

## Neuropathic pain in osteoarthritis: A review of pathophysiological mechanisms and implications for treatment



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### ABSTRACT

**Objectives:** Osteoarthritis (OA) is the leading cause of musculoskeletal pain and functional disability worldwide, affecting a growing number of individuals in the western society. Despite various conservative and interventional treatment approaches, the overall management of the condition is problematic, and pain—the major clinical problem of the disease—remains sub-optimally controlled. The objectives of this review are to present the pathophysiologic mechanisms underlying the complexity of pain in OA and to discuss the challenges for new treatment strategies aiming to translate experimental findings into daily clinical practice.

**Methods:** A narrative literature review of studies investigating the existence of a neuropathic component in OA pain was conducted. We searched PubMed, Embase and Scopus for English language publications. A hand-search of reference lists of relevant studies was also performed.

**Results:** Recent advances have shed additional light on the pathophysiology of osteoarthritic pain, highlighting the contribution of central pain pathways together with the sensitisation of peripheral joint receptors and changes of the nociceptive process induced by local joint inflammation and structural bone tissue changes. Thus, a neuropathic pain component may be predominant in individuals with minor joint changes but with high levels of pain refractory to analgesic treatment, providing an alternative explanation for osteoarthritic pain perception.

**Conclusion:** A growing amount of evidence suggests that the pain in OA has a neuropathic component in some patients. The deeper understanding of multiple mechanisms of OA pain has led to the use of centrally acting medicines that may have a benefit on alleviating osteoarthritic pain. The ineffective pain management and the increasing rates of disability associated with OA mandate for change in our treatment paradigm.

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### Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder, which refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. OA affects at least 50% of the elderly but also occurs in younger individuals usually following injury or rigorous physical activity, representing the leading cause of pain and disability worldwide [1]. The ageing of the population and the increasing prevalence of predisposing factors, such as obesity, in the western

and developing countries [2] are set to raise these figures over the next decades with adverse socioeconomic consequences, particularly in view of heightening the economic burden of OA in national health systems [3].

OA is a metabolically active repair process that takes place in all joint tissues and involves loss of cartilage and remodelling in the underlying bone. In the case of symptomatic disease, the process cannot compensate due to compromised repair potential or overwhelming trauma, resulting in continuing cartilage degradation, loss of tissue components and abnormal bone production mainly in the form of osteophytes [4]. OA can affect all the joints but it is far more common in the large weight-bearing joints, the spine and the hands. The disease is characterised by variability in clinical presentation and outcome, which can be observed between people as well as at different joints in the same person. Insidious residual

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and/or generalised joint pain is the most pertinent symptom, often accompanied by stiffness, joint deformity and loss of joint mobility, leading to limited movement and muscle weakness around arthritic joints [5]. It is the pain that drives patients to seek medical advice and usually associates with reduced functional ability [6]. However, the underlying causes of osteoarthritic pain remain poorly understood, as demonstrated by the failure of various pharmaceutical, physical and surgical treatment approaches to provide symptomatic relief and better quality of life to patients suffering with this condition [7].

This unmet clinical need highlights the complexity of OA-related pain mechanisms as there is currently no objective measurement, such as radiographs, ultrasound or magnetic resonance imaging, in which the extent of bone/cartilage damage or the intensity of synovial inflammation can predict the presence or the severity of pain [8]. Thus, it is not surprising that up to 40% of individuals with radiographic damage have no pain and patients with minimal and even non-radiographically detectable cartilage abnormality exhibit significant, debilitating pain [9]. On the other hand, in OA of the hands, patients with erosive changes report higher levels of discomfort and increased functional impairment compared to patients with non-erosive disease, suggesting that advanced tissue damage contributes to the severity of symptoms [10]. Better understanding of the so-called structure–symptom discordance has been achieved with recent studies employing novel design strategies. For example, Neogi et al. [11] compared radiographic abnormalities between two knees within the same patient who reported different levels of pain in the joints. This approach limits the impact of inter-individual characteristics, such as genetics, psychosocial factors, previous experience and current mood, which lead to subjective pain experience and contribute to variations of joint pain among patients with OA and comparable radiologic findings. They found a dose–response relationship between severity of radiographic knee OA with frequency, consistency and severity of knee pain. These observations concur with few other studies [12,13] suggesting that proper assessment of unmeasured and underestimated parameters that contribute to the natural variability of pain experience is of utmost importance for the identification of determinants of OA pain by avoiding inter-person confounding factors.

Osteoarthritic pain has long been considered as nociceptive pain caused by sensitisation of peripheral nerve terminals involving changes in joint nociceptors as well as activation of the nociceptive processing in the spinal cord, brain stem and thalamocortical system. However, since cartilage—the primary site of OA pathology—is an avascular and aneural tissue, other potential mechanisms such as joint inflammation, bone damage and, more importantly, central augmentation of pain perception have been proposed [14]. Several studies have reported the presence of hyperplasia [15], low thresholds for mechanical and thermal stimuli [16,17] and referred pain [18] in patients with OA, indicating a non-nociceptive pain component associated with abnormally excitable pain pathways in the peripheral and the central nervous systems. Despite great variability in recruitment practices, heterogeneity in studied populations and different pain outcome measurements, numerous publications support the notion that neuropathic pain mechanisms contribute to the pain experience for at least a subset of the OA population [19–23]. In this review, we discuss current concepts underlying the pathophysiology of pain perception in OA, mainly focusing on central amplification and the potential clinical implications of this hypothesis.

## Methods

A narrative review of studies investigating the existence of a neuropathic component in OA pain was carried out according to

published guidance on narrative reviews [24]. We searched PubMed, Embase and Scopus up to December 20, 2013. A combination of MeSH/Thesaurus terms and free-text terms was employed, including neuropathic pain, neuropathy, central sensitisation, osteoarthritis and rheumatic diseases. Studies were selected for inclusion if they examined the existence of neuropathy in osteoarthritis. The search was restricted to articles published in English. A hand-search of the reference lists of studies meeting the inclusion criteria was also performed.

## Peripheral pain mechanisms

OA has been described as a primary disorder of the cartilage, which is subjected to progressive accumulative wear and tear during lifetime. As the disease progresses, all tissues and structures of the joint can be affected, resulting in impaired joint mobility and increasing levels of pain. From the histological standpoint, OA is characterised by degradation of cartilage, bone lesions and mixed inflammatory infiltration that resembles rheumatoid synovitis quantitatively but not qualitatively. Whilst the role of mechanical loading in joint space narrowing and bone remodelling was known for decades, synovitis remained an under-appreciated phenomenon until recently, when the introduction of sensitive imaging modalities allowed the detection of subclinical joint inflammation in OA-affected hands, knees and hips [25,26]. Magnetic resonance imaging-based studies have identified structural abnormalities, predominantly large subchondral bone marrow lesions as well as synovitis and effusion, as predictors of pain in knee OA, providing a link between tissue damage and pain perception in this population [27]. Although the aetiology of synovitis has not been determined, inflammation triggers a cascade of events driven by inflammatory mediators, such as cytokines, chemokines, prostanoids, proteolytic enzymes and nerve and vascular growth factors—all of which are abundantly expressed in osteoarthritic joints—leading to enhanced cartilage turnover and matrix degradation. One potential recently proposed hypothesis suggests that OA is an auto-inflammatory disease during which traumatic and degenerative degradation of cartilage induces a reactive chondrocyte-mediated synthesis and release of pro-inflammatory mediators, which can cause pain and synovitis [28].

Regardless of the underlying mechanisms, inflammatory processes activate peripheral nociceptors that innervate the synovial capsule, periarticular ligaments, periosteum and subchondral bone, contributing to peripheral sensitisation and hyperexcitability of nociceptive neurons in the central nervous system [14]. Chronic synovitis is associated with marked changes in the central connexions of sensory nerves and changes in their synthesis and release of neurotransmitters and neuromodulators [29]. The magnitude of inflammation is related to the clinical manifestations, as pain in knee OA fluctuates in cases of refractory synovitis accompanied by recurrent effusions and bone marrow oedema in magnetic resonance imaging [30]. Stimulation of primary sensory neurons is further promoted by neovascularisation of the articular cartilage mediated by hypoxia and production of angiogenic growth factors by activated immune and endothelial cells in the inflamed synovium. The formation and the innervation of these vessels are important pathophysiological pathways causing the deep joint pain described by some OA patients even when the inflammation has subsided [31]. Angiogenesis perpetuates chondrocyte hypertrophy, endochondral ossification and osteophyte formation in the richly vascularised and innervated osteochondral junction, contributing to the exaggeration of pain. Finally, pain in the affected joints is also precipitated by periosteum irritation caused by abnormal bone formation, subchondral microfractures and cysts, bone marrow lesions and localised bone ischaemia due to elevated intraosseous pressure [32].

While both mechanopathology and inflammation participate in OA pain experience, their precise contribution may vary from time to time and from individual to individual. In addition, they are not sufficient to explain the disparity between the degree of pain perception and the joint damage in a significant proportion of patients, indicating that OA pain is multidimensional in its nature and mediated by multiple factors. In that respect, the role of central pain processing pathways has attracted the interest of rheumatologists and pain specialists, and recent advances in this field have provided a different point of view in the aetiology and management of pain in this population.

### Physiology of neuropathic pain

Neuropathic pain is a highly complex clinical situation and has been an enigma for the pain specialists for years, being difficult to diagnose and manage. This term was introduced by IASP's pain terminology in the year 1994 and was redefined in 2008 as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system" as proposed by a consensus conference [33]. In contrast to inflammatory or nociceptive pain, which is caused by actual tissue damage or potentially tissue-damaging stimuli, neuropathic pain is produced by damage to the peripheral or the central nervous system. Accordingly, this can be peripheral neuropathic pain or central neuropathic pain (depending on the site of lesion/dysfunction).

To understand why neuropathic pain is so complex in its origin and progress, we have to recognise the normal nociceptive pain transmission. Noxious stimuli like heat, chemicals, inflammation and pressure activate nociceptors, such as acid-sensing ion

channels (ASIC) and prostaglandin receptors. This leads to influx of sodium and calcium ions, resulting in depolarisation of the neurons. When the threshold limit is reached, this depolarisation is carried up to the cell body (situated in the dorsal root ganglion) and then transmitted to the dorsal horn within the spinal cord. Here, the neurons discharge neurotransmitters (mainly substance P and glutamate) into the synaptic cleft, which in turn depolarises the postsynaptic neurons and has both excitatory and inhibitory interneuronal effects. The depolarisation is then transmitted to higher centres in the brain by the ascending tracts, where it is processed as the experience of pain. The higher centres may then send excitatory or inhibitory signals back to the dorsal horn by the descending pathways.

The scenario is very different in neuropathic pain, and multiple alterations occur following damage to a sensory nerve. There can be peripheral disturbances causing abnormal impulse generation and transmission or/and central disturbances, causing abnormal processing of the information and abnormal excitability (Fig. 1).

#### Peripheral disturbances

In dysfunctional nerve fibres, ectopic impulse generation occurs from multiple sites (axons, neuromas and dorsal root ganglia) [34–36]. These ectopic sites are responsible for spontaneous discharge as well as amplification of nerve impulses (resulting in hyperalgesia and allodynia) [37]. The mechanism underlying this ectopic impulse generation is believed to be increased expression of voltage-gated sodium channels (Fig. 2) [38]. A further mechanism is cross excitation, when after an injured neuron starts to regenerate, new links between adjacent neurons develop (which were previously not connected). This phenomenon, known as

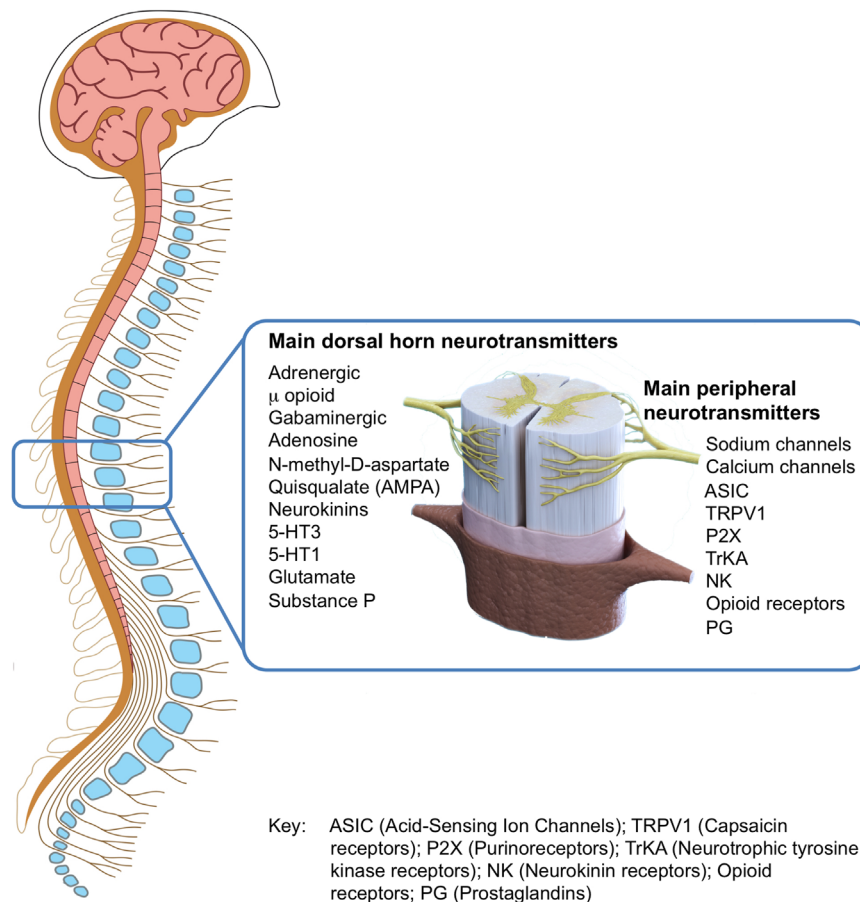


Fig. 1. Outline of main neuropathic pain neurotransmitters.

### Normal sensory function

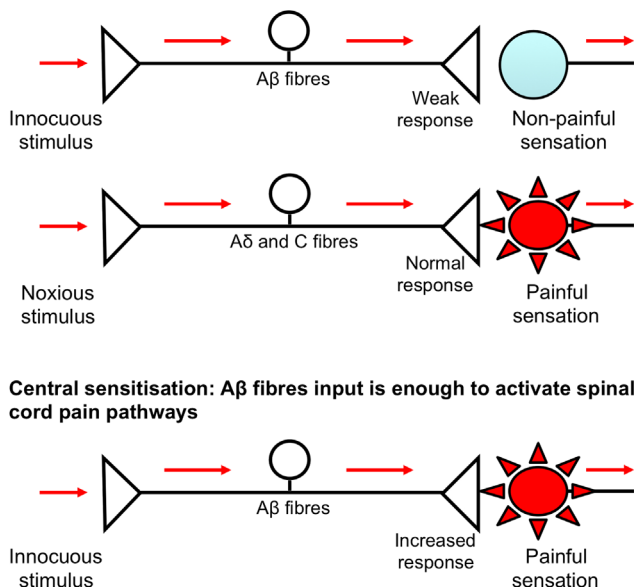


Fig. 2. Outline of pain transmission.

“sprouting” or “ephaptic cross talk” [35], can also take place at the dorsal horn. Loss of myelination and matrix metalloproteinase (MMP) activity [39] is believed to be the basis for this. The  $\alpha 2\delta 1$  subunit of the voltage-gated calcium channels is responsible for the neurotransmitter release at presynaptic terminals. Following a nerve injury, this is up-regulated in DRG cells, resulting in augmented release of neurotransmitters [40]. After a nerve injury, the abundance of immune and inflammatory mediators (catecholamine, prostaglandins, histamine, serotonin, TNF, cytokines and ATP) causes nociceptor sensitisation. This may be related to tissue inflammatory response. The up-regulation of voltage-gated sodium channels may also have a role in the sensitisation [41]. Studies have shown the number and function of GABA receptors to be diminished after nerve injury, which contributes to decrease of inhibition at the dorsal horn, resulting in hyperalgesia [42].

### Central disturbances

Central sensitisation signifies synaptic plasticity within the dorsal horn. Ectopic impulses can also be generated from affected neurons in the central nervous system, which may again be attributed to increased expression of sodium channels. The dorsal horn, which is the central point in modulation of normal pain, is sensitised, resulting in “secondary hyperalgesia” (broadening of the hyperalgesic area) [43]. The NMDA receptors play a vital role in this process. The abnormal stimulation of primary afferent neurons leads to increased release of neurotransmitters, such as glutamate, and activates the NMDA receptors in the dorsal horn. Activated NMDA receptors cause calcium influx, resulting in a phenomenon called “windup.” This is an exaggerated response to a given stimuli and encompasses prolonged depolarisation of the dorsal horn neuron, altered gene expression [44], causing increased excitability of these neurons. The NMDA receptor activation may also have a role in suppression of the inhibitory neurons augmenting the hyperexcitability state. The glial cells secrete inflammatory mediators that contribute to sensitisation of the spinal neurons [45], furthering the relationship between inflammatory response and central sensitisation.

The other important mechanism in central sensitisation is the up-regulation of cyclooxygenase [46] and purinergic P2X3 receptors [47]. The purinergic receptor P2X4 has been associated with

IL-1 $\beta$  secretion, which has a significant role in osteoarthritis. New studies have also found a causal relationship between P2X4 and MMP-3, MMP-9 production [48]. The MMP family is involved in the breakdown of extracellular matrix and during tissue remodeling processes, such as embryonic development and reproduction, as well as in disease processes, such as arthritis and tumour metastasis. The genetic variability in pore formation by P2X7Rs is found to be a key determinant of the differences in experimentally induced pain in mice and in chronic pain conditions in humans. Studies on P2X7R-deleted mutant mice and after pharmacological blockade of the same receptor have shown reduced pain sensitivity, which suggests a role for P2X7R in chronic pain behaviours. P2X7R-induced pore formation initiates various effects, which may mediate pain hypersensitivity, including the release of molecules such as interleukin 1 $\beta$  and ATP from microglia or macrophages [49].

Central sensitisation accentuates the pain caused by ectopic foci or sensitised nociceptors. The descending pain pathways arise from peri-aqueductal grey (PAG) and rostro-ventral medulla (RVM), which are the centre for modulation of the pain signals from the periphery (Fig. 3) [50]. Studies have shown the area in the PAG to be aberrant in humans with chronic pain. This is accompanied by reduction in the descending inhibitory control and enhanced facilitation of the pain signal transmission via the RVM [51,52]. Synaptic plasticity is also seen in higher brain centres, proven by human imaging studies [53]. Current studies now focus

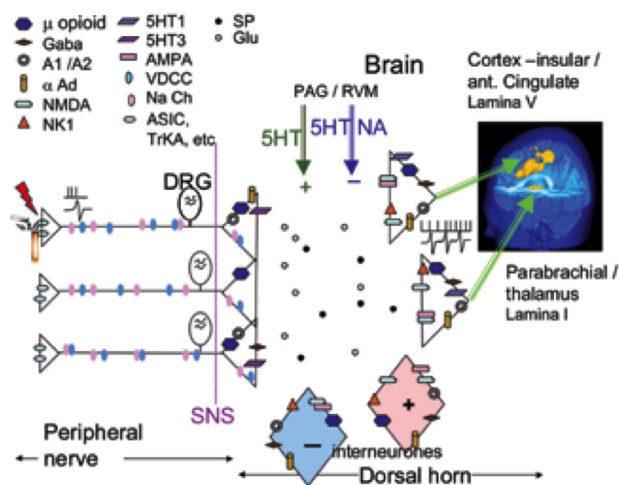


Fig. 3. Normal acute noxious input from the periphery, through the dorsal horn to the brain. From the left, noxious stimuli, such as heat, chemical or mechanical injury, are transduced via specific receptors, namely temperature-coding receptors, acid-sensing ion channels (ASIC), tyrosine kinase (TrkA) (inflammation) or pressure receptors. Transduction allows a flow of positive ions into the cell, which causes depolarisation and action potentials. This is transmitted along the neuron via sodium (NaCh)- and voltage-gated calcium (VDCC) channels to the dorsal root ganglion (DRG) and the dorsal horn. The sympathetic nervous system (SNS) lies close to the DRGs but is unaffected in acute noxious transmission. In the dorsal horn, extensive modulation of the input can occur. Neurotransmitters such as substance P (SP) or glutamate (Glu) amongst others are released from the primary afferent and diffuse across the synapse. An array of receptors can be triggered, including N-methyl D-aspartate (NMDA),  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), neurokinin 1 (NK1) and adenosine (A1/A2). Other neurotransmitters are also released either locally, such as enkephalins ( $\mu$  opioid receptor) and gamma-aminobutyric acid (GABA), which are inhibitory, or via descending pathways, such as noradrenalin ( $\alpha$  Ad receptor) and serotonin (5HT1 or 3 receptors). The overall modulated signal (either increased or decreased) is transmitted to the brain via ascending pathways to the CNS. This is presented simplistically as 2 ascending pathways: the spinothalamic from lamina V leading to the cortex and the parabrachial from lamina I leading to the hypothalamic areas. Descending pathways arise from the brain and pass through the peri-aqueductal grey (PAG) and rostro-ventral medulla (RVM) areas before terminating in the dorsal horn. (Adapted with permission from Urch [50].)

**Table 1**  
Studies suggesting a neuropathic component in OA pain

References	Type of study	Model or intervention	Participants	Results	Conclusion
Chappell et al. [68]	Randomised controlled study	Duloxetine vs placebo	Patients with knee OA, mean age of 61.9 years (placebo) vs 63.2 years (duloxetine) and average duration of OA symptoms of 6.7 (placebo) and 8.1 years (duloxetine). A total of 111 (86.7%) in the placebo group and 93 (72.7%) in the duloxetine group completed the study.	Patients treated with duloxetine had significant ( $p \leq 0.001$ ) greater improvement at all time points on BPI average pain and on BPI pain severity ratings ( $p \leq 0.05$ ), WOMAC total ( $p = 0.044$ ) and physical functioning scores ( $p = 0.016$ ) at the study end point.	Duloxetine led to significant pain reduction and improved function in patients with pain due to osteoarthritis of the knee.
Duarte et al. [21]	Cohort study	Intravenous lignocaine	A total of 28 patients with generalised OA, mean age of 59 years and average duration of symptoms of 8 years.	Pain intensity ( $p < 0.001$ ), pain relief ( $p < 0.003$ ) and mobility ( $p < 0.003$ ) significantly improved after administration of intravenous lignocaine. Mean clinical improvement was $30.2 \pm 21.4\%$ .	The results observed suggest that part of the pain mechanism in OA patients may be neuropathic and appears to contribute significantly to the patients' pain.
Harvey and Dickenson [69]	Basic science	Monosodium iodoacetate OA mice model	–	Significant mechanical hypersensitivity was observed in the ipsilateral hind paw in MIA-injected mice ( $p < 0.05$ ). Electrically evoked dorsal horn neuronal responses in MIA-injected mice were significantly elevated ( $p < 0.05$ ) with respect to A- and C-fibre firing, input, pinch and noxious von Frey.	Changes in behavioural measures and neuronal activity suggest that central changes are involved in this pain state, although a role for peripheral drives is also likely.
Hawker et al. [70]	Qualitative study	–	A total of 143 participants (52 hip OA; 91 knee OA) with a mean age of 69.5 years and median duration of symptoms of 6 years (hip) and 12 years (knee).	Several participants used descriptors suggestive of neuropathic pain (e.g., pins and needles, numbness and burning pain) to characterise their hip or knee OA pain.	The results suggest that patients with OA may experience pain due to both nociceptive and neuropathic mechanisms to varying degrees. If so, elicitation of such pain characteristics may identify patients who might benefit from neuropathic pain medications.
Hochman et al. [23]	Qualitative study	–	A total of 80 participants with knee OA with a mean age of 69.6 years and a median duration of OA symptoms of 12 years.	The proportion of participants who used neuropathic descriptors was 0.34 (95% confidence interval: 0.24–0.45).	Further elucidation of the role of neuropathic pain in OA may lead to improved mechanism-based pharmacologic treatment, which will result in reduced pain and disability and improved quality of life for people with OA.
Hochman et al. [71]	Cohort study	–	A total of 171 participants with knee OA with a mean age of 76 years and OA symptom duration of at least 10 years.	Overall, 28% of patients had neuropathic pain symptoms on a modified painDETECT questionnaire (19% among those without neurological conditions).	Among older adults with chronic symptomatic knee OA, over one-quarter had neuropathic pain symptoms localised to their knees using a modified painDETECT questionnaire.
Im et al. [72]	Basic science	Monosodium iodoacetate OA rat model	–	The comparison of several OA animal models and neuropathic pain models reveals that OA pain pathways may, at least in part, overlap with neuropathic pain mechanisms.	The results from this study suggest a mechanistic overlap between OA-induced pain and neuropathic pain.
Ivanavicius et al. [73]	Basic science	Monosodium iodoacetate OA rat model	–	Significantly increased ATF-3 immunoreactivity following MIA treatment was measured in L5 on days 8 and 14 ( $p < 0.05$ ), compared to saline controls.	The results suggest that this model of OA is associated with an early-phase neuropathy in the L5 innervation territory of the knee.
Ohtori et al. [20]	Cohort study	–	A total of 92 patients with a mean age of 70.3 years and average duration of knee OA symptoms of 37.5 months.	Using the painDETECT questionnaire, at least 5.4% of knee OA patients were likely to have neuropathic pain and 15.2% possibly had neuropathic pain.	Neuropathic pain tended to be seen in patients with less joint fluid and a Kellgren–Lawrence (KL) severity classification grade that corresponds to late stages of OA.
Shigemura et al. [74]	Cohort study	–	A total of 135 hip OA participants with a mean age of 58 years.	Based on the painDETECT questionnaire, 8 (5.9%) were classified as likely to have neuropathic pain and 17 (12.6%) as possibly having neuropathic pain.	The results suggest that in a certain percentage of patients, the mechanism of hip OA pain is predominantly neuropathic in origin.

**Table 1** (continued)

References	Type of study	Model or intervention	Participants	Results	Conclusion
Valdes et al. [19]	Cohort study	–	A total of 139 participants with knee OA with a mean age of 64.7 years (females) and 62.6 years (males) and duration of symptoms for 10.9 years (females) and 10.3 years (males).	Based on the painDETECT questionnaire 33.8% had scores corresponding to possible neuropathic pain and 14.8% had scores that correspond to likely neuropathic pain.	Neuropathic pain symptoms are highly prevalent in patients with clinically severe, painful OA and a significant contributor to decreased quality of life and higher pain intensity.

on the anterior cingulate cortex, an area of brain associated with the affective component of pain.

#### *Role of non-neuronal cell and inflammatory mediators*

Following nerve injury, there is enhanced expression and release of cytokines such as IL-1, IL-6 and TNF, which may alter both pre- and post-synaptic function [54]. There is an abnormal release of substance P from low-threshold A $\beta$  afferents after injury [55]. The synaptic plasticity has been attributed to be the result of multiple ligand–receptor interactions. They include NMDA, AMPA, mGluR receptors, BDNF and its receptor EphBR and substance P and its receptor NK1 [56].

Recent studies have led to the finding that non-neuronal cells, like glia and immune cells, have a significant role in neuropathic pain development. In experimental studies, it has been observed that in peripheral neuropathies (following injury or disease process), the Langerhans cells present in the epidermis become activated [57]. The neutrophils, lymphocytes and macrophages move to the site of injury (chemotaxis) [58] and to the distal end of the nerve where Wallerian degeneration is taking place. This immune response is initiated by the signals released by damaged axons and Schwann cells. Macrophages and neutrophils infiltrate the DRG [59] and the satellite cells adjacent to the cell body of DRG cells proliferate [60]. Inside the dorsal horn, the glial cells proliferate and undergo morphological changes. This involves hypertrophy of the cell body and retraction of their processes [61]. There is subsequent proliferation of astrocytes and lymphocyte infiltration. This microgliosis seems to be extending to higher centres like the brain stem and the thalamus. Interestingly, chemotherapy-induced neuropathy has been found not to evoke this microglial response (in contrast to traumatic neuropathy).

Emerging evidence demonstrates that the immune response contributes to the generation of neuropathic pain. The immune and glial cells can sensitise the nociceptive signal process by releasing IL-1, IL-6, TNF, chemokines, BDNF and purines. These mediators, while directly sensitising the primary afferents [62] in the periphery, also influence the central nervous system. Here, they increase the excitatory and reduce the inhibitory transmission [54] and enhance the descending facilitation [63]. The BDNF released from the glial cells can reduce the inhibitory effects of the neurotransmitter GABA [64].

These findings have opened up new avenues of research to find alternate modes of managing neuropathic pain. But it needs to be remembered that although there is a pro-inflammatory unhelpful component to the immune and glial response, this is an essential reparative process after neural injury.

#### **Neuropathic pain in OA**

In patients with osteoarthritis, the most prominent symptom is chronic pain. Management of pain in this cohort of patients is still disappointing. Hence the recent quest for understanding the

mechanism of OA pain. Several studies have suggested a neuropathic component in the pain of OA (Table 1). Research for pain in OA most often involves intra-articular injection of substances, such as monoiodoacetate (MIA), though some have been carried out with surgical models.

The complex changes of osteoarthritis normally take several decades to develop with influences from various genetic and environmental factors. To fully understand the complex inter-relationship between the different disease mechanisms, joint tissues and body systems, studying OA in animal models is necessary [65]. The use of models can exhibit many of the pathologic features that characterise the human disease. In vitro studies have proven invaluable in defining specific molecular and cellular events in degradation of joint tissues such as cartilage. But despite numerous available animal models for OA, there is no gold-standard model that can definitively represent human aetiology and pathophysiology. The limitations in using animal models are mostly due to differences in anatomy, dimensions, biomechanics, cartilage repair processes and cartilage thickness between animal and human joints [66]. There may be genetic differences present between the species used in the animal models and humans that will alter the pathology of the OA disease process. In addition, the efficacy of drugs may not accurately reflect the efficacy observed in humans.

OA models have been induced by different methods in a variety of animal species [67]. These include spontaneous–progressive worsening of disease associated with age or obesity (guinea pig and mouse); surgical instability–surgical destabilisation of the various ligaments/meniscus (rat, dog, rabbit, sheep, horse and guinea pig); collagenase-induced osteoarthritis (mouse) and post-inflammatory arthropathies induced by intra-articular injection of agents like MIA, Kaolin and Na urate (rat, mouse, cat, parrot and guinea pig). Mouse is used in most studies because this species offers the potential to use GM animals, an approach that helps our understanding of the molecular mechanisms of OA initiation and progression.

It needs to be remembered that the molecular mechanisms of both joint structural damage and pain may be distinct in animal models of OA induced or initiated by different means. This suggests the need to continue using multiple OA animal models but that the subsequent interpretation of the data and its extrapolation to the human condition must be more precise.

#### *Animal models*

The intra-articular injection of MIA into rat knee joints causes disruption in cartilage glucose metabolism. This leads to chondrocyte death and subchondral bone lesions. There is extensive neovascularisation, subchondral bone collapse with replacement by fibrous tissue and trabecular bone. All this takes a few days to develop [75]. This is in contrast to the slowly developing idiopathic human OA model [72]. The amount of sensitisation of afferent

nerves from the joint is proportional to the MIA dose. There is also evidence for ongoing pain in the MIA model [76].

Surgically induced changes are similar to those occurring naturally with aging [77]. These models usually have rapid and severe cartilage degeneration after the instability is created [78]. The first signs of hyperalgesia may appear after a few weeks [79]. Pain may be difficult to detect as initially there are no pain-related behavioural changes apart from allodynia [80].

In the MIA model, a proportion of neurons in the DRG expressed ATF-3 immunoreactivity, which is a marker of neuronal injury, suggesting development of neuropathic pain [73]. There is also up-regulation of galanin and neuropeptide Y and down-regulation of substance P and CGRP in the DRG neurons, which again is a replica of neuropathic finding [72]. Furthermore, there is spinal microglial activation, suggesting a neuropathic component. Nerve growth factor (NGF) has been the target in most clinical studies recently. NGF is essential for the development of structural and functional integrity in the nociceptors. It enhances the neuronal current through the TRPV channels and reduces the threshold of thermal excitation. Long-term exposure to NGF increases the expression of TRPV1, bradykinin receptors and purinergic P2X receptors as well as synthesis of substance P and CGRP in DRG neurons. NGF also stimulates the inflammatory cells to release inflammatory compounds. Orita et al. [81] found NGF to be raised in the late phase in addition to raised TNF and IL-6 in the first phase of a MIA model.

#### *Human studies*

The disruption in cartilage glucose metabolism leading to chondrocyte death and subchondral bone lesions observed in MIA models is consistent with the pathologic changes seen in OA in humans [82].

During the initial stages of OA, pain in joints is intermittent; occurs during movements and loading of the joint and may be evoked by specific activities (mechanical hyperalgesia). During later stages, constant resting pain may occur associated with depressive symptoms and sleep disorder [83]. Inflammatory mediators, like IL-6 and TNF, may cause this initial mechanical hyperalgesia. Inflammation of the affected joints initially sensitises the joint nociceptors towards mechanical stimuli. This mechanosensitisation is caused by classical inflammatory mediators like cytokines and prostaglandins [84]. In humans with moderate to severe OA, injections of Tanezumab (monoclonal Ab against NGF) resulted in persistent pain relief for 56 weeks [85].

Nociceptor input from chemokines and pro-inflammatory cytokines can induce both peripheral and central nerve sensitisation. Primary hyperalgesia occurs in the periphery, where both specific and polymodal nociceptors show altered thresholds, which can be observed by quantitative sensory testing [86]. Secondary hyperalgesia occurs within the central nervous system (CNS) and is the prelude to central sensitisation. Both neural and glial elements of the CNS at such sites as sensory cortex, hypothalamus and mid-brain, together with the dorsal horn of the spinal cord, show changes of central sensitisation that modulate afferent nociceptive input and contribute to neuropathic pain. Tactile allodynia, pressure hyperalgesia and increased temporal summation are found symmetrically in the periphery, and secondary changes in brain activity can be detected by electrophysiological or imaging techniques [87].

#### *Central sensitisation*

It is common for the neurons to be hyper-excitable during the state of central sensitisation, resulting in amplification of the painful sensations. There is a state of hyperexcitability of neurons

from the inflamed joints. Along with lowering of the excitation threshold, there seems to be increased response to stimuli from a greater area around the joint. The patients of advanced OA report pain from an extensive area, which may be away from the affected joint. This is a common phenomenon known as secondary hyperalgesia seen in neuropathic pain with central sensitisation. Another indicator of central sensitisation is hyperpathia (increased pain score upon repetitive stimulation), which is again a common feature of neuropathic pain [17]. There is enhanced release of substance P and CGRP (seen in MIA and surgical model) from the sensitised nociceptors [88] as well as activated microglia [81] (MIA model), both of which are seen typically in neuropathic pain. The descending inhibitory pathway seems to be incapacitated in patients with severe OA pain, but reestablished after surgical replacement [89].

Functional imaging of patients with hip OA has shown amplified activation of PAG in the brain stem during cutaneous stimulation of referred painful areas [87]. This again supports the theory of central sensitisation in patients with long-term OA. In other imaging studies of the brain, the cortical pain matrix is seen to be activated during arthritis [90].

A recent study by Hochman et al. [71] using the modified painDETECT questionnaire has demonstrated that OA pain occurs along with pain at other sites and neurological disturbance. A similar study reiterated the neuropathic component in patients with OA of the hip joint [74]. A study using the painDETECT, VAS, WOMAC, KL grading of OA and measurement of joint fluid identified 5.4% patients with OA as having neuropathic pain and 15.2% as possibly having neuropathic pain, which coexists with less joint fluid and advanced KL grade [20].

Pain in knee OA fluctuates with changes of bone marrow lesions and synovitis. Zhang et al. [30] have found the pain severity to be related to worsening synovitis and effusions. The fact that there is discordance between radiographic finding of joints and painful symptoms may actually indicate a higher/advanced disease activity. Knees with recurrent pain displayed higher degree of medial cartilage loss [91]. Similarly, patients with erosive OA of interphalangeal joints suffer from more pain and functional impairment. Another theory is development of angiogenesis. In pathological conditions, new vessels along with nerve fibres enter the regenerated cartilage during the reparative process. This facilitates the painful stimuli to be initiated from the previously denervated healthy cartilage.

All these studies give us insight to understand the pain in osteoarthritis, which has led to the conclusion that the nature of OA pain progresses from nociceptive to neuropathic with advanced stage of the disease.

#### **Clinical implications in OA treatment paradigm**

Clinical and basic research have shed light in the aetiology of osteoarthritic pain, which encompasses different pathologic procedures being driven by joint, muscles and peripheral nerves pathology, as well as by central pain amplification. The better understanding of pain mechanisms, the growing appreciation of adequate pain control and the failure of peripherally directed therapies to provide good and sustained clinical outcomes have led to the consideration of novel treatment approaches of OA.

Historically the management of OA includes analgesics, non-steroidal anti-inflammatory drugs and topical agents, such as local steroid injections and capsaicin [92] (Table 2). Particularly, steroid injections are very commonly used in primary and secondary care despite the great variability in clinical outcomes and the lack of evidence for predictors of pain relief in knee and hip OA. However, the presence of synovitis and the radiographic severity are

**Table 2**  
Pharmacological treatments for management of OA pain

Treatment	Target mechanism
NICE recommended (nociceptive)	
Paracetamol	Indirect activation of cannabinoid CB(1) receptors
Topical NSAIDs	Inhibition of the cyclooxygenase (COX) enzyme
Topical capsaicin	Inhibition of substance P
Oral NSAIDs	Inhibition of the cyclooxygenase (COX) enzyme
COX-2 inhibitors	Inhibition of the cyclooxygenase-2 (COX-2) enzyme
Glucosamine/chondroitin	Stimulation of the anabolic process of the cartilage metabolism
Opioids	Increased phosphorylation of the p38 mitogen-activated protein kinases (MAPK)
Intra-articular injections (corticosteroids)	Phospholipase-A2 inhibition, local reduction of IL-1 and IL-6
Intra-articular injections (hyaluronans)	Direct or indirect effects on substance P
Neuropathic	
Amitriptyline	Inhibits the reuptake of norepinephrine and serotonin
Duloxetine	Potentiates serotonergic and noradrenergic activity in the CNS
Lignocaine	Blocks the gated sodium (Na <sup>+</sup> ) channels in the neuronal cell membrane

associated with good response in both unguided and ultrasound-guided intra-articular steroid injections as indicated by a recent systematic review [93] and a randomised controlled trial [94]. Biologic therapies targeting inflammatory cytokines have changed the natural history of rheumatoid arthritis, but the efficacy of such regimens in OA is questionable [95]. Only a handful of studies—one randomised [96] and two open-label [97,98]—have assessed the efficacy of tumour necrosis factor blockade in severe erosive OA of the hands with inconclusive reports. Intra-articular injection of interleukin-1 receptor antagonist, anakinra, failed to confirm beneficial effects on knee pain, function, stiffness or cartilage turnover in patients with knee OA [99]. In general, biologic treatment is not recommended in patients with OA for several reasons, including the different pathophysiologic background, the lack of evidence as well as the economic burden.

Non-pharmaceutical interventions, such as physiotherapy and hydrotherapy, application of heat or cold packs and transcutaneous electrical nerve stimulation are equally important and necessary for symptomatic pain relief [100]. In cases refractory to conservative treatment, surgery may improve the functional ability and diminish the levels of pain and joint discomfort [101]. In patients to whom such therapies are not effective, modulation of different mechanisms of pain perception should be evaluated.

Intravenous lignocaine infusion is an effective treatment for neuropathic pain conditions [102–104]. Osteoarthritis patients receiving intravenous lignocaine infusion obtained significant pain relief and improvements in psychosocial factors such as quality of life, sleep and social life activities [21]. Intravenous lignocaine selectively blocks tetrodotoxin (TTX)-resistant sodium channels and inhibits repetitive depolarisation in a use-dependent manner [105] and has been demonstrated to produce dose-dependent suppression of allodynia without blocking nerve conduction [106]. This therapy can also be a useful predictor of patients who will potentially respond to subsequent long-term oral therapy with lignocaine congeners for neuropathic pain, such as mexiletine [104,107].

While centrally acting drugs have different mode of action and are approved for other indications, the evidence for central pain perception in OA provides the rationale for the administration of such therapies in patients with severe chronic joint pain of degenerative nature. Weak opioids are useful alternatives when treatment with analgesics or non-steroid anti-inflammatory drugs is ineffective or contraindicated [101]. Antiepileptics and antidepressants may also have analgesic effects, particularly for the treatment of neuropathic pain, and their use is expanding in an increasing number of chronic pain conditions, such as fibromyalgia and osteoarthritis. These agents have a positive effect on other functional symptoms and/or syndromes highly prevalent in these

patients, such as fatigue, sleep distress, memory loss, anxiety and depression. The nomenclature “pain modulators” has been proposed for these agents to highlight the notion that analgesic effects are tightly linked with improvement on mood disturbances and other psychological factors [108]. For example, duloxetine, a selective noradrenaline and serotonin reuptake inhibitor, has been shown to be effective in the treatment of OA and low back pain, resulting in significant improvement in pain intensity, physical functioning and patient rating of overall improvement [68,109]. Whether such treatment options can complement the peripheral acting regimens and become part of a multi-pronged approach that targets various mechanisms of pain perception in OA remains to be determined in future controlled studies.

Pain is a subjective experience unique to each individual. The advances in delineating the pathophysiologic mechanisms accounting for the variability of pain severity across OA patients and the fact that central factors are superimposed upon the traditional peripheral factors in some groups of patients underline the importance for a broader and more flexible approach to diagnosis and management, which will allow the implementation of tailored treatment strategies adjusted to the clinical and psychological characteristics of each individual.

The increasing amount of evidence indicating a neuropathic pain element may change the therapeutic approach, and in the near future, the initiation of centrally acting medications may be used in parallel with analgesics and anti-inflammatories in selected subgroups of patients. Other treatment options such as bisphosphonates/strontium ranelate for bone marrow lesions or even methotrexate for knee OA are under investigation and may open new horizons in the management of the disease.

## Conclusion

In summary, pain in OA is driven by both structural joint changes and abnormal excitability in peripheral and central pain pathways. A growing amount of evidence suggests that neuropathic type of pain is at least partially responsible for the pain in OA. Subsequently, the deeper understanding of multiple mechanisms of OA pain has led to the use of centrally acting medicines that may have a benefit on alleviating osteoarthritic pain, particularly in patients with other centrally mediated symptoms such as fatigue or mood disturbances. The ineffective pain management and the increasing rates of disability associated with OA mandate for change in our treatment paradigm. Although the sequence of events that lead to the initiation and progression of osteoarthritic pain requires further investigation, recent findings have provided a rationale for using different types of agents. The recognition of



subsets of individuals with prominent central nervous contribution refractory to peripherally based treatment to their symptoms may identify eligible candidates for alternative therapies targeting modulation of central pain pathways.

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