and depressive symptoms in the general population. An analysis of the 1st National Health and Nutrition Examination Survey data. *Pain*. 1990;43:299–307.
2. Verhaak PF, Kerssens JJ, Dekker J, et al. Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain*. 1998;77:231–239.
3. Pain in Europe. A 2003 Report. Pain Alliance Europe; 2003.
4. Becker A, Held H, Redaelli M, et al. Low back pain in primary care: costs of care and prediction of future health care utilization. *Spine (Phila Pa 1976)*. 2010;35:1714–1720.
5. McCarberg BH, Nicholson BD, Todd KH, et al. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an internet survey. *Am J Ther*. 2008;15:312–320.
6. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287–333.
7. Gifford LS, Butler DS. The integration of pain sciences into clinical practice. *J Hand Ther*. 1997;10:86–95.
8. Smart KM, O'Connell NE, Doody C. Towards a mechanisms-based classification of pain in musculoskeletal physiotherapy? *Phys Ther Rev*. 2008;13:1–10.
9. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1–32.
10. Vardeh D, Mannion RJ, Woolf CJ. Toward a mechanism-based approach to pain diagnosis. *J Pain*. 2016;17:T50–T69.
11. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain*. 2016;157:1382–1386.
12. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science*. 2000;288:1769–1772.
13. Kuner R. Central mechanisms of pathological pain. *Nat Med*. 2010;16:1258–1266.
14. Gifford L. Pain, the tissues and the nervous system: a conceptual model. *Physiotherapy*. 1998;84:27–36.
15. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140:441–451.
16. Dallel R, Voisin D. Towards a pain treatment based on the identification of the pain-generating mechanisms? *Eur Neurol*. 2001;45:126–132.
17. Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci*. 2002;5:1062–1067.
18. 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.
19. Smart KM, Blake C, Staines A, et al. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (+/− leg) pain. *Man Ther*. 2012;17:336–344.
20. Smart KM, Blake C, Staines A, et al. Mechanisms-based classifications of musculoskeletal pain: part 2 of 3: symptoms and signs of peripheral neuropathic pain in patients with low back (+/− leg) pain. *Man Ther*. 2012;17:345–351.
21. Smart KM, Blake C, Staines A, et al. Mechanisms-based classifications of musculoskeletal pain: part 3 of 3: symptoms and signs of nociceptive pain in patients with low back (+/− leg) pain. *Man Ther*. 2012;17:352–357.
22. International Association for the Study of Pain. Task Force on Taxonomy. IASP Terminology. 2017. Available at: http://web.archive.org/web/20200130092932/https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698. Accessed January 30, 2020.
23. Kolski MC, O'Connor A, Van Der Laan K, et al. Validation of a pain mechanism classification system (PMCs) in physical therapy practice. *J Man Manip Ther*. 2016;24:192–199.
24. Dewitte V, De Pauw R, De Meulemeester K, et al. Clinical classification criteria for nonspecific low back pain: a Delphi-survey of clinical experts. *Musculoskelet Sci Pract*. 2018;34:66–76.
25. Dewitte V, De Pauw R, Danneels L, et al. The interrater reliability of a pain mechanisms-based classification for patients with nonspecific neck pain. *Braz J Phys Ther*. 2019;23:437–447.
26. Petrushenko OA, Luk'yanetz OO. Some physiological mechanisms functioning in models of pain-related processes. *Neurophysiology*. 2019;51:223–231.
27. Ford B. Pain in Parkinson's disease. *Clin Neurosci*. 1998;5:63–72.
28. Chimenti RL, Frey-Law LA, Sluka KA. A mechanism-based approach to physical therapist management of pain. *Phys Ther*. 2018;98:302–314.
29. Ohtori S, Orita S, Yamashita M, et al. Existence of a neuropathic pain component in patients with osteoarthritis of the knee. *Yonsei Med J*. 2012;53:801–805.

30. Roubille C, Raynauld JP, Abram F, et al. The presence of meniscal lesions is a strong predictor of neuropathic pain in symptomatic knee osteoarthritis: a cross-sectional pilot study. *Arthritis Res Ther*. 2014;16:507.
31. Hansson P. Neuropathic pain: clinical characteristics and diagnostic workup. *Eur J Pain*. 2002;6(suppl A):47–50.
32. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
33. Buchbinder R, Goel V, Bombardier C, et al. Classification systems of soft tissue disorders of the neck and upper limb: do they satisfy methodological guidelines? *J Clin Epidemiol*. 1996; 49:141–149.
34. Lluch E, Torres R, Nijs J, et al. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *Eur J Pain*. 2014;18:1367–1375.
35. Clarke C, Lindsay DR, Pyati S, et al. Residual limb pain is not a diagnosis: a proposed algorithm to classify postamputation pain. *Clin J Pain*. 2013;29:551–562.
36. Bryce TN, Budh CN, Cardenas DD, et al. Pain after spinal cord injury: an evidence-based review for clinical practice and research. Report of the National Institute on Disability and Rehabilitation Research Spinal Cord Injury Measures meeting. *J Spinal Cord Med*. 2007;30:421–440.
37. O'Connor AB, Schwid SR, Herrmann DN, et al. Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain*. 2008;137:96–111.
38. Sanchis MN, Lluch E, Nijs J, et al. The role of central sensitization in shoulder pain: a systematic literature review. *Semin Arthritis Rheum*. 2014;44:710–716.
39. Meeus M, Vervisch S, De Clerck LS, et al. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum*. 2012;41:556–567.
40. Schafer AG, Hall TM, Rolke R, et al. Low back related leg pain: an investigation of construct validity of a new classification system. *J Back Musculoskelet Rehabil*. 2014;27:409–418.
41. Schafer A, Hall TM, Ludtke K, et al. Interrater reliability of a new classification system for patients with neural low back-related leg pain. *J Man Manip Ther*. 2009;17:109–117.
42. Schafer A, Hall T, Briffa K. Classification of low back-related leg pain—a proposed patho-mechanism-based approach. *Man Ther*. 2009;14:222–230.
43. Stanos S, Brodsky M, Argoff C, et al. Rethinking chronic pain in a primary care setting. *Postgrad Med*. 2016;128:502–515.
44. Kumar SP, Saha S. Mechanism-based classification of pain for physical therapy management in palliative care: a clinical commentary. *Indian J Palliat Care*. 2011;17:80–86.
45. Vitali C, Del Papa N. Pain in primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol*. 2015;29:63–70.
46. Seaman DR, Cleveland C III. Spinal pain syndromes: nociceptive, neuropathic, and psychologic mechanisms. *J Manipulative Physiol Ther*. 1999;22:458–472.
47. Muir IWW, Woolf CJ. Mechanisms of pain and their therapeutic implications. *J Am Vet Med Assoc*. 2001;219:1346–1356.
48. Woolf CJ. What is this thing called pain? *J Clin Invest*. 2010;120: 3742–3744.
49. Micheletti L, Radici G, Lynch PJ. Provoked vestibulodynia: inflammatory, neuropathic or dysfunctional pain? A neurobiological perspective. *J Obstet Gynaecol*. 2014;34:285–288.
50. Omoigui S. The biochemical origin of pain: the origin of all pain is inflammation and the inflammatory response. Part 2 of 3—inflammatory profile of pain syndromes. *Med Hypotheses*. 2007;69:1169–1178.
51. Omoigui S. The biochemical origin of pain—proposing a new law of pain: the origin of all pain is inflammation and the inflammatory response. Part 1 of 3—a unifying law of pain. *Med Hypotheses*. 2007;69:70–82.
52. Schaible HG. Emerging concepts of pain therapy based on neuronal mechanisms. *Handb Exp Pharmacol*. 2015;227:1–14.
53. Marchand S. The physiology of pain mechanisms: from the periphery to the brain. *Rheum Dis Clin North Am*. 2008;34: 285–309.
54. Schaible HG, Richter F. Pathophysiology of pain. *Langenbecks Arch Surg*. 2004;389:237–243.
55. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288:1765–1769.
56. Horowitz SH. The diagnostic workup of patients with neuropathic pain. *Anesthesiol Clin*. 2007;25:699–708.
57. Bennett GJ. Can we distinguish between inflammatory and neuropathic pain? *Pain Res Manag*. 2006;11:11A–15A.
58. Franz S, Schulz B, Wang H, et al. Management of pain in individuals with spinal cord injury: Guideline of the German-Speaking Medical Society for Spinal Cord Injury. *Ger Med Sci*. 2019;17:Doc05.
59. Ford B. Pain in Parkinson's disease. *Mov Disord*. 2010;25(suppl 1): S98–S103.
60. Ha AD, Jankovic J. Pain in Parkinson's disease. *Mov Disord*. 2012;27:485–491.
61. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. *BMJ*. 2014;348:f7656.
62. O'Neill OR, Burchiel KJ. Role of the sympathetic nervous system in painful nerve injury. *Neurosurg Clin N Am*. 1991;2: 127–136.
63. Nijs J, Torres-Cueco R, van Wilgen CP, et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. *Pain Physician*. 2014;17:447–457.
64. Starkweather AR, Heineman A, Storey S, et al. Methods to measure peripheral and central sensitization using quantitative sensory testing: a focus on individuals with low back pain. *Appl Nurs Res*. 2016;29:237–241.
65. Backonja MM. Defining neuropathic pain. *Anesth Analg*. 2003; 97:785–790.
66. Clauw DJ. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s). *Best Pract Res Clin Rheumatol*. 2015;29:6–19.
67. Dimitroulas T, Duarte RV, Behura A, et al. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. *Semin Arthritis Rheum*. 2014;44: 145–154.
68. Sifuentes-Giraldo WA, Morell-Hita JL. Diagnostic protocol of chronic musculoskeletal pain. *Medicine (Spain)*. 2017;12: 1609–1613.
69. Kumar SP, Prasad K, Kumar VK, et al. Mechanism-based classification and physical therapy management of persons with cancer pain: a prospective case series. *Indian J Palliat Care*. 2013;19:27–33.
70. Horgas AL. Pain assessment in older adults. *Nurs Clin North Am*. 2017;52:375–385.
71. Schneiderhan J, Orizondo C. Chronic pain: how to approach these 3 common conditions: fibromyalgia, osteoarthritis, and low back pain require multimodal, evidence-based treatment plans. Tailoring those plans to the underlying mechanisms of pain is key. *J Fam Pract*. 2017;66:145–157.
72. Mahnig S, Landmann G, Stockinger L, et al. Pain assessment according to the International Spinal Cord Injury Pain classification in patients with spinal cord injury referred to a multidisciplinary pain center. *Spinal Cord*. 2016;54:809–815.
73. Clauw DJ, Hassett AL. The role of centralised pain in osteoarthritis. *Clin Exp Rheumatol*. 2017;35:S79–S84.
74. Nijs J, Apeldoorn A, Hallegraeff H, et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician*. 2015;18:E333–E346.
75. Lampa J. Pain without inflammation. *Best Pract Res Clin Rheumatol*. 2019;33:101439.
76. Sluka KA. *Mechanisms and Management of Pain for the Physical Therapist*. Philadelphia, PA: Wolters Kluwer Health,; 2016.
77. Hawke F, Burns J. Understanding the nature and mechanism of foot pain. *J Foot Ankle Res*. 2009;2:1.
78. Jarrell J, Arendt-Nielsen L. Quantitative sensory testing in gynaecology: improving preoperative and postoperative pain diagnosis. *J Obstet Gynaecol Can*. 2013;35:531–535.

79. Bannister K, Kucharczyk M, Dickenson AH. Hopes for the future of pain control. *Pain Ther*. 2017;6:117–128.
80. Stynes S, Konstantinou K, Dunn KM. Classification of patients with low back-related leg pain: a systematic review. *BMC Musculoskelet Disord*. 2016;17:226.
81. Nijs J, Leysen L, Adriaenssens N, et al. Pain following cancer treatment: guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. *Acta Oncol*. 2016;55:659–663.
82. Backryd E. Pain in the blood? Envisioning mechanism-based diagnoses and biomarkers in clinical pain medicine. *Diagnostics (Basel)*. 2015;5:84–95.
83. Ibor PJ, Sanchez-Magro I, Villoria J, et al. Mixed pain can be discerned in the primary care and orthopedics settings in Spain: a large cross-sectional study. *Clin J Pain*. 2017;33:1100–1108.
84. Coyne KS, Currie BM, Donevan S, et al. Discriminating between neuropathic pain and sensory hypersensitivity using the Chronic Pain Questions (CPQ). *Postgrad Med*. 2017;129: 22–31.
85. Young Blood MR, Ferro MM, Munhoz RP, et al. Classification and characteristics of pain associated with Parkinson's disease. *Parkinsons Dis*. 2016;2016:6067132.
86. Finco G, Locci E, Mura P, et al. Can urine metabolomics be helpful in differentiating neuropathic and nociceptive pain? A proof-of-concept study. *PLoS One*. 2016;11:e0150476.
87. Walk D, Poliak-Tunis M. Chronic pain management: an overview of taxonomy, conditions commonly encountered, and assessment. *Med Clin North Am*. 2016;100:1–16.
88. Nagakura Y. Challenges in drug discovery for overcoming 'dysfunctional pain': an emerging category of chronic pain. *Expert Opin Drug Discov*. 2015;10:1043–1045.
89. Barrie J, Loughlin D. Managing chronic pain in adults. *Nurs Stand*. 2014;29:50–58.
90. Moloney NA, Hall TM, Leaver AM, et al. The clinical utility of pain classification in non-specific arm pain. *Man Ther*. 2015;20:157–165.
91. Rabey M, Beales D, Slater H, et al. Multidimensional pain profiles in four cases of chronic non-specific axial low back pain: an examination of the limitations of contemporary classification systems. *Man Ther*. 2015;20:138–147.
92. Hassan H, Walsh DA. Central pain processing in osteoarthritis: implications for treatment. *Pain Manag*. 2014;4:45–56.
93. Jones LE, O'Shaughnessy DF. The pain and movement reasoning model: introduction to a simple tool for integrated pain assessment. *Man Ther*. 2014;19:270–276.
94. Haanpaa ML, Backonja MM, Bennett MI, et al. Assessment of neuropathic pain in primary care. *Am J Med*. 2009;122:S13–S21.
95. Fil A, Cano-de-la-Cuerda R, Munoz-Hellin E, et al. Pain in Parkinson disease: a review of the literature. *Parkinsonism Relat Disord*. 2013;19:285–294.
96. Wasner G, Deuschl G. Pains in Parkinson disease—many syndromes under one umbrella. *Nat Rev Neurol*. 2012;8:284–294.
97. Finnerup NB, Baastrup C. Spinal cord injury pain: mechanisms and management. *Curr Pain Headache Rep*. 2012;16: 207–216.
98. Kumar SP. Cancer pain: a critical review of mechanism-based classification and physical therapy management in palliative care. *Indian J Palliat Care*. 2011;17:116–126.
99. Smart KM, Curley A, Blake C, et al. The reliability of clinical judgments and criteria associated with mechanisms-based classifications of pain in patients with low back pain disorders: a preliminary reliability study. *J Man Manip Ther*. 2010;18: 102–110.
100. Schafer A, Hall T, Muller G, et al. Outcomes differ between subgroups of patients with low back and leg pain following neural manual therapy: a prospective cohort study. *Eur Spine J*. 2011;20:482–490.
101. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152:S2–S15.
102. Fainsinger RL, Nekolaichuk C, Lawlor P, et al. An international multicentre validation study of a pain classification system for cancer patients. *Eur J Cancer*. 2010;46:2896–2904.
103. Walsh J, Hall T. Classification of low back-related leg pain: do subgroups differ in disability and psychosocial factors? *J Man Manip Ther*. 2009;17:118–123.
104. Lluch E, Nijs J, Courtney CA, et al. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. *Disabil Rehabil*. 2017;40:2836–2845.
105. Sagripanti M, Viti C. Primary headaches in patients with temporomandibular disorders: diagnosis and treatment of central sensitization pain. *Cranio*. 2017;36:381–389.
106. Arthur J, Tanco K, Haider A, et al. Assessing the prognostic features of a pain classification system in advanced cancer patients. *Support Care Cancer*. 2017;25:2863–2869.
107. Akinci A, Al Shaker M, Chang MH, et al. Predictive factors and clinical biomarkers for treatment in patients with chronic pain caused by osteoarthritis with a central sensitisation component. *Int J Clin Pract*. 2016;70:31–44.
108. Micheletti L, Radici G, Lynch PJ. Is the 2003 ISSVD terminology and classification of vulvodynia up-to-date? A neurobiological perspective. *J Obstet Gynaecol*. 2015;35:788–792.
109. Arthur J, Yennurajalingam S, Nguyen L, et al. The routine use of the Edmonton Classification System for Cancer Pain in an outpatient supportive care center. *Palliat Support Care*. 2015; 13:1185–1192.
110. Vining R, Potocki E, Seidman M, et al. An evidence-based diagnostic classification system for low back pain. *J Can Chiropr Assoc*. 2013;57:189–204.
111. Cardenas DD, Felix ER. Pain after spinal cord injury: a review of classification, treatment approaches, and treatment assessment. *PM R*. 2009;1:1077–1090.
112. Marchi A, Vellucci R, Mameli S, et al. Pain biomarkers. *Clin Drug Investig*. 2009;29(suppl 1):41–46.
113. Fainsinger RL, Nekolaichuk CL. A "TNM" classification system for cancer pain: the Edmonton Classification System for Cancer Pain (ECS-CP). *Support Care Cancer*. 2008;16:547–555.
114. Caraceni A, Weinstein SM. Classification of cancer pain syndromes. *Oncology*. 2001;15:1627–1640.
115. Rigor BM Sr. Pelvic cancer pain. *J Surg Oncol*. 2000;75: 280–300.
116. Donovan WH, Dimitrijevic MR, Dahm L, et al. Neurophysiological approaches to chronic pain following spinal cord injury. *Paraplegia*. 1982;20:135–146.
117. Vibe Fersum K, O'Sullivan PB, Kvale A, et al. Inter-examiner reliability of a classification system for patients with non-specific low back pain. *Man Ther*. 2009;14:555–561.
118. Pérez C, Margarit C, Sánchez-Magro I, et al. Chronic pain features relate to quality of life more than physiopathology: a cross-sectional evaluation in pain clinics. *Pain Pract*. 2017;17:866–878.
119. McCarberg B, D'Arcy Y, Parsons B, et al. Neuropathic pain: a narrative review of etiology, assessment, diagnosis, and treatment for primary care providers. *Curr Med Res Opin*. 2017;33: 1361–1369.
120. Yarnitsky D, Granot M, Granovsky Y. Pain modulation profile and pain therapy: between pro- and antinociception. *Pain*. 2014;155:663–665.
121. Babos MB, Grady B, Wisnoff W, et al. Pathophysiology of pain. *Dis Mon*. 2013;59:330–358.
122. Hush JM, Stanton TR, Siddall P, et al. Untangling nociceptive, neuropathic and neuroplastic mechanisms underlying the biological domain of back pain. *Pain Manag*. 2013;3: 223–236.
123. Stump PRNAG, Dalben GS. Mechanisms and clinical management of pain. *Braz Oral Res*. 2012;26:115–119.
124. Jensen TS, Finnerup NB. Neuropathic pain: peripheral and central mechanisms. *Eur J Pain Suppl*. 2009;3:33–36.
125. Widerström-Noga E. Multidimensional clinical pain phenotypes after spinal cord injury. *Pain Manag*. 2012;2:467–478.
126. Garcia-Larrea L. Objective pain diagnostics: clinical neurophysiology. *Neurophysiol Clin*. 2012;42:187–197.
127. Vellucci R. Heterogeneity of chronic pain. *Clin Drug Investig*. 2012;32:3–10.
128. Crockett A, Panickar A. Role of the sympathetic nervous system in pain. *Anaesth Intens Care Med*. 2011;12:50–54.

129. Nijs J, Van Houdenhove B, Oostendorp RAB. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther*. 2010;15:135–141.
130. Jensen TS. Pathophysiology of pain: from theory to clinical evidence. *Eur J Pain Suppl*. 2008;2:13–17.
131. Katz WA, Rothenberg R. Section 3: The nature of pain: pathophysiology. *J Clin Rheumatol*. 2005;11:S11–S15.
132. Mackey S. Mechanisms of inflammatory pain: therapeutic implications. *J Clin Rheumatol*. 2004;10:S5–S11.
133. Lee S, Zhao X, Hatch M, et al. Central neuropathic pain in spinal cord injury. *Crit Rev Phys Rehabil Med*. 2013;25:159–172.
134. Russell IJ. Future perspectives in generalised musculoskeletal pain syndromes. *Best Pract Res Clin Rheumatol*. 2011;25:321–331.
135. O'Sullivan PB, Beales DJ. Diagnosis and classification of pelvic girdle pain disorders—part 1: a mechanism based approach within a biopsychosocial framework. *Man Ther*. 2007;12:86–97.
136. O'Sullivan PB, Beales DJ. Diagnosis and classification of pelvic girdle pain disorders, part 2: illustration of the utility of a classification system via case studies. *Man Ther*. 2007;12:e1–e12.
137. Schwartzman RJ, Grothusen J, Kiefer TR, et al. Neuropathic central pain: epidemiology, etiology, and treatment options. *Arch Neurol*. 2001;58:1547–1550.
138. Portenoy RK. Mechanisms of clinical pain. Observations and speculations. *Neurol Clin*. 1989;7:205–230.
139. Katavich L. Pain mechanisms underlying peripheral nerve injury—implications for mobilisation of the nervous system. *NZ J Physiother*. 1999;27:24–27.
140. Truini A, Barbanti P, Pozzilli C, et al. A mechanism-based classification of pain in multiple sclerosis. *J Neurol*. 2013;260: 351–367.
141. Johnson BW Jr. Tutorial 23: Mechanisms of chronic pain. *Pain Digest*. 1996;6:97–110.
142. Pinkowish MD, Gallagher RM, Minagar A. Chronic pain: multiple causes, multiple pathways to relief. *Patient Care*. 2004; 7:11.
143. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain*. 2015;156:1003–1007.
144. Zusman M. A note to the musculoskeletal physiotherapist. *J Back Musculoskelet Rehabil*. 2012;25:103–107.
145. Lidbeck J. Central hyperexcitability in chronic musculoskeletal pain: a conceptual breakthrough with multiple clinical implications. *Pain Res Manag*. 2002;7:81–92.
146. Jones M. Clinical reasoning and pain. *Man Ther*. 1995;1:17–24.
147. Siddall PJ, Taylor DA, Cousins MJ. Classification of pain following spinal cord injury. *Spinal Cord*. 1997;35:69–75.
148. Arnér S. Pain analysis in prediction of treatment outcome. *Acta Anaesthesiol Scand*. 1998;42:24–28.
149. Wu C, Jarvi K. Mechanisms of chronic urologic pain. *Can Urol Assoc J*. 2018;12:S147–S148.
150. Duffy SS, Lees JG, Perera CJ, et al. Managing neuropathic pain in multiple sclerosis: pharmacological interventions. *Med Chem*. 2018;14:106–119.
151. Bryce TN, Ragnarsson KT. Pain after spinal cord injury. *Phys Med Rehabil Clin N Am*. 2000;11:157–168.
152. Schoth DE, Blankenburg M, Wager J, et al. Association between quantitative sensory testing and pain or disability in paediatric chronic pain: protocol for a systematic review and meta-analysis. *BMJ Open*. 2019;9:e031861.
153. Sharma D, Brandow AM. Neuropathic pain in individuals with sickle cell disease. *Neurosci Lett*. 2020:134445.
154. Vila-Cha N, Cavaco S, Mendes A, et al. Sleep disturbances in Parkinson's disease are associated with central parkinsonian pain. *J Pain Res*. 2019;12:2137–2144.
155. Marques A, Attal N, Bouhassira D, et al. How to diagnose parkinsonian central pain? *Parkinsonism Relat Disord*. 2019;64: 50–53.
156. Caraceni A, Shkodra M. Cancer pain assessment and classification. *Cancers (Basel)*. 2019;11:510.
157. Orhurhu VJ, Roberts JS, Cohen SP. *Ketamine in Acute and Chronic Pain Management*. Treasure Island, FL: StatPearls Publishing; 2019.
158. Tracey I, Woolf CJ, Andrews NA. Composite pain biomarker signatures for objective assessment and effective treatment. *Neuron*. 2019;101:783–800.
159. Renton T. Chronic pain and overview or differential diagnoses of non-odontogenic orofacial pain. *Prim Dent J*. 2019;7:71–86.
160. Bechakra M, Moerdijk F, van Rosmalen J, et al. Opioid responsiveness of nociceptive versus mixed pain in clinical cancer patients. *Eur J Cancer*. 2018;105:79–87.
161. Stampacchia G, Massone A, Gerini A, et al. Reliability of the Italian version of the International Spinal Cord Injury Pain Basic Data Set. *Spinal Cord*. 2019;57:128–133.
162. Silverdale MA, Kobylecki C, Kass-Iliyya L, et al. A detailed clinical study of pain in 1957 participants with early/moderate Parkinson's disease. *Parkinsonism Relat Disord*. 2018;56: 27–32.
163. Rukavina K, Leta V, Sportelli C, et al. Pain in Parkinson's disease: new concepts in pathogenesis and treatment. *Curr Opin Neurol*. 2019;32:579–588.
164. Varrassi G, Alon E, Bagnasco M, et al. Towards an effective and safe treatment of inflammatory pain: a Delphi-Guided Expert Consensus. *Adv Ther*. 2019;36:2618–2637.
165. Woodbury A, McCrary MR, Yu SP. Molecular targets and natural compounds in drug development for the treatment of inflammatory pain. *Curr Drug Targets*. 2018;19:1905–1915.
166. Leysen L, Pas R, Nijs J, et al. Chronic pain in breast cancer survivors: nociceptive, neuropathic, or central sensitization pain? *Pain Pract*. 2019;19:183–195.
167. Clauw DJ, Essex MN, Pitman V, et al. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. *Postgrad Med*. 2019;131:185–198.
168. De Groef A, Schillebeeckx F, Morlion B, et al. Neuropathic Pain—assessment in rehabilitation settings. *J Rehabil*. 2019;85: 34–43.
169. Fink RM, Gallagher E. Cancer pain assessment and measurement. *Semin Oncol Nurs*. 2019;35:229–234.
170. Gierthmühlen J, Greinacher J, Höper J, et al. Sensory symptoms in low back pain-how do they matter? *Curr Med Res Opin*. 2018;34:657–667.
171. Vagaska E, Litavcova A, Srotova I, et al. Do lumbar magnetic resonance imaging changes predict neuropathic pain in patients with chronic non-specific low back pain? *Medicine*. 2019;98:e15377–e15377.
172. He Y-j, Lü D, Wang Z, et al. Present status of treatment of chronic pain. *Chin J Contemp Neurol Neurosurg*. 2018;18: 703–704.
173. Arendt-Nielsen L. Central sensitization in humans: assessment and pharmacology. *Handb Exp Pharmacol*. 2015;227:79–102.
174. Smart KM, Blake C, Staines A, et al. 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 (±leg) pain. *Man Ther*. 2012;17:119–125.
175. Smart KM, Blake C, Staines A, et al. The discriminative validity of "nociceptive," "peripheral neuropathic," and "central sensitization" as mechanisms-based classifications of musculoskeletal pain. *Clin J Pain*. 2011;27:655–663.
176. Mystakidou K, Parpa E, Tsilika E, et al. Comparison of pain quality descriptors in cancer patients with nociceptive and neuropathic pain. *In Vivo*. 2007;21:93–97.
177. O'Sullivan P, Waller R, Wright A, et al. Sensory characteristics of chronic non-specific low back pain: a subgroup investigation. *Man Ther*. 2014;19:311–318.
178. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the Central Sensitization Inventory. *Pain Pract*. 2012;12:276–285.
179. Forster M, Mahn F, Gockel U, et al. Axial low back pain: one painful area—many perceptions and mechanisms. *PLoS ONE*. 2013;8:e68273.
180. de Resende MA, Nascimento OJ, Rios AA, et al. Neuropathic pain profile: the basic neurological exam of 33 patients. *Rev Bras Anestesiol*. 2010;60:144–153.

181. Spahr N, Hodkinson D, Jolly K, et al. Distinguishing between nociceptive and neuropathic components in chronic low back pain using behavioural evaluation and sensory examination. *Musculoskelet Sci Pract*. 2017;27:40–48.
182. Tjakkes GH, De Bont LG, Van Wijhe M, et al. Classification of chronic orofacial pain using an intravenous diagnostic test. *J Oral Rehabil*. 2009;36:469–475.
183. Dobratz MC. Word choices of advanced cancer patients: frequency of nociceptive and neuropathic pain. *Am J Hosp Palliat Care*. 2008;25:469–475.
184. Fainsinger RL, Nekolaichuk CL, Lawlor PG, et al. A multicenter study of the revised Edmonton Staging System for classifying cancer pain in advanced cancer patients. *J Pain Symptom Manage*. 2005;29:224–237.
185. Hagen NA. Reproducing a cancer patient's pain on physical examination: bedside provocative maneuvers. *J Pain Symptom Manage*. 1999;18:406–411.
186. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain*. 1999;82:263–274.
187. Bruera E, MacMillan K, Hanson J, et al. The Edmonton Staging System for cancer pain: preliminary report. *Pain*. 1989;37:203–209.
188. Vermote R, Ketelaer P, Carton H. Pain in multiple sclerosis patients. A prospective study using the McGill Pain Questionnaire. *Clin Neurol Neurosurg*. 1986;88:87–93.
189. Ghia JN, Mueller RA, Duncan GH, et al. Serotonergic activity in man as a function of pain, pain mechanisms, and depression. *Anesth Analg*. 1981;60:854–861.
190. Nogueira LAC, Chaves ADO, Wendt ADS, et al. Central sensitization patients present different characteristics compared with other musculoskeletal patients: a case-control study. *Eur J Physiother*. 2016;18:147–153.
191. Ezenwa MO, Molokie RE, Wang ZJ, et al. Safety and utility of quantitative sensory testing among adults with sickle cell disease: indicators of neuropathic pain? *Pain Pract*. 2016;16:282–293.
192. Aasa B, Berglund L, Michaelson P, et al. Individualized low-load motor control exercises and education versus a high-load lifting exercise and education to improve activity, pain intensity, and physical performance in patients with low back pain: a randomized controlled trial. *J Orthop Sports Phys Ther*. 2015;45:77–85.
193. Kozma CM, Provenzano DA, Slaton TL, et al. Complexity of pain management among patients with nociceptive or neuropathic neck, back, or osteoarthritis diagnoses. *J Manag Care Spec Pharm*. 2014;20:455–466.
194. Schliessbach J, Siegenthaler A, Streitberger K, et al. The prevalence of widespread central hypersensitivity in chronic pain patients. *Eur J Pain*. 2013;17:1502–1510.
195. Westermann A, Krumova EK, Pennekamp W, et al. Different underlying pain mechanisms despite identical pain characteristics: a case report of a patient with spinal cord injury. *Pain*. 2012;153:1537–1540.
196. Geletka BJ, O'Hearn MA, Courtney CA. Quantitative sensory testing changes in the successful management of chronic low back pain. *J Man Manip Ther*. 2012;20:16–22.
197. Ghia JN, Toomey TC, Mao W. Towards an understanding of chronic pain mechanisms: the use of psychologic tests and a refined differential spinal block. *Anesthesiology*. 1979;50:20–25.
198. Rapo-Pylkkö S, Haanpää M, Liira H. Chronic pain among community-dwelling elderly: a population-based clinical study. *Scand J Prim Health Care*. 2016;34:159–164.
199. Wilkie DJ, Huang H, Reilly N, et al. Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality descriptors. *J Pain Symptom Manage*. 2001;22:899–910.
200. Bruera E, Schoeller T, Wenk R, et al. A prospective multicenter assessment of the Edmonton Staging System for cancer pain. *J Pain Symptom Manage*. 1995;10:348–355.
201. Ghia JN, Duncan GH, Teeple E. Differential spinal block for diagnosis of chronic pain. *Compr Ther*. 1982;8:55–61.
202. Goetz CG, Tanner CM, Levy M, et al. Pain in Parkinson's disease. *Mov Disord*. 1986;1:45–49.
203. Benzon HT, Linde HW, Hawes DD, et al. Stellate ganglion block using physiologic saline solution. *Anesthesiology*. 1980;52:511–512.
204. Solaro C, Cella M, Signori A, et al. Identifying neuropathic pain in patients with multiple sclerosis: a cross-sectional multicenter study using highly specific criteria. *J Neurol*. 2018;265:828–835.
205. Falling C, Stebbings S, Baxter GD, et al. Musculoskeletal pain in individuals with inflammatory bowel disease reflects three distinct profiles. *Clin J Pain*. 2019;35:559–568.
206. Soni A, Wanigasekera V, Mezue M, et al. Central sensitization in knee osteoarthritis: relating presurgical brainstem neuroimaging and PainDETECT-based patient stratification to arthroplasty outcome. *Arthritis Rheumatol*. 2019;71:550–560.
207. Teles AR, Ocay DD, Bin Shebreen A, et al. Evidence of impaired pain modulation in adolescents with idiopathic scoliosis and chronic back pain. *Spine J*. 2019;19:677–686.
208. Falling C, Stebbings S, Baxter GD, et al. Profile of musculoskeletal pain in patients with inflammatory bowel disease: a study protocol for assessing the multidimensional experience of self-reported pain. *Phys Ther Rev*. 2018;23:227–235.
209. Ji Y, He Y, Nian X, et al. Inflammatory or neuropathic pain: characteristics and their relationships with disease activity and functional status in axial spondyloarthritis patients. *Pain Med*. 2019;20:882–888.
210. Smart K, Doody C. The clinical reasoning of pain by experienced musculoskeletal physiotherapists. *Man Ther*. 2007;12:40–49.
211. Smart K, Doody C. Mechanisms-based clinical reasoning of pain by experienced musculoskeletal physiotherapists. *Physiotherapy*. 2006;92:171–178.
212. Bryce TN, Dijkers MP, Ragnarsson KT, et al. Reliability of the Bryce/Ragnarsson spinal cord injury pain taxonomy. *J Spinal Cord Med*. 2006;29:118–132.
213. Nekolaichuk CL, Fainsinger RL, Lawlor PG. A validation study of a pain classification system for advanced cancer patients using content experts: the Edmonton Classification System for Cancer Pain. *Palliat Med*. 2005;19:466–476.
214. Merskey H. and International Association for the Study of Pain. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle, WA: IASP; 2002.
215. Bryce TN, Biering-Sorensen F, Finnerup NB, et al. International Spinal Cord Injury Pain Classification: part I. Background and description. March 6-7, 2009. *Spinal Cord*. 2012;50:413–417.
216. Freynhagen R, Parada HA, Calderon-Ospina CA, et al. Current understanding of the mixed pain concept: a brief narrative review. *Curr Med Res Opin*. 2019;35:1011–1018.
217. Ross E. Moving towards rational pharmacological management of pain with an improved classification system of pain. *Expert Opin Pharmacother*. 2001;2:1529–1530.
218. Nashan D, Meiss F, Gralow I. Pain: basics and relevance in dermatology. *J Dtsch Dermatol Ges*. 2009;7:704–717.
219. Matanle D. Definition and assessment of pain. *J Oper Depart Pract*. 2005;2:11–13.
220. Woolf CJ, Bennett GJ, Doherty M, et al. Towards a mechanism-based classification of pain? *Pain*. 1998;77:227–229.
221. Heidrich DE. The physiologic basis of pain medications. *Ohio Nurses Rev*. 2002;77:12–14.
222. Galloway KT, Buckenmaier CC III, Polomano RC. Understanding pain and pain mechanisms. *Am Nurse Today*. 2011;6:3–7.
223. Cox F. Basic principles of pain management: assessment and intervention. *Nurs Stand*. 2010;25:36–39.
224. Beiteke U, Bigge S, Reichenberger C, et al. Pain and pain management in dermatology. *J Dtsch Dermatol Ges*. 2015;13:967–987.
225. Kumar SP. Musculoskeletal pain—moving from symptoms and syndromes to mechanisms. *J Phys Ther*. 2010;2:41–45.

226. Wasner G, Baron R. Pain: clinical pain assessment: from bedside to better treatment. *Nat Rev Neurol*. 2009;5: 359–361.
227. Briggs E. Understanding the experience and physiology of pain. *Nurs Stand*. 2010;25:35–39.
228. Ritchie M. Mixed pain. *GM*. 2011;41:624–627.
229. Jones NS. Classification and diagnosis of facial pain. *Hosp Med*. 2001;62:598–606.
230. Laverty D. The assessment and management of patients with chronic pain. *Cancer Nurs Pract*. 2009;8:17–20.
231. Campbell J. The nature of pain. *Podiatry Now*. 2012;15:21–26.
232. Toda K. Central sensitization pain should be included in (central) neuropathic pain. *Pain Physician*. 2014;17:E783.
233. Vecht CJ. Nociceptive nerve pain and neuropathic pain. *Pain*. 1989;39:243–246.
234. Winfield JB. Pain and arthritis. *N C Med J*. 2007;68:444–446.
235. van Dieen JH, Reeves NP, Kawchuk G, et al. Analysis of motor control in patients with low back pain: a key to personalized care? *J Orthop Sports Phys Ther*. 2019;49:380–388.
236. Pergolizzi JV Jr, Gharibo C. Maximum control: a multi-modal approach to multi-mechanistic pain. *Chiropr Econ*. 2018;64: 17–20.
237. Doshi P. How to assess pain? *J Assoc Physicians India*. 2015; 63:8–13.
238. Somov PG. Time perception as a measure of pain intensity and pain type. *J Back Musculoskelet Rehabil*. 2000;14: 111–121.
239. Eloqayli H. Clinical decision-making in chronic spine pain: dilemma of image-based diagnosis of degenerative spine and generation mechanisms for nociceptive, radicular, and referred pain. *Biomed Res Int*. 2018;2018:8793843.
240. Baron R. Reflex sympathetic dystrophy and causalgia. *Suppl Clin Neurophysiol*. 2004;57:24–38.
241. Jay GW, Barkin RL. Neuropathic pain: etiology, pathophysiology, mechanisms, and evaluations. *Dis Mon*. 2014;60: 6–47.
242. Rockett M. Diagnosis, mechanisms and treatment of complex regional pain syndrome. *Curr Opin Anaesthesiol*. 2014;27: 494–500.
243. Stanton-Hicks M, Janig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. 1995;63:127–133.
244. Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP Classification of Chronic Pain for ICD-11: chronic primary pain. *Pain*. 2019;160:28–37.
245. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630–1635.
246. Jensen TS, Baron R, Haanpaa M, et al. A new definition of neuropathic pain. *Pain*. 2011;152:2204–2205.
247. Iqbal S, Pipon-Young L. The Delphi method. *Psychologist*. 2009;22:598–601.
248. Wortman PM. Consensus panels: methodology. In: Smelser NJ, Baltes PB, eds. *International Encyclopedia of the Social & Behavioral Sciences*. Oxford, UK: Pergamon; 2001: 2609–2613.
249. Gopalakrishnan S, Ganeshkumar P. Systematic reviews and meta-analysis: understanding the best evidence in primary healthcare. *J Family Med Prim Care*. 2013;2:9–14.
250. Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ*. 1997;315:672–675.
251. Greenhalgh T, Thorne S, Malterud K. Time to challenge the spurious hierarchy of systematic over narrative reviews? *Eur J Clin Invest*. 2018;48:e12931.
252. Torebjork E. Nociceptor activation and pain. *Philos Trans R Soc Lond B Biol Sci*. 1985;308:227–234.
253. Ackerley R, Watkins RH. Microneurography as a tool to study the function of individual C-fiber afferents in humans: responses from nociceptors, thermoreceptors, and mechanoreceptors. *J Neurophysiol*. 2018;120:2834–2846.
254. Raja SN. Nerve blocks in the evaluation of chronic pain. *Anesthesiology*. 1997;86:4–6.
255. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. *Pain*. 2008;137:473–477.
256. Staud R, Nagel S, Robinson ME, et al. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. *Pain*. 2009;145:96–104.
257. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. *Ann Neurol*. 2013;74:630–636.
258. Max MB. Clarifying the definition of neuropathic pain. *Pain*. 2002;96:406–407.
259. Grayston R, Czanner G, Elhadd K, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: implications for a new paradigm in fibromyalgia etiopathogenesis. *Semin Arthritis Rheum*. 2019;48:933–940.
260. Dimitroulas T, Duarte RV, Behura A, et al. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. *Semin Arthritis Rheum*. 2015;44: 145–154.
261. Granan LP. We do not need a third mechanistic descriptor for chronic pain states! Not yet. *Pain*. 2017;158:179.
262. Brummett C, Clauw D, Harris R, et al. We agree with the need for a new term but disagree with the proposed terms. *Pain*. 2016;157:2876.
263. Hansson P. Translational aspects of central sensitization induced by primary afferent activity: what it is and what it is not. *Pain*. 2014;155:1932–1934.
264. Cohen M, Quintner J, Buchanan D. Is chronic pain a disease? *Pain Med*. 2013;14:1284–1288.
265. Cohen M, Quintner J, Buchanan D, et al. Stigmatization of patients with chronic pain: the extinction of empathy. *Pain Med*. 2011;12:1637–1643.
266. Groeneweg G, Huygen FJ, Coderre TJ, et al. Regulation of peripheral blood flow in complex regional pain syndrome: clinical implication for symptomatic relief and pain management. *BMC Musculoskelet Disord*. 2009;10:116.
267. Tajerian M, Clark JD. New concepts in complex regional pain syndrome. *Hand Clin*. 2016;32:41–49.
268. Dimova V, Herrnberger MS, Escolano-Lozano F, et al. Clinical phenotypes and classification algorithm for complex regional pain syndrome. *Neurology*. 2020;94:e357–e367.
269. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
270. Freynhagen R, Baron R, Gockel U, et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911–1920.
271. Rabey M, Slater H, O'Sullivan P, et al. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain*. 2015;156:1874–1884.