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Osteoarthritis (T Appleton, Section Editor)

Understanding the Complexity of Pain in Osteoarthritis Through the Use of Pain Phenotyping: Current Evidence

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Abstract

Purpose of review This narrative review highlights recent literature pertaining to pain phenotyping in osteoarthritis (OA) by summarizing recent novel approaches and promising future directions.
Recent findings We report on four studies in knee OA that have added knowledge regarding longitudinal validation of pain phenotypes constructed with phenotypic domains other than pain that are highly stable over time; the existence of a pain susceptibility phenotype, defined by the presence of sensitivity to pressure pain thresholds and a lack of presence of psychosocial factors; the novelty and importance of movement-evoked pain supporting the association of positive quantitative sensory testing (QST) findings with greater intensity and frequency of spontaneous pain; and the external validation of a chronic pain phenotype in an independent data set that was previously identified by a systematic review. One study of people with hip OA subgrouped participants using daily pain ratings over 6 weeks demonstrating that both intermittent and constant pain are highly present in early stages of the disease, and those with higher pain intensity experience greater variability of pain.
Summary Collectively these studies have contributed new and important knowledge to our understanding of OA pain phenotypes through longitudinal or external validation, which has been a missing element in the literature. The novel examination of a movement-evoked pain phenotype may provide an avenue to greater understanding of pain variability and its correlates, and with their definitive associations with QST, further supports the importance of a mechanism-based approach to pain assessment.

Introduction

The prevalence of osteoarthritis (OA), currently estimated at over 300 million worldwide, has increased by 97% in the last quarter century and is now the 12th overall cause of years lived with disability globally [1]. Importantly, reduced mobility and its overall impact on morbidity and mortality have been emphasized in recent years, making the case for the seriousness of the disease [2]. Despite progress in research demonstrating that OA is a serious disease, we have been unable to unravel the complexity of pain that is a hallmark of the disease and a significant contributor to the progressive decline in physical function and quality of life [3].

While pain with its chronicity, multidimensional nature, and complex underlying mechanisms is common to many other musculoskeletal disorders including OA, there are features unique to OA to consider. The most notable is the heterogeneity of the OA disease process with multiple tissues implicated in processes of repair and deterioration that potentially contribute to OA pain, and therefore, the challenge of effective pain management. This heterogeneity has led to the concept of multiple phenotypes or pathophysiologic pathways, rather than one single process [4]. A phenotype is broadly defined as the composite of an organism's observable characteristics or traits, including morphology or physical form and structure; its developmental processes; its biochemical and physiological properties; its behavior; and the products of behavior [5]. This phenotypic approach to OA has been substantiated by two recent systematic reviews reporting the existence of multiple OA phenotypes in the literature [6, 7]. Phenotyping of pain in OA is a relatively recent development in the literature, with one of the first studies published on the topic in 2011 [8] and 10 others published through to September 2016 [6, 7]. Importantly, a "chronic pain/sensitization" phenotype was identified and supported by several studies, and while there were similarities found among them, they were also divergent in their approaches [6, 7]. A new advance in the past 5 years has been the use of quantitative sensory testing (QST) as a means to identify neurobiological mechanisms that may contribute to the pain experience in OA. Specifically, pain sensitization and conditioned pain modulation are increasingly being incorporated into assessments attempting to identify unique aspects of pain phenotypes in OA. Pain sensitization refers to increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs in the peripheral and/or central nervous system [9]. These phenomena are measured using QST such as pressure pain thresholds (PPTs) or temporal summation. PPTs when measured locally at the symptomatic knee, for example, are thought to reflect peripheral sensitization. Central sensitization is commonly measured using PPTs measured at a remote anatomical site or using temporal summation. The latter implicates the central nervous system regardless of where it is measured. Conditioned pain modulation is another QST tool which measures the efficiency of endogenous pain inhibitory pathways using a "pain inhibits pain" premise [10] and involves the use of two different QST techniques. It is hypothesized that the use of mechanical stimuli in QST is most relevant to OA, a mechanically driven disease.

While prior OA phenotyping studies have used different approaches with regard to which variables were considered, most have identified unique groups of individuals with knee or hip OA with greater pain severity, defined by either a unidimensional (e.g., psychophysical testing) or multidimensional (e.g., psychological factors and pain intensity) construct. Table 1 summarizes the different studies supporting an OA pain phenotype reported in either one of these previously published systematic reviews (6.7) listed in order of year of publication.

It is likely that the heterogeneity in this small body of literature reflects that there is as yet no agreed upon definition of a "pain phenotype" in OA. It is perhaps an important distinction to make when discussing clinical phenotypes versus pain phenotypes. Arguably, the clinical presentation of OA goes beyond pain but overlaps with many of the multidimensional constructs of pain. The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) has proposed a definition for pain phenotypes by adapting the aforementioned phenotype definition for the context of pain. They suggested that pain phenotypes include patient self-reported characteristics (e.g., psychosocial functioning), patient-reported symptoms (e.g., sleep disruption), and verbal or behavioral responses to standardized psychophysical tests of pain sensitization and further recommended specific variables and measures for pain phenotyping based on current best evidence [21]. In doing so, IMMPACT has provided an initial way forward to

Table 1. Summary of OA pain phenotypes studies reported in previous systematic reviews

Study	Year	OA population	Domains/variables used for clustering	Phenotypes reported
Murphy [8]	2011	Hip and knee	Knee pain, depression, fatigue, sleep problems, and total burden of somatic symptoms	1) High levels of depression, pain, fatigue, illness burden, and sleep problems 2) Intermediate levels of depression, moderate fatigue and illness burden, low pain, and sleep problems 3) High levels of sleep problems and low severity of other symptoms
Knoop [11]	2011	Knee	KL grade, BMI, muscle strength (mean score of the right and left quadriceps and hamstring strength), and depression	1) Minimal joint disease 2) Strong muscle 3) Non-obese and weak muscle 4) Obese and weak 5) Depressive
Cruz-Almeida [12]	2013	Knee	Depression, coping strategies, hypervigilance/general reactivity/arousability, dispositional optimism, affect, attention to pain, and general anger	1) High optimism, low negative affect 2) Low positive affect 3) Low optimism 4) Somatic sensitivity/pain hypervigilance
King [13]	2013	Knee	Stratified participants as low or high symptom severity based on WOMAC and compared subgroups using questionnaires and four QST measures	Subgroups significantly differed on the presence of WSP, pain, and disability in the past 6 months measured by Graded Chronic Pain Scale, knee pain duration, and QST (PPT, TS and thermal) except CPM.
Pereira [14]	2013	Knee	Depressive symptoms, KL grade, pain severity; adjusted for age, sex, BMI	1) Those without depressive symptoms had greater likelihood of having both greater pain and radiographic OA. 2) Those with depressive symptoms had lower likelihood of having both greater pain and radiographic OA.
Egsgaard [15]	2015	Knee	WOMAC subscales, Lequesne index, QoL, pain catastrophizing, QST measures (PPT, TS, and CPM), CIM, CIIIM, CRP, and CRPM*	1) Low sensitivity to pain 2) Mild sensitization (positive in some but not all QST) 3) Pain sensitization alone 4) Pain sensitization and catastrophizing
Kittelson [16]	2015	Knee	KL grade, BMI, quadriceps strength, palpation tenderness at joint used as a surrogate for QST, pain with patellar grind test, comorbidities,	1) Higher levels of comorbidity 2) Higher knee joint sensitivity 3) Higher levels of psychological distress and number of pain sites

Table 1. (Continued)

Study	Year	OA population	Domains/variables used for clustering	Phenotypes reported
			number of pain sites, presence of depression, and pain catastrophizing	4) Mild radiographic OA
Osgood [17]	2015	Knee	PPT (knee and elbow), CPM, low-threshold mechanoreceptive function, cold allodynia (knee and elbow)	1) Peripheral and central sensitization with dysfunctional CPM 2) None or central sensitization and intact CPM 3) Peripheral sensitization and dysfunctional CPM 4) None or peripheral sensitization and intact DNIC
Van der Esch [18]	2015	Knee	Upper leg muscle strength, BMI, KL grade, and depressive mood	1) Minimal radiographic OA 2) Strong muscle strength 3) Severe radiographic OA 4) Obese 5) Depressive mood
Cardoso [19]	2016	Knee	PPTs, heat pain, TS of heat pain, cold pain, and mechanical pain	1) Low pressure pain sensitivity 2) Average pain sensitivity 3) High TS of punctate pain 4) High Cold pain sensitivity 5) High heat pain sensitivity and TS of heat pain
Frey Law [20]	2016	Knee	Heat thresholds and tolerance, punctate pain intensity, PPTs, and noxious heat TS	1) Low pain sensitivity 2) Average pain sensitivity 3) High temporal summation 4) High heat and pressure pain 5) High punctate pain

*CIM is a measure of balance of connective tissue. Cartilage loss is a measure of articular cartilage degradation. CIIIM may be a measure of synovial fibrogenesis in OA. CRP and CRPM may be a measure of local inflammation

distinguish pain phenotypes from clinical ones, with the overall aim of improving treatment targets to provide a more personalized approach by addressing the complexity of pain. With the existence of OA pain phenotypes now substantiated, this paper will review papers of pain phenotypes in OA from the last 3 years to enhance our developing understanding of this nascent field.

Knee pain phenotypes

Two studies notable for their longitudinal analysis have recently contributed novel insights into knee pain phenotypes. In one of the most robust studies to date, Pan et al. [22••] used population-based data of 963 older adults (with or without knee OA) in Tasmania who had variable degrees of knee pain at baseline. Using a latent class model, the authors constructed phenotypes agnostically using a number of risk factors for pain, which included the number of painful sites, sex, BMI, emotional problems, education level, comorbidities, and knee structural pathology on MRI (cartilage defects, synovitis, bone marrow lesions). They reported a three-class model as being optimal with the following groups: class 1 had high prevalence of emotional problems and low prevalence of structural damage, class 2 had high prevalence of structural damage and low prevalence of emotional problems, class 3 had low prevalence of emotional problems and low prevalence of structural damage. This study is notable as it is one of a few that have included a wider spectrum of variables using a combination of those inside and outside the pain domain (demographics, BMI, comorbidities, MRI). The clinical relevance of these groupings was further supported by examining the association of the phenotypes with WOMAC pain and number of painful sites over a 10-year period, demonstrating that class 1 had more severe pain and a greater number of painful sites compared with classes 2 and 3 at each time point. WOMAC pain was also different between classes 2 and 3; however, the classes were similar in the number of painful sites [22••]. Importantly, this study provides preliminary evidence of the stability of homogenous pain phenotypes over time, and an indication of clinical prognosis.

The second study by Carlesso et al. [23••] also took a novel approach using similar agnostic latent class modeling to determine pain susceptibility phenotypes analyzing data from 852 adults in the community-based MOST study. Rather than starting with people who were considered to be symptomatic, the study included only those who reported being free from knee pain over a 2-month period to determine the initial phenotypes. Additionally, the intent was to examine factors other than structural pathology as potential contributors to a pain susceptibility phenotype. As such, QST in the form of pressure pain thresholds and temporal summation, depressive symptoms, pain catastrophizing, sleep quality, and widespread pain were considered in the modeling. The optimal model resulted in 4 phenotypes (latent classes) that were distinctly defined by the QST variables, particularly pressure pain thresholds, whereas the remaining variables did not differ substantially among the groups (see Fig. 1). Finally, they determined the relation of the phenotypes to the development of persistent knee pain (having pain on most days over a 2-month period) 2 years later. The phenotypes with the greatest pain sensitivity defined by PPT were twice as likely to develop persistent knee pain at 2 years compared with the phenotypes that had low or absent pain sensitivity based on QST measures. This study is the first to determine pain susceptibility phenotypes, incorporating a longitudinal analysis to validate the findings, and represents an initial step in helping to more clearly understand symptom persistence and the potential role of sensitization in the transition from intermittent to persistent pain [23••]. These initial findings regarding the role of sensitization in the development of pain also indicate its potential value in determining early OA phenotypes.

The assessment of movement-evoked pain (MEP) in people with knee OA has received little attention in the literature but is likely another important step in understanding the transition from intermittent to persistent pain. Cruz-Almeida et al. [24•] have added to the understanding of knee pain phenotypes by assessing MEP (pain severity ratings) in symptomatic individuals with knee OA during measures of physical performance (standing balance, 4-m walking speed, and chair stands). Three phenotypes were reported: (1) individuals with the highest physical function and minimal MEP, (2) individuals with moderate physical function and mild MEP, and (3) individuals with the lowest functional performance along with severe MEP. Of note, these identified phenotypes highlight the tight linkage between pain and function. Those in group 3 reported significantly greater spontaneous pain intensity and frequency during the past 6 months, more painful sites, higher WOMAC scores, greater depressive symptoms, use of active and passive coping strategies, catastrophizing, pain hypervigilance, and negative affect compared with those in group 1. Similar group differences were also found regarding QST with those in

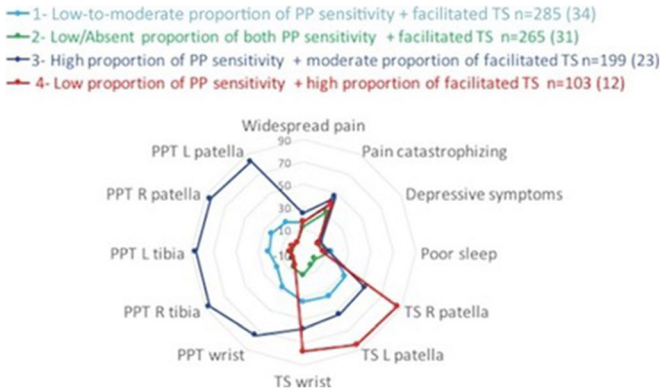

Fig. 1. Spidergram plot of identified classes, showing proportions of each indicator variable in each of the respective phenotypes. PP pressure pain, TS temporal summation, PPT, pressure pain threshold.

group 3 having significantly lower pressure and cold pain sensitivity and higher punctate pain sensitivity, and greater temporal summation of heat and punctate pain at the knee and at other distal sites compared with individuals in group 1 [24•]. Although we do not know about the intermittent or persistent nature of pain in this cohort, these QST results support the findings of Carlesso et al. [23••] by reporting that greater sensitivity was associated with greater intensity and frequency of spontaneous pain over a 6-month period, though this was in a relatively small sample ($n = 270$) which could lead to errors in subgroup formation.

External validation has been limited in the literature to date, largely reflecting that the same data elements are typically not acquired across different studies. One study that has attempted to overcome this challenge was published by Dell'Isola and Steultjens [25], in which they sought to replicate the phenotypes found initially in their previous systematic review [6] by using those data to classify participants in the OAI dataset of people with knee OA. They analyzed 599 of the 600 subjects from the OAI FNIH case-control sample for examination of the replicability of the initially reported 6 OA phenotypes (inflammatory, chronic pain, metabolic disorder, bone and cartilage metabolism, malaligned biomechanical, and minimal joint disease). As the variables available in the OAI FNIH cohort were different than those used by the studies reported in the original review, the authors proposed OAI FNIH variables that were deemed to be representative of the phenotypic domains reported. Criteria used for the determination of "chronic pain phenotype" were presence of depressive symptoms defined by CES-D score ≥ 16/20 and presence of widespread pain defined as ≥ 6/10 painful body areas using the ACR criteria of above and below the waist, on both sides of the body, and axially, though excluding the knees. Thus, this "chronic pain phenotype" reflects a fibromyalgia-like set of symptoms with a psychological component. A three-step process for classification was used resulting in 83% of subjects being classified in at least one phenotype with an overlap of 20% among the 6 original OA phenotypes. Seventeen percent were unable to be classified. Those in the chronic pain phenotype overlapped with those in the inflammatory, metabolic disorder, bone and cartilage metabolism, and malaligned biomechanical phenotypes, but not the minimal joint disease phenotype. This overlap is not surprising given that depressive symptoms and widespread pain can be frequently present in patients with knee OA. A seventh phenotype of "complex OA" was created for those who fulfilled the criteria for more than one of the 6 predefined phenotypes. Characteristics of the chronic pain phenotype included having the largest percentage of women (81%), history of injury (47%), and longest disease duration (4.4 years); however, it was second to the complex OA phenotype (i.e., the group with overlapping categories) in regard to WOMAC pain and function scores [25]. However, a major caveat to the interpretation of these derived phenotypes is that the FNIH sample was a selected case-control sample, matched on certain factors. Therefore, those matched factors would not be validly interpretable in the phenotypes. Further, case-control samples should not be reused for a cohort design with outcomes other than that which the original sample was selected for since exposures no longer reflect their distribution in the source population. Thus, one cannot readily make inferences about differences between groups defined in a different manner than the original case/control definitions.

Hip osteoarthritis

The intermittent versus persistent nature of pain in OA was also studied by Teirlinck et al. [26], who conducted a secondary analysis of trial data that had examined the effect of general practitioner care plus exercise in people with hip OA. Study participants recorded daily pain intensity ratings for 6 weeks and at the end of this period also filled out the ICOAP questionnaire. The authors used the questions from the ICOAP to subgroup participants with high intensity or frequency of intermittent pain by daily pain rating into 5 possible subgroups based on answers for each question respectively (none to extreme pain; rare to very often). While no differences were found for the frequency of intermittent pain, several were reported for intensity. Those with a higher intensity of intermittent pain reported a greater frequency, mean, standard deviation, and maximum value of peaks (defined as ≥ 2 point increase in daily NRS). There was however no difference in duration of peaks. The analysis was repeated using the constant pain subscale of the ICOAP, and the results were similar. These results suggest that in those with more severe pain, both intermittent pain and constant pain are experienced concurrently and with great fluctuation [26]. Previous qualitative work has suggested that this is typical of end-stage disease in people with hip and knee OA [27]. However, 70% or more had KL ≤ 2, suggesting that both constant pain and intermittent pain occurring simultaneously are present similarly in the early stages of the disease, in addition to in later stages of the disease. This contradiction with the qualitative data may be partly due to the fact that structural severity using the KL grade is a poor correlate with pain [3]. Rather, it is likely more important that duration and trajectory of disease in a given sample will better reflect symptom progression. In addition, unlike the other studies, this did not use similar and preferable methods for phenotyping, such as agnostic latent variable modeling, but relied on a simple splitting of the data on a single variable. The findings of all the studies found are summarized in Table 2.

Discussion

We have highlighted new and important findings contributing to our understanding of pain phenotypes in the past 3 years. In the literature on knee OA, this includes four studies that have added knowledge regarding longitudinal validation of pain phenotypes constructed with phenotypic domains other than pain that are highly stable over time; the existence of a pain susceptibility phenotype, defined by the presence of sensitivity to pressure pain thresholds and a lack of influence by psychosocial factors; the novelty and importance of movement-evoked pain supporting the association of positive QST findings with greater intensity and frequency of spontaneous pain; and the replication of a chronic pain phenotype in an independent data set. Interestingly, the chronic pain phenotype did not have the greatest pain severity when compared with a complex OA phenotype characterized by potentially greater inflammation locally and systemically. Finally, we reported on one study of people with hip OA in which both intermittent pain and constant pain were commonly present in the early stages of the disease, and higher pain intensity was associated with greater variability of pain. Most *pain* phenotyping studies have been cross-sectional and limited in their inclusion of different domains representing the multidimensional nature of pain (e.g., psychological and physical factors) or variables considered associated with, but not directly indicative of the pain experience (e.g., strength, comorbidities) [7]. The importance of including variables not directly associated with the pain experience is a topic of debate, particularly as their influence on pain phenotype creation is relatively unknown and it can be argued that they are surrogate markers (e.g., consequences of pain

Table 2. Summary of findings of recent articles on OA phenotypes

Study authors	Year	OA population	Novel findings
Cruz-Almeida	2017	Knee	Three phenotypes based on function and movement-evoked pain with increasing functional limitation and severity of movement evoked pain. Severity of phenotypes directly associated with severity of psychological factors and QST.
Dell'Isola	2018	Knee	Examined previous chronic pain phenotype found in a systematic review in an independent sample, and reported the new finding of a "complex OA phenotype," reflecting an overlap of several phenotypes, with greater pain severity
Carlesso	2019	Knee	Four knee pain susceptibility phenotypes defined using QST, psychological and physical factors in those who were free of persistent pain, and developed persistent pain 2 years later. Pain susceptibility phenotypes were predominantly differentiated by sensitivity to pressure pain thresholds.
Pan	2019	Knee	Three pain phenotypes identified in a population-based longitudinal cohort using multiple domains (demographics, psychological, lifestyle, comorbidities, and MRI) and correlated with WOMAC pain over 10 years, as well as widespread pain.
Teirlinck	2019	Hip	Subgrouping based on 6 weeks of daily pain ratings of those with high intensity or frequency of intermittent pain. Those with greater intensity had more frequent pain and greater peak values of pain. Findings were similar when repeated using constant pain.

or risk factors for pain), which may not properly represent the overall pain experience in OA. Some suggest that the heterogeneity of the disease would best be reflected by including multiple domains of OA such as clinical presentation, patterns of joint involvement, pathophysiology, prognosis, and possibly biomarkers [28], while others have opined that regardless of whether phenotypes are based on single or multiple domains, phenotypes are meaningful if they reflect differential treatment effects, prognosis or etiology [29]. The articles by Pan et al. and Carlesso et al. are reflective of these two lines of thought and demonstrate the utility of each respective approach but with two very different outcomes. Further, the two approaches address different research questions. One addressed which of a larger universe of factors could contribute to the OA pain experience, while the latter addressed factors other than structural pathology that have been broadly linked to pain that could provide insights into what may predispose certain individuals to develop persistent pain. As the literature on OA pain phenotypes is still in its infancy, greater understanding will occur as more studies are undertaken to help determine the efficacy of different approaches. Both of the above-mentioned articles can be considered to be hypothesis generating and require further validation in independent samples for hypothesis testing before proceeding to broader validation [30]. Given that OA is now understood to be a disease affecting the whole joint as an organ [4], an additional avenue to consider for future study of OA pain phenotypes is to identify and prioritize additional relevant domains that are most promising for multidimensional phenotyping of knee OA. An example of a relevant domain to combine with pain phenotyping is that of inflammation, as it has been linked with the experience of pain. For example, features of joint inflammation

(synovitis and effusion) have been reported as predictors for the development and possible worsening of sensitization [31]. However, inflammation in OA is a complex process that is impacted by aging, trauma, metabolism, and obesity, among others. Further, on a molecular level, multiple pro- and anti-inflammatory mediators are implicated in the pain process [32]. The complexity of multiple sources and mediators of inflammation would likely benefit from further study to help identify optimal variables prior to engaging in multidimensional phenotyping. We propose that logical next steps are to confirm the most important factors for inclusion in OA pain phenotypes through hypothesis testing and broad validation using approaches exemplified by Pan et al. and Carlesso et al., prior to embarking on multidimensional phenotyping with other (non-pain) domains, where heterogeneity regarding definitive characteristics is also an issue [7]. This approach can derive greater insights regarding pain itself through testing inclusion of non-pain domains in pain phenotyping work and comparing its ability to determine prognosis or treatment effects versus a conceptualization of a pain phenotype aligned with more typical pain-related domains. Again, the different approaches should be driven by the specific research question to be addressed. This evidence gained through validation can then serve as a strong foundation from which future OA phenotyping studies can benefit.

Pain variability and its relationship to movement is another area in which there is a paucity of studies and even fewer that have attempted to phenotype it accordingly. Attention has recently been on the related concept of "pain flares" for which definitions widely vary [33] and for which there are reported associations with activity [34–36]. Given that pain in OA is known to have poor correlations with structural damage [37] and to be both intermittent or constant in nature [27, 38], the importance of pain variability as it relates to movement or when spontaneously occurring is necessary to furthering understanding of pain as it relates to disease progression. Cruz-Almedia et al. have provided an initial step towards this with phenotyping of movement-evoked pain. They limited their phenotypes to the inclusion of physical performance tests and movement-evoked pain, demonstrating associations with QST and psychological factors. Given these initial results, future study of movement-evoked pain phenotypes could examine grouping all of these domains together with longitudinal examination of their relation to activity levels and disease progression, specifically their association with structural changes or inflammatory markers for which there is preliminary evidence with pain variability [39] Movement-evoked pain phenotypes could also provide insight into intermittent and constant pain and their underlying mechanisms, as well as greater clarity on the pain-function relationship.

Collectively, these studies have contributed new and important knowledge to our understanding of OA pain phenotypes. Validation of OA pain phenotypes longitudinally and replication in other datasets have been the missing elements in the literature. The use of a mechanism-based approach to pain assessment is supported by the demonstrated associations of QST with the development of persistent knee pain and with movement-evoked pain. Further approaches such as use of movement-evoked pain as an OA pain phenotype may provide greater understanding of pain variability and its correlates. For example, identifying phenotypes of those susceptible to pain or by movement-evoked pain may in the future allow pain management strategies to be tailored

to an individual's needs, with the aim of achieving better clinical outcomes. Significant challenges exist as external validation of any phenotype is required, and currently there are few datasets that are longitudinal with similar variables available for replication. Further, with the prominent importance of QST in many of the existing pain phenotypes, clinical feasibility is challenging without the development of easy-to-use QST measures or a validated questionnaire that is an adequate substitute. Both are currently unsupported but would facilitate testing whether mechanism-based approaches to pain management would result in better patient outcomes. The ultimate aim of such pain phenotyping exercises is to translate these insights into clinical practice. Ideally, we need to provide clinicians tools by which to identify which patients are at risk for worse pain and OA outcomes, and management strategies that can be tailored to address the underlying mechanisms operational in a given individual patient.

Compliance with Ethical Standards

Conflict of Interest

Dr. Neogi reports personal fees from Pfizer/Eli Lilly, personal fees from EMD Merck-Serono, and personal fees from Novartis, outside the submitted work. Dr. Carlesso declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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This population-based prospective longitudinal study is notable for its data spanning 10 years and its combined use of variables inside and outside the pain domain for phenotype creation. Three phenotypes characterized by varying levels of emotional problems and structural damage and their relation to pain severity and widespread pain over the study period are reported.

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This large prospective longitudinal community-based study is the first to examine knee pain susceptibility phenotypes using those free from knee pain. Employing a multidimensional representation of pain, four phenotypes were found that were largely dominated by pressure pain thresholds and temporal summation with a relative absence of psychosocial factors. The phenotypes with the largest degree of sensitization were twice as likely to develop incident persistent knee pain 2 years later.

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