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REVIEW

Clinical Assessment of Osteoarthritis Pain: Contemporary Scenario, Challenges, and Future Perspectives

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ABSTRACT

The multifaceted nature of osteoarthritis (OA) pain presents a challenge in understanding and managing the condition. The diverse pain experiences, progression rates, individual responses to treatments, and complex disease mechanisms contribute to heterogeneity in the clinical studies outcomes. The lack of a standardized methodology for assessing and classifying OA pain challenges healthcare practitioners. This complicates the establishment of universally applicable protocols or standardized guidelines for treatment. This article explores the heterogeneity observed in clinical studies evaluating OA pain treatments, highlighting the necessity for refined methodologies, personalized patient categorization, and consistent outcome measures. It discusses the role of the multidimensional nature of OA pain, underlying pain mechanisms, and other contributing factors to the heterogeneity in outcome measures. Addressing these variations is crucial to establishing a more consistent framework for evidence-based treatments and advancing care of the patient with OA pain.

Keywords: Osteoarthritis; Clinical studies; Chronic pain; Pain sensitization; Heterogeneity; Quality of life

Key Summary Points

Pain interventions can significantly improve osteoarthritis (OA) pain but with high heterogeneity between studies.

Factors such as pain complexity, subjective assessment, and the placebo effect contribute to observed heterogeneity.

The observed heterogeneity emphasizes a need for standardized methodologies and outcome measures.

OA pain's diversity requires categorizing patients based on pain phenotypes.

Holistic assessment of OA pain is required in clinical studies.

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disorder that causes pain, swelling, and stiffness. It can lead to instability and physical disability, thus impairing quality of life (QoL). Approximately 528 million individuals globally—a 113% rise since 1990—live with OA [1]. There is currently no known cure for OA. The pharmacological and non-pharmacological treatment approaches generally focus on pain relief and improved joint mobility. Several guidelines, including the American College of Rheumatology/Arthritis Foundation (ACR/AF) and the European League Against Rheumatism (EULAR), provide recommendations for managing OA pain but lack consistency [2–4]. This creates a challenge for healthcare professionals to find the best treatment. Smedslund et al. conducted a network meta-analysis of 445 randomized controlled trials assessing interventions for OA pain [5]. Interventions showed significant improvement in OA pain but with high heterogeneity between studies. Heterogeneity was attributed to the differences in study design, patient populations, measurement tools, and placebo effect.

OA pain is considered to be multifaceted and poorly understood (Fig. 1). The clinical presentation and underlying mechanisms of OA pain can vary widely among individuals [6]. To date, clinicians and researchers rely upon subjective observations to assess and infer the pain experienced by other people. However, the OA pain can be influenced by physiological, psychological (such as depression and catastrophizing), and demographic factors (like age, sex, and comorbidities), leading to significant variation in individuals' pain experience (Fig. 2) [7]. Furthermore, there is significant variability in the pain trajectory, as some individuals experience progression while others remain stable over several years [8]. Interestingly, the OA pain trajectory was found to be not correlated with the disease progression [9]. This raises the fundamental question of how the inherent subjectivity of OA pain can and should be addressed and integrated within its assessment. Thus, this review aims to comprehensively explore the reasons behind the variations in outcomes from clinical studies on OA pain. It discusses the role of the multidimensional nature of OA pain, underlying pain mechanisms, and other contributing factors to the heterogeneity in outcome measures. Moreover, the review also explores different methods that offer a glimpse into more precise and tailored pain assessment strategies.

METHODS

The databases Medline, Embase, and Google Scholar were searched for relevant studies using combinations of the following basic and medical subject heading terms: "osteoarthritis pain", "osteoarthritis pain assessment", "osteoarthritis pain phenotypes", "pain sensitivity", "osteoarthritis pain biomarkers", "real-world evidence", "heterogeneity", "clinical trials", and "placebo effect". The inclusion criteria targeted peer-reviewed original research articles and reviews with no timeline restriction, focusing on subjects suffering from osteoarthritis and associated pain. The selection criteria were limited to articles published in English language. On the other hand, case reports, editorials, and any article focusing on a condition other than osteoarthritis were excluded. Additionally, studies that did not provide specific outcomes related to osteoarthritis pain, presented incomplete data, or lacked clear methodology were also excluded, alongside non-English language studies. The primary literature articles were screened on the basis of title and abstract. Full text articles retrieved for the selected articles were further examined against the inclusion and exclusion criteria. The reference lists of retrieved articles were also screened for additional studies. Ethical approval was not required as the data used in this article were obtained from previously conducted studies and do not involve data generation in human participants or animal performed by any of the authors.

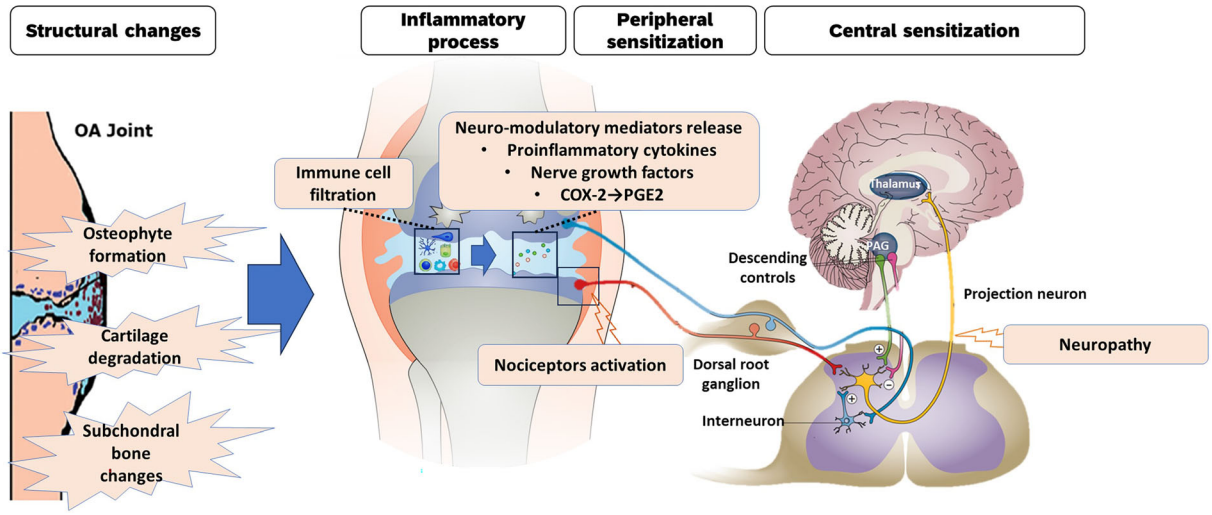


Fig. 1 The joint, densely innervated, primarily serves pain detection. Nociception arises from immediate tissue damage, triggering pain. Neuromodulatory mediators sensitize nociceptors, lowering pain receptor activation levels. Continuous nociceptor stimulation causes prolonged CNS pain circuit hyperactivity, termed central sensitization. This results in heightened neural activity, reduced activation levels, and widened pain perception. Additionally, somatosensory nervous system damage can lead to neuropathic pain, distinct from nociception [6]. *COX-2* cyclooxygenase-2, *PGE2* prostaglandin E2

Pain Characteristic of OA Is Multifaceted and Misunderstood

Complex Pathophysiological Pathways Are Involved in OA Pain

Based on the etiology and clinical presentation, studies have suggested three distinct dimensions related to the pain mechanisms involved, i.e., nociceptive, neuropathic, and nociplastic, consisting of the overlapping role of mechanical and inflammatory pathways [10]. The development of inflammation within the OA joints can be due to early cartilage degradation events [11]. Synovitis, overexpression of inflammatory mediators, and pain often predate the development of radiographic damage in OA [11, 12]. The joint is an organ with extensive innervation. The sensory innervation consists of nociceptors (derived from the Latin term "noxa", which means damage and receptors) that communicates pain signals to the central nervous system (CNS) and spinal cord. During OA, the sensitivity of the nociceptor increases (also referred to as peripheral sensitization), and nociception occurs even at a lower threshold and leads to physical limitations. The continuous stimulation of nociceptors leads to subsequent sensitization and possibly the development of neuropathic-like pain [13, 14]. Central sensitization causes receptive field enlargement, decreased activation thresholds, and increased spontaneous neuronal activity. Even outside the initial trigger zone, it presents as allodynia (perception of non-noxious stimuli as painful) and hyperalgesia (increased sensitivity to noxious stimuli). Increasing evidence suggests that the phenomenon of central sensitization is integral to OA pain [15].

Neuropathic pain refers to the pain as a consequence of a lesion or disease of the nerve fiber [16]. Following nerve injury, there is an enhanced expression of inflammatory mediators (Interleukin (IL)-1, IL-6, Tumor necrosis factor (TNF)-α) and non-neuronal cells like glia and immune cells [17]. Synovitis was found to be positively associated with the presence of neuropathic-like pain [18]. The prevalence of neuropathic pain in people with knee or hip OA can range from 20 to 41%, based on different scales [19]. Participants with neuropathic pain report higher pain levels and impaired function

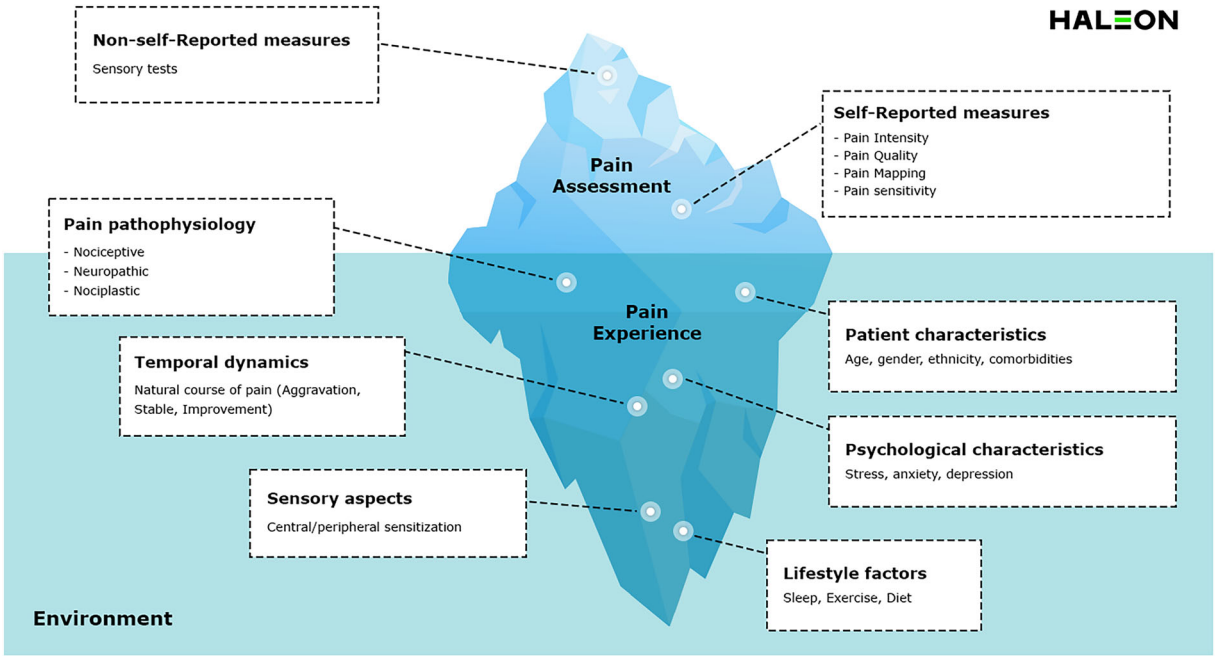


Fig. 2 The illustration highlights pain as a holistic experience, shaped by environmental and contextual factors, influencing how individuals respond to various assessment methods in research and practical settings. Although nearly universal, pain between subjects is highly variable, impacting pain assessment and management. The environment encompasses all aspects surrounding the individual in pain, including geography, seasons, and social aspects

[20]. The quality of the neuropathic pain is described as tingling, burning, and numbness [21, 22].

In addition to nociceptive and neuropathic pain, the International Association for the Study of Pain (IASP) introduced the term "nociplastic pain" as a third mechanistic pain descriptor [23]. The term was used to denote the sensitization that might occur without actual tissue damage of the somatosensory system (a requirement to fulfill the definition of neuropathic pain). Peripheral sensitization may have a role in nociplastic pain, even if central sensitization is most likely the dominant mechanism. Patients with OA, rheumatoid arthritis, and other nociceptive pain diseases have a high incidence of nociplastic pain states, such as fibromyalgia [5]. Patients with nociplastic pain might experience concurrent pain, which makes its management very challenging [24].

Pain Sensitization Is a Consequence of an Altered Pain Mechanism

Sensitization significantly contributes to pain and disability in the OA population [25, 26]. The significant inter-individual variability in the experience of pain can be a consequence of differences in pain sensitivity [27]. Within a particular subgroup of pain-sensitive OA patients, there are people with low degrees of radiographic OA but high self-reported pain intensities [9]. This could contribute to the poor correlation between pain severity and radiological OA classes. Also, studies have reported a correlation between higher pain sensitization and increased pain severity, persistent pain, disability, decreased QoL, poor prognosis post joint replacement, and less responsiveness to analgesics, but not to the duration of disease [15, 28–32]. As chronicity increases, central pain augmentation may become less dependent on peripheral nociceptive input. It is due to anatomical alterations in the CNS or long-

lasting functional changes brought about by epigenetic modification [33, 34]. Thus, OA patients with central sensitization might present with chronic, severe, and more extensive areas of pain, leading to reduced response to conventional analgesics [35].

Temporal Dynamics of OA Pain

Traditionally considered a condition prevalent among the elderly, OA is now being diagnosed at progressively younger ages, highlighting the necessity to address pain management effectively and safely over extended periods [36, 37]. This also increases the need to understand OA pain trajectory. The progression of OA pain is poorly understood, making it challenging to forecast a patient's prognosis and adequately assess the efficacy of the administered therapy [8]. Pain, initially receptive to analgesics, may transform in nature and develop into chronic, widespread, and difficult-to-treat characteristics as the disease progresses [17, 38]. Thus, the natural progression of OA pain is found to be variable and highly individual. A systematic review found high heterogeneity across studies assessing the course of OA pain and within study populations [39]. In some patients, the natural course of OA pain was aggravated, while in others, it remained stable or even improved. High baseline pain intensity, bilateral knee symptoms, and depression were significantly associated with this.

Patient Characteristics Can Also Impact Pain Perception

Certain personality traits or characteristics could influence how individuals perceive and cope with pain. Psychological elements like depression and anxiety may worsen pain [40]. A recent study found that patients with more significant emotional problems report consistently greater Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores and several painful sites and are at greater risk for total knee replacement, even with low structural damage [41]. Depression has been prospectively associated with increasing pain and OA patient's knee functioning, even though it has not been connected to the condition's structural course [42, 43]. Kolasinski et al. suggest that patients suffering from OA pain might also experience additional symptoms including mood disorders, such as depression and anxiety, altered sleep, chronic widespread pain, and impaired coping skills [3]. However, causal effects are complex because of the bidirectional relationships between psychological factors and pain [44].

Worse WOMAC scores include patients' poor physical health, high obesity, and comorbidities [45–47]. Obese OA patients with comorbid depression are susceptible to a more significant increase in cartilage degradation and pain severity [48]. People with OA experience worse pain and performance-based physical function when they have a higher comorbidity burden [44]. Diabetes, hypertension, and back pain are examples of concomitant cardiac diseases that may have varying effects on symptom severity [44]. Kloppenburg et al. also suggest that apart from disease localization and severity, comorbidities should also be considered in the management of hand OA [4].

Joint Pain Is More than Structural Damage

Currently, imaging-based methods that assess the joint's structural integrity are the mainstay for classifying OA patients according to the severity of the disease. However, studies have indicated a discrepancy between the degree of structural damage and the intensity of the pain [9]. For many patients, a higher degree of joint deterioration is generally associated with higher intensity of pain, but to what extent this correlation applies is not clear [30]. A systematic literature analysis reported a high variation in the number of individuals (15–81%) with radiographic knee OA who also had knee pain [49]. Furthermore, the structural changes most strongly correlated with pain were synovitis and bone marrow edema [12, 50]. In contrast, ligament tears, meniscal changes, bone cysts, and

Table 1 Correlation between joint structures assessed by MRI and OA pain (adapted from [105])

MRI features	Level of evidence
Cartilage defects	Conflicting
Meniscal lesion	Conflicting
Bone attrition	Conflicting
Osteophytes	Limited
Knee ligament abnormalities	Limited
Subchondral cysts	Limited
Effusion and synovitis	Moderate
Bone marrow lesion	Moderate

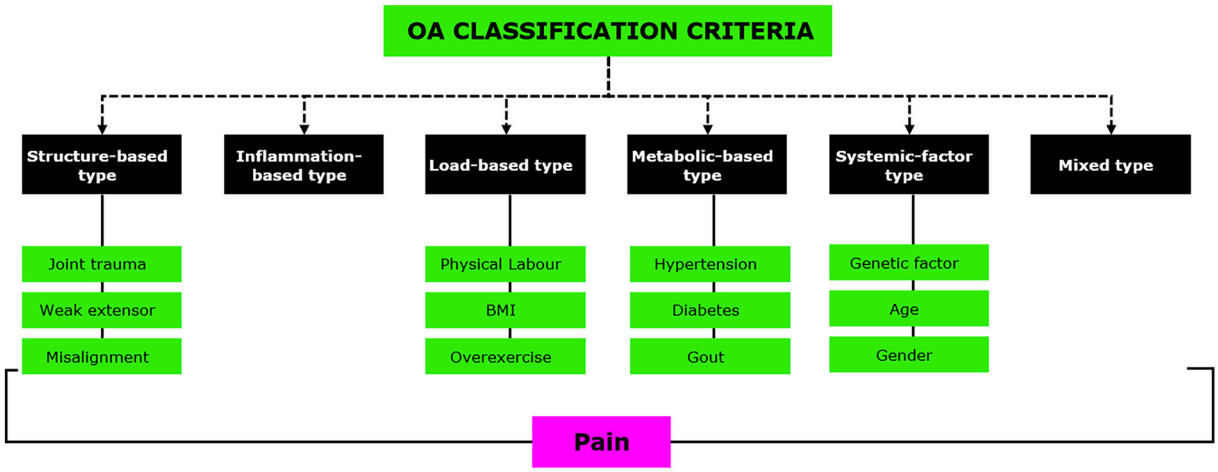


Fig. 3 Different phenotypes of OA. Osteoarthritis can be classified into different phenotypes based on the pathogenesis involved [106]. Structure-based OA: joint instability, structural abnormalities, injuries to bone/cartilage/ligaments/meniscus, and muscle weakness result from cartilage movement, contributing to biomechanical alterations. Inflammation-based OA: inflammatory mediators triggered by various inflammatory arthritis types impact synovial cells, causing synovitis and cartilage destruction. Load-based OA: arising from excessive joint load, occupation-related risks, physical activity, and high body weight, leading to stress on the joint and potential cartilage damage. Metabolic-based OA: stemming from metabolic disorders, hindering bone formation, and contributing to cartilage destruction. Systemic factor-based OA: incidence varies because of age, gender, and genetic factors, with unclear mechanistic pathways. Mixed type: associated with multiple factors discussed earlier, lacking a dominant factor

osteophytes were not associated with OA pain (Table 1). Recent studies have identified different clinical phenotypes of OA (Fig. 3). Cluster analyses have identified phenotypes across multiple dimensions, including psychological, biomechanical, biochemical, and clinical factors [51]. However, there is no consensus regarding specific OA subtypes. This indicates the need to consider factors beyond structural modification at the joint to segregate patients accordingly. The link between structural and functional results is complex, emphasizing the need for more precise criteria for classifying OA that consider pain detection.

Subjective Assessment of Pain Intensity Might Not Be Sufficient

Pain intensity in OA is commonly assessed using questionnaire-based techniques such as numerical rating (NRS), visual analog scales (VAS), and WOMAC pain subscale [52]. Losina et al. identified 287 registered studies on ClinicalTrals.gov investigating different interventions (pharmacological, behavioral, or surgical procedures/devices) on OA pain [53]; 68% of studies used VAS, while 50% used the WOMAC pain subscale to measure pain intensity. Gregori et al. performed a network meta-analysis of clinical trials conducting long-term (≥ 12 months) investigation of pharmacological intervention on OA pain [54]. WOMAC pain was the most often used outcome measure in 27 trials (64%), with VAS global knee pain coming in second with seven trials (17%) and another VAS measure of pain with eight trials (19%). ACR/AF sorted outcome measures assessing pain and function in hip and knee OA and established a hierarchy based on the published literature (Table 2) [3]. The list was created based on the responsiveness of the patient-reported outcomes. Scales based on a single item were downgraded if their validity and reliability were not established [3, 55].

Table 2 Hierarchy of clinical outcome measures for hip and knee OA based on the published literature [3]

Level	Pain outcome measures
1	WOMAC pain subscale (Likert/100 mm) or KOOS or HOOS
2	Pain during activity (VAS)
3	Pain during walking (VAS)
4	Global knee pain (VAS)
5	Pain at rest (VAS)
6	SF-36 (bodily pain subscale)
7	HAQ (pain subscale), Lequesne algofunctional index (pain subscale), AIMS (pain subscale), knee-specific pain scale, McGill pain questionnaire (pain intensity)
8	Pain at night (VAS), pain during activity (NRS), pain on walking (NRS), number of painful days (days)

AIMS Arthritis Impact Measurement Scale, *HAQ* Health Assessment Questionnaire, *HOOS* Hip Disability and Osteoarthritis Outcome Score, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *NRS* numerical rating scale, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

These questionnaire-based techniques are subjective and cannot provide sufficient information about the underlying pain mechanisms. Furthermore, the usefulness of subjective pain assessment scales is frequently questioned, mainly when used in isolation, as they do not capture the complexity of the pain experience [56–59]. The description of pain dimensions in OA has rarely been addressed [60]. Also, subjective pain scales, as the primary outcome in trials, may not allow optimal sensitivity to change [61]. A meta-epidemiological study of 28 clinical trials found lower assay sensitivity of subjective pain scale [62]. Trials using such scales are often susceptible to misinterpretation [63, 64]. Individuals may situationally overstate (to guarantee treatment) or underestimate (to evade social criticism) their pain, which can result in either an overtreatment of the pain or an undertreatment of the pain, both of which can lead to unfavorable outcomes [65–68]. Furthermore, appropriate assessments of OA pain intensity are complex over prolonged periods, considering the possibility of recall bias in patients with different pain trajectories, as it can vary considerably [69, 70].

The Powerful Placebo Effect in OA Pain

According to some meta-analyses, the extent of the placebo effect in randomized controlled trials of pain has grown over the past decade [71, 72]. It has long been assumed that the high placebo effect contributes to most non-significant OA trial results (Fig. 4) [73]. Placebo in such clinical trials can result in stiffness improvement of 83%, functional improvement

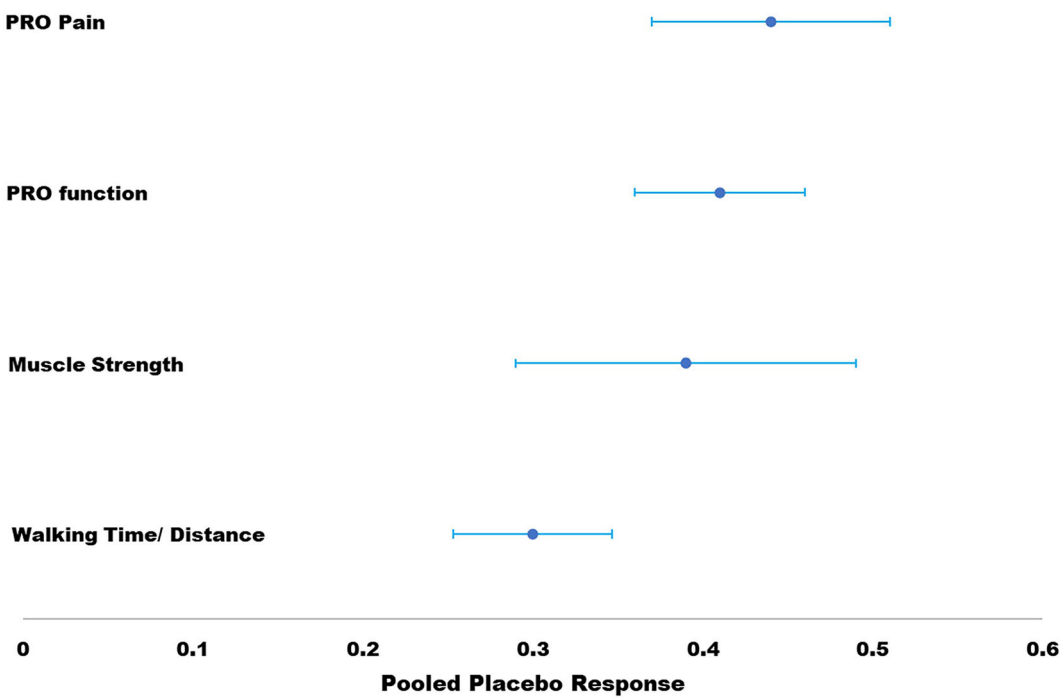


Fig. 4 The pooled placebo effect of each outcome measure from 21 clinical trials of OA on pharmacological interventions (the circle indicates the pooled mean, and the horizontal bar indicates standard deviation). Data were extracted from a meta-analysis conducted by Huang et al. [107]. The overall placebo effect was highest for the patient-reported outcomes (PRO) for pain and function

of 71%, and mean pain relief of 75% [74]. Wen et al. conducted a model-based meta-analysis to study the placebo effect in clinical trials on OA patients [75]. They discovered that the placebo effect was more pronounced in studies involving high-efficacy medications—such as acetaminophen, diacerein, and non-steroidal anti-inflammatory drugs—compared to studies involving low-efficacy medications, like herbal remedies. This effect was most noticeable in studies that used subjective pain scales compared to other parameters. The study also reported that the placebo effect was observed more in the studies with treatment duration < 8 weeks. Thus, to guide the design of OA clinical trials in the future, a comprehensive understanding of the placebo effect distribution and its affecting elements is needed.

Understanding Variability in Pain Experience Is Important

Assessment Should Be Based on Pain Phenotypes

Previous sections have discussed how multiple domains, such as peripheral, neurological, and psychological, can influence pain experience, making it difficult to assess. To enhance therapy goals and offer a more individualized approach to medicine, there has been a surge in interest in identifying OA phenotypes recently [76]. Our understanding around OA pain phenotype might be more clinically meaningful than structural changes. Pan et al. identified different types of pain experienced by considering various dimensions of pain, such as magnetic resonance imaging (MRI)-detected structural damage, body mass index (BMI), comorbidities, and psychological and neurological factors [41]. They identified three specific pain phenotypes categorized as individuals with a high

occurrence of emotional issues and low levels of structural damage (Class 1), those with an increased event of structural damage and low levels of emotional issues (Class 2), and individuals with low levels of both emotional issues and structural damage (Class 3). The study revealed that participants in Class 1 had more intense pain and a more significant number of painful areas over 10.7 years compared to those in Classes 2 and 3. According to Deveza et al. poor clinical outcomes were linked to radiographic severity, psychological distress, pain sensitization, muscle strength, inflammation, BMI, and comorbidities [77].

Distinct phenotypes could signify various subgroups that might respond more favorably to different forms of treatment. However, there is no consensus yet on OA pain phenotypes, as they were identified by cross-sectional studies. These studies were unable to confirm the stability of the identified phenotypes and assess whether these phenotypes are pertinent to clinical results, such as prognosis and responses to treatment. Furthermore, the precise etiology and mechanisms contributing to each phenotype need further elucidation.

Understanding Pain Trajectories Is Important

Investigating pain trajectories offers insights into the underlying mechanisms influencing pain fluctuations. Researchers and clinicians can utilize these trajectories as benchmarks for evaluating treatment effectiveness. Factors associated with the patient, such as lower educational attainment, increased comorbidities, and the presence of depression, have been identified with a substantial to moderate level of evidence as predictors indicating a more challenging pain trajectory [8]. Early intervention strategies can be employed for individuals at risk of worsening pain, mitigating the impact of the disease [70].

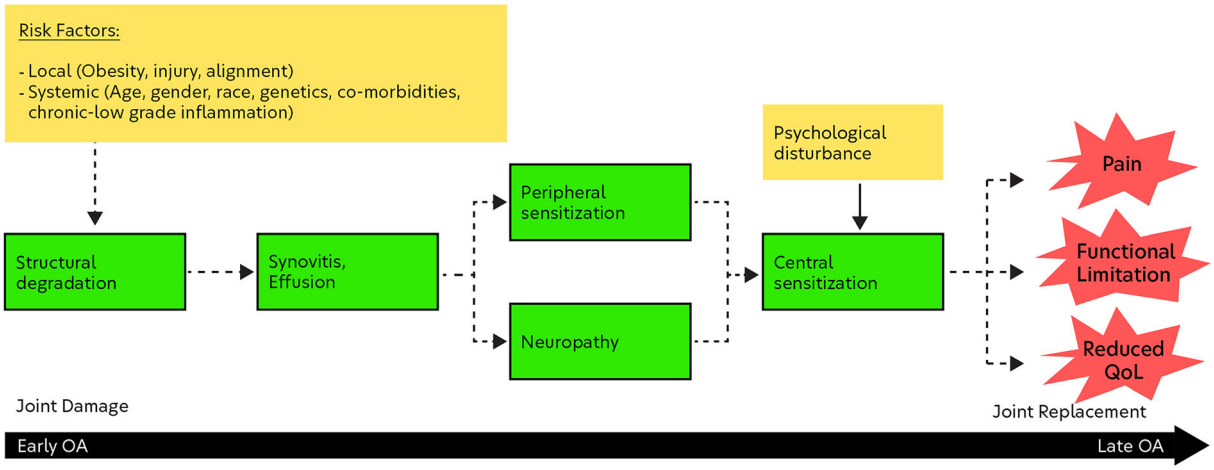
Exploring Real-World Databases for Understanding Pain Perception in OA Patients

Real-world evidence stems from varied sources like prescription data, insurance claims, patient registries (specific to diseases, medications, or medical devices), health records (including retrospective chart reviews and electronic health records), and patient-reported outcomes. These sources collectively contribute to real-world evidence for healthcare assessments. They aid in understanding pain experiences, patterns, and trends across populations. For example, the United Kingdom (UK) Biobank, a mixed-sex cohort in the UK, recruited 500,000 adults aged 40–69 between 2006 and 2010 [78]. It was created to provide a helpful resource for studying a wide range of critical chronic conditions of adulthood, such as OA. Data of half of the patients from UK Biobank who reported knee pain were hospital-diagnosed (N = 10,083) and self-reported (N = 12,658 cases) OA [79]. Meng et al. found several significant genetic correlations between knee pain and several educational phenotypes using UK biobank data [80]. Faber et al. reported that osteophyte but not joint space width is strongly associated with pain in patients with hip OA [81]. Incorporating real-world evidence in OA pain assessment can enhance understanding and potentially improve patient outcomes. Standardizing data and ensuring quality control are crucial for reliable findings across diverse databases and studies.

Holistic Assessment of OA Pain Is Required in Clinical Studies

Assessment of Multidimensional Aspects of OA Pain

Recent advancements in the field of research have led to the development of assessment tools and questionnaires that delve into various facets of OA pain, including pain severity, quality as well as patterns, functional limitations, psychological well-being, and quality of life. A DELPHI survey updating outcome measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) core domain set for clinical trials in OA reported 100% agreement for pain and physical function assessment and > 90% agreement for QoL and patient's global assessment of target joints [82]. Experts also recommended that OA clinical trials encompass cognitive function, fatigue, sleep, effects on family or caregivers, and psychosocial impacts as part of their evaluation criteria.



(a)

	Subjective Assessment	Sensory Tests	Biomarkers	Imaging Techniques
OA Risk factors	Clinical Assessments			
Structural Degradation	-	-	Adhesion molecules (sVCAM-1, sICAM-1); Cartilage/bone turnover (TIMP-1, CTX-II)	X-ray, MRI
Synovitis or effusion	-	-	Inflammatory markers (TNF-α); MMPS; Macrophage; Growth factors (VEGF, TGF-β2&3); PGs	US, X-ray, MRI
Neuropathy	painDETECT;LANSS	-	Growth factors (BDNF)	-
Peripheral Sensitization	-	QST	Protein biomarkers (CRPM)	-
Central Sensitization	CSI; MPQ	QST	Growth factors (BDNF)	fMRI
Psychological Disturbance	DASS; HAMA;HAMD;SF-36; MHI-5;PCS	-	-	-
Pain Intensity	NRS: VAS	-	Inflammatory cytokines, CRP, MMPs, Cartilage/bone turnover, macrophage markers	-
Pain Quality	ICOAP	-	-	-
Pain Localization	Pain Mapping	-	-	-
Functionality Limitation	WOMAC; AUSCAN; Gait analysis	-	-	-
Quality of Life	KOOS; HOOS	-	-	-

(b)

◀**Fig. 5** **A** Schematic flow chart depiction of OA pain pathway; **B** different clinical tools used to assess OA pain pathway at multiple steps. Green color denotes pathway-related characteristics, yellow color denotes patient-related characteristics, and red color denotes study outcomes. *AUSCAN* Australian/Canadian Osteoarthritis Hand Index, *CSI* Central Sensitisation Inventory, *CTX-II* C-terminal cross-linked telopeptide of type II collagen, *DASS* Depression Anxiety Stress Scales, *fMRI* functional magnetic resonance imaging, *HAMA* Hamilton Anxiety Rating Scale, *HAMD* Hamilton Depression Rating Scale, *HOOS* Hip Disability and Osteoarthritis Outcome Score, *ICOAP* the intermittent and constant pain score, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *LANSS* Leeds Assessment of Neuropathic Symptoms and Signs, *MHI-5* Mental Health Inventory-5, *MMP* matrix metalloproteinases, *MPQ* McGill Pain Questionnaire, *MRI* magnetic resonance imaging, *NRS* numerical rating scale, *PCS* pain catastrophizing scale, *PGs* prostaglandins, *QST* quantitative sensory testing, *SF-36* 36-Item Short Form Survey, *sICAM-1* soluble intercellular adhesion molecule-1, *sVCAM* circulating vascular cell adhesion molecule-1, *TGF-β* transforming growth factor-β, *TIMP-1* tissue inhibitor of metalloproteinases-1, *TNF-α* tumor necrosis factor α, *US* ultrasound, *VAS* visual analogue scale, *VEGF* vascular endothelial growth factor, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis

Experimental Assessments of Pain Sensitivity

Human quantitative and mechanical pain assessment instruments (e.g., Quantitative Sensory Testing; QST) offer possibilities for diagnosing OA patients' phenotypes and the corresponding level of sensitization (Fig. 5). Using regulated mechanical, chemical, electrical, vibratory sensory thresholds, and/or thermal test modalities, QST evaluates somatosensory evoked responses to noxious or benign stimuli [83]. The most used QST methods for detecting pain sensitization are pressure pain threshold (PPT), conditioned pain modulation (CPM), and temporal summation (TS) [84]. QST findings indicate that individuals reporting pain with neuropathic features displayed higher levels of TS. This heightened temporal summation suggests an increased activity of centrally mediated pain sensitization processes [85]. Also, studies revealed that as compared to control, knee OA patients usually have a lower PPT threshold [86], inefficient CPM [87], and facilitated TS [88], which supports the discriminant validity of QST. Numerous recent studies have proposed that QST measures are more strongly linked to the severity of pain experienced rather than the severity of OA itself [30].

Applicability of Biomarkers

Identifying specific biomarkers dedicated to pain can significantly assist in understanding the pathophysiology of pain. Biomarkers found in serum or synovial fluid, like cytokines and chemokines associated with inflammation in the nervous system, provide insights into the pathophysiology of OA and its diverse pain characteristics [89, 90]. Various biomarkers have been associated with different facets of OA pain, such as inflammatory markers, macrophage/immune markers, and cartilage/bone turnover markers, along with protein biomarkers, growth factors, and adhesion molecules (Fig. 5). These biomarkers show associations with various aspects of OA pain, including pain severity, pain during function, pain at rest, weight-bearing pain, and pain sensitization [91]. The levels of these biomarkers fluctuate in accordance with pain severity, with elevated levels associated with more severe pain while reduced levels of certain markers linked to increased pain severity [91].

Biomarkers are also associated with the changes in pain observed during the progression of OA. Early and late OA synovial tissue exhibits increased expression of inflammatory markers, suggesting inflammation's role in OA's onset and peripheral sensitization [92]. Brain-derived neurotrophic factor (BDNF) serum levels indicate centralization, while a rise in a C-reactive protein (CRP) metabolite corresponds to the degree of central sensitization [93, 94]. Both animal and human studies indicate that prostaglandin E2 induces nociceptor sensitization [95, 96]. While some studies have correlated biomarkers with pain severity or OA stage [91], few have directly associated biomarkers with specific pain types, sensitization, or centralization in OA. Further studies distinguishing between biomarkers related to various OA pain characteristics could facilitate

personalized treatment by combining markers with pain descriptions. This approach may lead to more precise strategies for managing OA pain.

Integrated Imaging Tools

Functional magnetic resonance imaging (fMRI) techniques integrated with other cutting-edge technologies are the most popular neuroimaging tools for recording brain activity linked to pain sensation and changes in pain perception. These techniques provide an essential extension to clinical, ultrastructural, and biochemical assessment of the perception and progression of pain. Sofat et al. revealed the presence of specific brain activity components in OA patients with pain that explained their symptoms [97]. In chronic hip OA, Gwilym et al. found that QST decreased the pain threshold and increased the activation of the thalamus, anterior cingulate, and insular cortex, three brain regions involved in processing pain [33].

Digital Data Can Provide Real-World Evidence for Better Research

Recent technological advancements have opened new avenues for measuring OA-associated pain using digital devices like wearables and smartphones. These tools not only aid in monitoring diseases and collecting health-related data but also present promising prospects for understanding pain variations on a day-to-day basis. For instance, Mardini et al. investigated the link between pain and movement in OA patients using the Real-time Online Assessment and Movement Monitor, revealing a temporal relationship between pain and mobility [98]. Participants reported daily average pain levels, with 40% reporting intensities $\geq$ 2. Another study equipped participants with a Huawei Watch 2 and the Knee OA Linking Activity and Pain (KOALAP) app, showcasing the feasibility of collecting patient-reported outcomes multiple times daily over a minimum of 3 months [99]. These smart tools are expected to capture pain fluctuations and help us to better understand their impact on life-space mobility.

Knee Pain Map

In OA, understanding the number of affected joints is crucial for understanding pain perception, likely influenced by centralized sensitization [100]. Mapping the location of OA pain is an effective method to monitor its development and spatial characteristics, transitioning from localized to diffuse. A knee pain map representing both knees enables patients to indicate the areas of discomfort [101]. Pain location can be classified as localized, regional, or disseminated. Thompson et al. noted that the knee pain map consistently shows remarkable reliability in repeated testing and demonstrates strong agreement among different subjects in identifying local and regional pain [102]. The knee pain map is user-friendly for patients to complete, yet it does not provide specific details regarding pain frequency and intensity.

CONCLUSION

Individual responses to the pharmacological effect of an analgesic might vary across different stages of OA development [103]. Thus, predicting pain intensity by structural changes could be feasible at an individual level, but it may not be reliable for the entire population. Structural, psychological, and neurological data play a crucial role in identifying different OA pain characteristics. For proper stratification of OA patients such factors must be considered, enabling a mechanism-based approach to pain management. Healthcare providers must consider factors beyond just the pain itself. However, clinical measurements (including pain sensitization), biochemical, and imaging dimensions have seldom been integrated in a single published analysis [54, 104].

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Declarations

Conflict of Interest. Vidhu Sethi is an employee of Haleon (formerly GSK Consumer Healthcare), Singapore. Oscar Della Pasqua is an employee of GSK, United Kingdom. Chetan Anand does not have any conflicts to declare.

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