Predictive factors and clinical biomarkers for treatment in patients with chronic pain caused by osteoarthritis with a central sensitisation component

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SUMMARY

Aims: The aim of this non-systematic review was to provide a practical guide for clinicians on the evidence for central sensitisation in chronic osteoarthritis (OA) pain and how this pain mechanism can be addressed in terms of clinical diagnosis, investigation and treatment. **Methods:** The authors undertook a non-systematic review of the literature including a MEDLINE search (search terms included *central sensitisation*, *osteoarthritis*, *osteoarthrosis*) for relevant and current clinical studies, systematic reviews and narrative reviews. Case reports, letters to the editor and similar literature sources were excluded. Information was organised to allow a pragmatic approach to the discussion of the evidence and generation of practical recommendations. **Results:** There is good evidence for a role of central sensitisation in chronic OA pain in a subgroup of patients. Clinically, a central sensitisation component in chronic OA pain can be suspected based on characteristic pain features and non-pain features seen in other conditions involving central sensitisation. However, there are currently no diagnostic inventories for central sensitisation specific to OA. Biomarkers may be helpful for confirming the presence of central sensitisation, especially when there is diagnostic uncertainty. Several non-pharmacological and pharmacological treatments may be effective in OA patients with central sensitisation features. Multimodal therapy may be required to achieve control of symptoms. **Discussion:** Clinicians should be aware of central sensitisation in patients with chronic OA pain, especially in patients presenting with severe pain with unusual features.

Review criteria

This non-systematic literature review identified recent meta-analyses, clinical and epidemiological studies and narrative reviews from author input supplemented by a MEDLINE search of terms including central sensitisation, osteoarthritis and osteoarthrosis. Case reports, letters to the editors and similar forms of publications representing weak levels of evidence were excluded.

Message for the clinic

Recent evidence suggests a key role for central sensitisation in the pain of osteoarthritis (OA). The presence of central sensitisation in OA is predictive of several adverse outcomes and requires an altered clinical and investigative approach to assess the likelihood of this condition, if suspected. Furthermore, treatment of central sensitisation in OA mandates a multimodal approach combining pharmacological and non-pharmacological approaches aimed at the pathophysiological mechanisms involved.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide and one of the most frequent causes of musculoskeletal pain (1). Pain is commonly classified as nociceptive or neuropathic pain (previously called non-nociceptive pain) based on mechanistic and clinical criteria. Nociceptive pain arises in response to classic painful stimuli such as inflammation, ischaemia, and/or mechanical trauma (2). Clinically, nociceptive pain is usually intermittent and sharp, especially with movement or mechanical provocation. However, it may also be perceived as a constant dull ache or throb at rest. Nociceptive pain is typically localised to the area of injury or dysfunction, perhaps with some somatic referral, and has a clear, proportionate mechanical/anatomical relationship with aggravating and easing factors. Finally,

nociceptive pain normally resolves with the resolution of the agent that provoked it. In contrast, neuropathic pain, as defined by the International Association for the Study of Pain, is 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' (3). As such, neuropathic pain involves a history of nerve injury or pathology of somatosensory pathways in the spinal cord and brain, and is also referred in a dermatomal distribution. In terms of mechanisms, neuropathic pain represents the interrelation of peripheral and central sensitisation mechanisms, which can lead to similar phenomena but differ substantially in terms of the contribution of pathophysiological mechanisms in the pathogenesis of pain (4,5). Peripheral sensitisation is marked by a reduction in threshold ('heterosensitisation') and amplification of responsiveness ('autosensitisation') of nociceptors (5).

In contrast, central sensitisation enrols new inputs to the nociceptive system, including mechanoreceptors and other fibres not normally involved in nociceptive input (5) and, by definition, is an exaggerated responsiveness of central neurons to input from unimodal and polymodal receptors (6). Central sensitisation also encompasses several other mechanisms not involved in nociceptive pain or peripheral sensitisation, including altered brain processing of sensory inputs, descending antinociceptive dysfunction, increased activity of pain facilitatory pathways, temporal summation ('wind-up') and long-term potentiation of neuronal synapses in the anterior cingulate cortex (6).

Recent evidence supports the contribution of central sensitisation in OA pain and the potential for ameliorating chronic OA pain by addressing central sensitisation mechanisms (7). The presence of central sensitisation in OA is predictive of several adverse clinical outcomes including more severe, unpredictable pain that is difficult to treat with conventional analgesics, other comorbidities, reduced quality of life and functional disability. These features contradict traditional notions that have considered pain in OA as only acute and nociceptive as well as being primarily related to inflammation and mechanical factors such as cartilage damage (8). Radiographical evidence and other findings have questioned the notion that chronic OA pain can be explained by simple acute nociceptive pain mechanisms alone and suggest that a central sensitisation component may also be present in many patients with chronic OA pain (8,9).

Sensitisation is a process by which repeated administration of a stimulus results in the progressive amplification of a response. For many practitioners, this fundamental pain mechanism is not commonly considered among patients with OA. Therefore, this narrative review aims to meet a clinical information need associated with a lack of literature and consensus on central sensitisation and poor linkage between research and clinical practice on this topic. These deficiencies have resulted in diverse practices towards treatment of this condition or a general disregard for addressing central sensitisation altogether.

The key objective of this educational review article was to provide practical guidance for clinicians on the central sensitisation mechanisms involved in chronic OA pain. Although chronic neuropathic pain appears to be highly prevalent in patients with OA, the term 'neuropathic' implies the presence of both peripheral and central sensitisation mechanisms, and a disease of somatosensory structures (10,11). As such, discussion of peripheral mechanisms and

manifestations of chronic neuropathic pain is outside the scope of this review.

Material and methods

This is a non-systematic review of the literature designed to provide a practical and educational overview of the current evidence regarding central sensitisation in patients with chronic OA pain. Clinical studies and narrative reviews identified by the authors were supplemented by a MEDLINE search (search terms included central sensitisation, osteoarthritis, osteoarthrosis) of the recent literature. Osteoarthrosis was included in the initial search to ensure a broad retrieval of results even though it was found to link to the MeSH (Medical Subject Heading) term osteoarthritis. In addition, reference lists of retrieved articles were scanned for relevant articles. Publication types deemed suitable for inclusion were broad but included systematic reviews and meta-analyses, randomised controlled trials, epidemiological studies (e.g. case–control studies, cohort studies) as well as highly relevant narrative reviews. However, case reports, letters to the editors and similar forms of publications representing weak levels of evidence were excluded. There was no limit placed on publication year, although priority was given to more recent relevant articles.

As a result of this methodology, this review is not designed to be comprehensive but to provide a pragmatic, clinical evidence-based approach towards patients who present after a diagnosis of OA with unusual or difficult-to-treat pain features. To meet these broad educational needs and provide specific guidance for clinicians, retrieved articles were organised according to a structure developed to present the literature in a logical manner. This structure begins with general considerations (What is central sensitisation?) and moves to areas covering clinical diagnosis in a rational order (history, clinical examination, use of clinical biomarkers and other investigational techniques).

What is central sensitisation?

Pain perception reflects a balance between the effects of ascending nociceptive and descending modulatory pathways that interact in the central nervous system. Modulation of pain signals can involve either the amplification or inhibition of pain and is known to occur at two key sites: (i) the spinal dorsal horn and (ii) cortical and subcortical regions of the brain (1,5).

Central sensitisation reflects a change in the properties of central neurons that regulate pain percep-

tion. Changes leading to central sensitisation are often initiated by inflammatory and mechanical processes and accompanying peripheral sensitisation but may persist, become disconnected from pain stimuli, and resistant to treatment (12). In terms of mechanisms, central sensitisation is an exaggerated response (hypersensitivity) of central pain-signalling neuronal pathways mainly caused by (i) increased membrane excitability and synaptic transmission of dorsal horn neurons, (ii) reduced inhibition of descending pathways and (iii) altered sensory processing in the brain (Figure 1) (5,13). Increased membrane excitability in dorsal horn neurons is primarily mediated by the excessive release and action of the neurotransmitters glutamate and substance P acting on several different postsynaptic receptors. The sustained activity of these nociceptive pathways activates intracellular signalling pathways leading to the phosphorylation of various membrane receptors and ion channels, including the N-methyl-D-aspartate (NMDA) and α-amino-3-hy-

droxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. These posttranslational (intracellular) changes eventually lead to enhanced synaptic pain transmission via lowered activation threshold, resulting in intracellular entry of calcium, which activates intracellular mechanisms that help maintain central sensitisation (14).

The descending pain pathways involved in central sensitisation arise from periaqueductal grey (PAG) matter and the rostroventral medulla. These pathways, which exert inhibitory and excitatory control over synaptic pain transmission in dorsal horn neurons, are modified in central sensitisation. Amplification of pain signals from modulation of descending pathways acting on dorsal horn neurons is mediated by glutamate and aspartate, whereas inhibition is mediated by norepinephrine, opioids and gamma-aminobutyric acid. Serotonin (5-HT) can both amplify and attenuate pain signals in these pathways. The net result of these changes is that
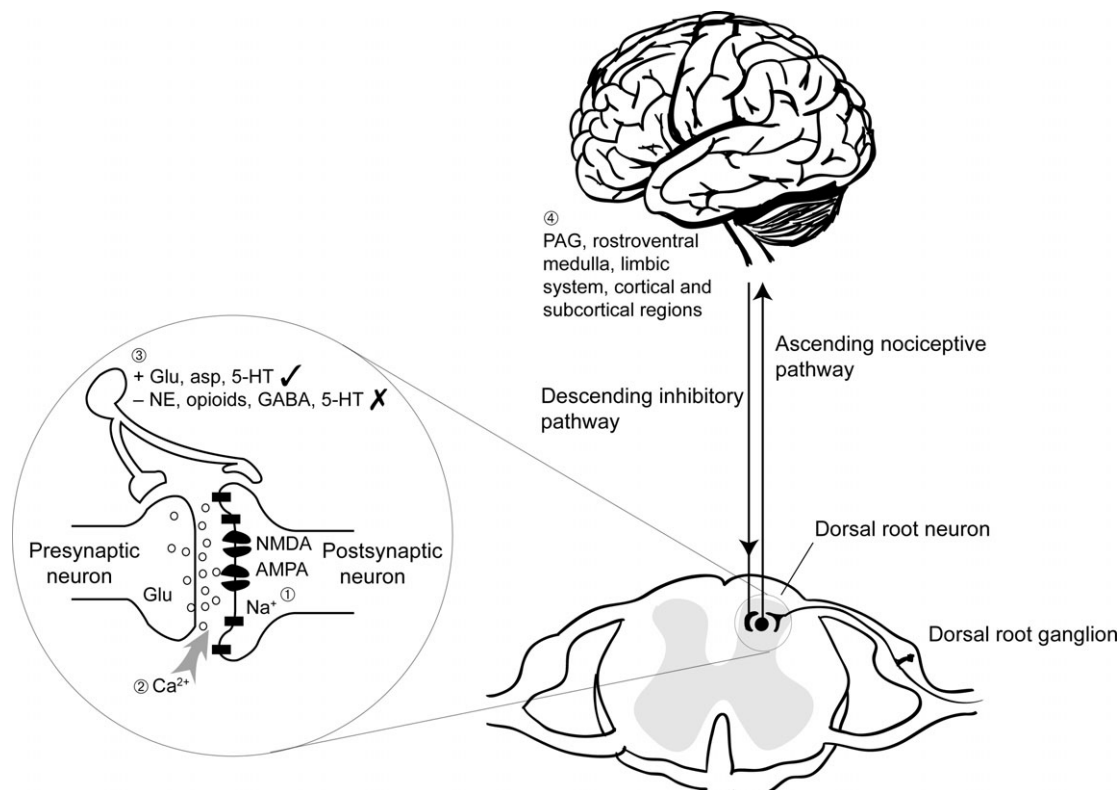

Figure 1 Neurological changes involved in modulation of ascending and descending pathways in central sensitisation. Cellular and neurological changes involved in central sensitisation include: 1. increased sodium-channel expression produced by continuous nociceptive stimuli leads to increased glutamate release from nerve endings ('spontaneous activity'), activating intracellular signalling pathways and consequent phophorylation of NMDA and AMPA; 2. excess action of glutamate on postsynaptic receptors (especially NMDA and AMPA) triggers influx of calcium (intracellular changes); 3. reduced descending inhibition and possibly amplification of descending facilitatory pathways further increases excitability of dorsal horn neurons; 4. involvement of higher centres, especially the PAG and rostroventral medulla. 5-HT, serotonin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid; Asp, aspartate; Ca^{2+}, calcium; GABA, gamma-aminobutyric acid; Glu, glutamate; Na^+, sodium; NE, norepinephrine; NMDA, N-methyl-D-aspartate; PAG, periaqueductal grey matter

central sensitisation pain shifts to involve hypersensitive painful responses to both threshold stimuli (hyperalgesia) and non-pain stimuli ('allodynia') (Figure 2) (5,13). In addition to these characteristic pain features, central sensitisation also often leads to increased generalised responsiveness to various peripheral stimuli including mechanical pressure, light, sound and heat/cold (5,6). Furthermore, the original pain area typically extends over time in patients with secondary hyperalgesia (pain outside the site of injury) (6). These changes constitute the clinical picture of central sensitisation in chronic pain that includes primary and secondary hyperalgesia, and allodynia (6).

Evidence for central sensitisation in OA

There is evidence for central sensitisation in a proportion of patients with OA as well as those with rheumatoid arthritis and other musculoskeletal conditions (10,13,15,16). This evidence comes from multiple sources, including epidemiological studies and literature reviews. In one cohort study of 113 participants with knee OA, quantitative sensory testing (QST) was used to detect central sensitisation. Multivariate analyses revealed significantly heightened pain sensitivity in a subgroup of patients who lacked radiographic evidence of moderate-to-severe pathologic OA changes (9). The authors suggested that central sensitisation may be a key component of knee pain in these patients. A case–control study of patients with hip OA analysed clinical manifestations such as referred pain and skin sensitivity changes to determine whether supraspinal influences that underlie these clinical manifestations could be identified (17). In this study, 20 patients with hip OA displaying signs of referred pain were compared

with age- and sex-matched controls via pain psychology questionnaires and QST in addition to functional brain imaging studies [magnetic resonance imaging (MRI) with cold and/or punctate stimuli of the areas of referred pain]. Compared with age-matched controls, patients with OA were found to have significantly lower thresholds to perception of punctate stimuli and were hyperalgesic in their areas of referred pain with functional brain imaging showing significantly greater activation in the brainstem (PAG) (17). The most comprehensive evidence for the role of central sensitisation in OA comes from a systematic literature review of 36 eligible studies [mostly case–control ($n = 19$) and cohort studies ($n = 12$)] (7). The presence of central sensitisation was assessed using a variety of subjective and objective parameters across these studies, including clinical manifestations, QST, induced referred pain, altered spinal reflexes, dysfunctional endogenous nociceptive inhibition and neuroimaging. In a subgroup of approximately 30% of patients with OA, central sensitisation was found to contribute to the clinical picture in addition to nociceptive pain (7).

Implications of central sensitisation in OA and related conditions

The presence of central sensitisation in OA predicts several disease features, prognostic aspects and comorbidities. First, patients with central sensitisation are significantly more likely to report more severe levels of pain, which are typically less responsive to traditional pain medication than patients with peripheral nociceptive pain (18). Second, central sensitisation can be seen as a consequence of ongoing peripheral nociceptive input and as a mecha-
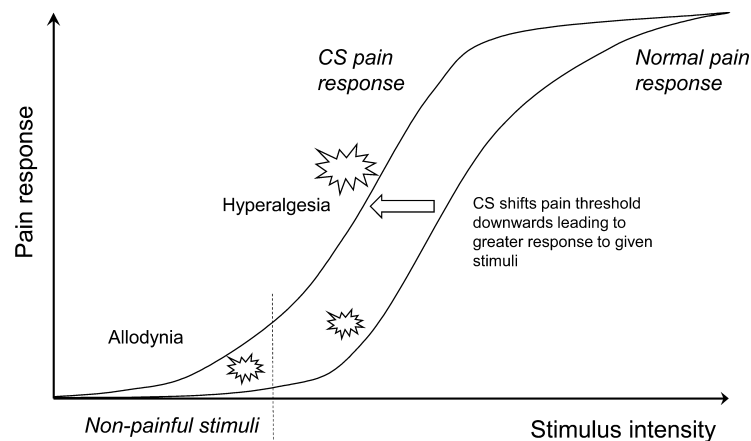

Figure 2 Shift in pain stimulus–response curve in central sensitisation (CS)

nism by which pain in OA is maintained (1,19). Once central sensitisation is established, it can persist even if new peripheral nociceptive input is absent (1). Finally, the presence of established central sensitisation is predictive of a more complex clinical picture and reduced likelihood of achieving treatment success (1). As part of this complexity, patients with central sensitisation are more likely than those with peripheral nociceptive pain to have poorer general health-related quality of life, greater levels of functional disability and psychological comorbidities including anxiety and depression (18). Indeed, reduced quality of life in OA patients with possible central sensitisation has been linked with pain intensity (20).

Clinical features of central sensitisation

Currently, there are no evidence- or consensus-based recommendations or criteria regarding the identification of central sensitisation in patients with OA or other musculoskeletal conditions (1). Identifying central sensitisation in patients with OA therefore requires a careful and thorough clinical history, clinical examination and the judicious use of investigational objective biomarkers, if available, for differential diagnosis.

Clinical history
The first step in identifying central sensitisation in patients with OA is to take a detailed history focusing particularly on (i) pain features suggestive of central sensitisation, (ii) non-pain symptoms characteristic of central sensitisation and (iii) accompanying non-specific features that are not necessarily characteristic of central sensitisation but often occur in association with central sensitisation (e.g. as part of central sensitisation).

Pain features
Several distinct features of the pain present in patients with OA can alert practitioners to the possible presence of central sensitisation. First, the presence of pain continuing at rest is a sensitive marker of a possible central sensitisation component and is more common in OA than specific central sensitisation pain features such as allodynia, hyperalgesia, secondary hyperalgesia, temporal summation and sensory after-effects (13). In addition, pain in patients with central sensitisation often follows an unpredictable pattern, is disproportionate to the nature and extent of the pathological changes, is associated with high levels of functional disability, is more constant, and is highly severe (21).

Non-pain symptoms
Central sensitisation is associated with a range of non-pain symptoms and other somatic and psychological comorbidities such as dysaesthesias (e.g. burning, crawling sensations) (21). Furthermore, central sensitisation has a strong association with several psychosocial issues including negative emotions, poor self-efficacy and maladaptive beliefs and pain behaviours, as well as problems and conflicts in different areas of life (e.g. family, work and social) (21).

Non-specific features of central sensitisation
Central sensitivity syndrome is a clinical entity that unites various non-specific features that are assumed to share central sensitisation as a key causal factor (22). Currently, OA is not included in the recognised group of central sensitisation conditions that comprise central sensitivity syndrome, although some authors have suggested that it should be included (1). However, the comorbid symptoms and non-specific features of central sensitivity syndrome are commonly present in patients with central sensitisation, regardless of the cause (1). A validated Central Sensitization Inventory has been developed to identify key symptoms associated with central sensitivity syndrome, quantify the degree of these symptoms and differentiate between chronic pain patients who have different levels of impairment (Table 1) (22). However, in the setting of OA patients, the symptoms and presenting issues validated in this inventory can help identify presenting issues that may be comorbid symptoms of central sensitisation (22).

Clinical examination
Clinical examination should be undertaken to confirm or exclude features of central sensitisation suggested by the history (Table 2) (6). Primary hyperalgesia or allodynia can be confirmed by testing for disproportionate, inconsistent, non-mechanical or non-anatomical patterns of pain provocation in response to movement, mechanical testing or non-painful stimuli (21). Pressure algometers provide a more reliable and accurate method for gauging sensitivity to stimuli, although use of light touch during palpation of the affected areas may also be used (6). Patients with OA may also have a significantly greater number of trigger points whereby low intensity input may result in pain when a latent trigger point is activated (23). Secondary hyperalgesia corresponds to increased sensitivity of dorsal horn neurons and, compared with primary hyperalgesia or allodynia that also occur with peripheral sensitisation, can be seen as more pathognomonic of central sensitisation. Secondary hyperalgesia can be confirmed by testing for reduced pain threshold in tissues innervated by

Table 1 Central Sensitization Inventory: areas for questioning

Physical symptoms	Bruxism (teeth clenching or grinding)
	Diarrhoea/constipation
	Headaches
	Pain in jaw
	Pain all over body
	Tension in neck and shoulder
	Bladder/urination pain
	Frequent urination
	Pelvic pain
	Skin problems
	Restless legs
Sleep and energy levels	Unrefreshed in the morning
	Poor sleep
	Low energy
	Easily tired with physical activity
	Muscles are stiff or achy
	Anxiety attacks
Psychological symptoms and issues	Stress exacerbates symptoms
	Sad or depressed
	Need help with daily activities
	Difficulty concentrating
	Poor memory
	Childhood trauma
Sensitivity	Sensitive to bright lights
	Certain smells make dizzy

Adapted from Mayer et al. (22).

Table 2 Clinical examination of patients with suspected central sensitisation

Examination	Rationale
Assess at sites remote from the symptomatic site: • pressure pain thresholds • sensitivity to touch (algometer or manual) • sensitivity to cold	Provides evidence of generalised hyperalgesia
Assess at neighbouring segmental sites: • pressure pain thresholds • sensitivity to touch (algometer or manual) • sensitivity to cold	Provides evidence of secondary hyperalgesia
Assess for painful response to light touch or other non-painful stimuli	Provides evidence of allodynia
Assess pressure pain thresholds during and after exercise	Patients with central sensitisation often have an increased response during or after exercise

Adapted from Nijs et al. (6).

neighbouring segments to those thought to be involved in primary nociception (6). Generalised hyperalgesia can be confirmed by testing for pressure pain thresholds outside the area of primary nociception expected based on segmental nerve supply (i.e. dermatomal pattern) (6). Non-anatomic areas of pain or tenderness on palpation are often diffuse (21).

Both generalised and secondary hyperalgesia can also be detected by testing for a painful response to heat, cold or vibration at sites either within or outside the area of expected nociception. Generalised neuronal excitability associated with central sensitisation can be confirmed by testing for an increased (painful) response to stimuli following exercise.

Biomarkers

Several objective biomarkers have been used in research settings to detect central sensitisation components in patients with OA. Objective biomarkers for detecting central sensitisation include changes in nociceptive withdrawal reflexes (NWRs), QST, increases in cortical event-related potential amplitudes, functional MRI and magnetic source imaging (13). These biomarkers vary in terms of complexity, practicality and discriminative ability. Although biomarkers are still considered investigational and are not in widespread clinical use, there has been a progressive adoption of these into practice.

Nociceptive withdrawal reflex

The NWR is a spinal reflex of the lower limb elicited by painful somatic stimuli (either single or repeated to assess temporal summation). NWR has been used to evaluate the excitability of the nociceptive system using graded low-frequency electrical stimulation to elicit features of central sensitisation (24). In one study of healthy volunteers, the NWR was elicited within the same innervation area at graded stimulation intensities that led to an intensity-independent, long-lasting facilitation of the NWR with a significant mean $\pm$ standard deviation increase in the reflex size ($31 \pm 4\%$, $p < 0.001$), the number of reflexes ($22 \pm 10\%$, $p < 0.01$) and blood flow ($40 \pm 10\%$, $p < 0.001$). These findings suggested that NWR can measure activity-dependent central sensitisation elicited using a stimulation frequency that lies within the physiological firing range of primary afferents. Although there are few clinical studies in which the NWR has been used to assess the presence of central sensitisation, joint mobilisation has been shown to reduce withdrawal reflexes in patients with knee OA (25).

Quantitative sensory testing

Batteries of both invasive and non-invasive stimuli (e.g. warm/cold, mechanical detection, vibration) are

used in QST to quantify muscular pain perception, which can provide comprehensive information via pain thresholds regarding peripheral pain perception and central sensitisation (26). Although many QST stimuli are similar to those used in regular clinical assessment, they are systematically applied to indicate sensation or pain at different anatomical sites. Although relatively expensive and time consuming, QST can be useful to differentiate pain syndromes presenting with similar symptom patterns, allow semiquantitative assessment when there is poor correlation between symptoms/signs with pathological changes, and evaluate the response to therapeutic approaches (26).

A systematic review and meta-analysis has shown that people with OA have lower pressure pain thresholds both at the affected joint and at remote sites compared with healthy controls (19).

Cortical event-related potential amplitudes
Cortical event-related potential amplitudes have been assessed via electroencephalographic responses elicited by mechanical stimulation (e.g. of the hand dorsum) with flat-tip probes that activate Aδ nociceptors and are widely used to assess the presence of secondary hyperalgesia (27). Corresponding pin-prick-evoked potentials recorded in response to this stimulation are thought to: (i) reflect cortical activities triggered by somatosensory input, (ii) allow quantification of secondary mechanical hyperalgesia and (iii) be a potential diagnostic tool to detect mechanical hyperalgesia in patients thought to have central sensitisation (27).

Functional magnetic resonance imaging
Functional MRI allows functionally activated brain regions to be detected by increases in blood oxygen level dependent signals (28). Using functional MRI, punctate stimulation of an area of heat/capsaicin-induced secondary hyperalgesia to simulate central sensitisation in healthy subjects led to an extensive bilateral activation of the pain matrix in the cerebellum, brainstem, thalamus, putamen, insula, secondary somatosensory cortices and inferior parietal lobule (29). Another study with functional MRI combined with QST reported increased activation of brain pain processing centres, including the anterior cingulate cortex, the right dorsolateral prefrontal cortex, the left middle frontal gyrus and the left lateral occipital cortex, in patients with chronic hip OA (17).

Magnetic source imaging
Magnetic source imaging relies on magnetocephalography in combination with high-resolution MRI to display functional brain activity in an anatomic location. Similar to functional MRI, magnetic source imaging has been shown to detect secondary hyperalgesia via Aβ-fibres induced by cutaneous injection of capsaicin. Despite their discriminative ability, the specialised equipment and personnel involved in functional MRI and magnetic source imaging mean that these techniques are unlikely to be cost- or time-effective in the routine investigation of central sensitisation.

Other markers
In addition to these specific investigations, the finding of a discrepancy between pain severity and radiographic features of OA can suggest central sensitisation. Such discrepancies have been observed in clinical studies in support of the existence of central sensitisation mechanisms (9,30). Therefore, X-ray evaluation of affected joints via anteroposterior and lateral views in conjunction with the pain history, clinical examination and questionnaires may be a simple method for detecting a central sensitisation component.

Assessing the individual likelihood of central sensitisation

Central sensitisation is only present in a subgroup of patients with OA and other musculoskeletal disorders. Therefore, isolated clinical features suggestive of central sensitisation provide only weak evidence for central sensitisation in an individual patient. However, the likelihood of central sensitisation increases when positive findings are confirmed across the assessments of history, clinical examination and investigations. A diagnostic algorithm summarising a practical approach to assessing the presence of central sensitisation in patients with OA is presented in Figure 3. According to this algorithm, the presence of central sensitisation may be confirmed if there are strong indicators via the history and clinical examination. Individual evaluation may progress to specific investigations if the symptoms and signs of central sensitisation are not confirmed via the history and/or clinical examination.

Rapid screening assessment for central sensitisation in patients with OA
For rapid screening assessment of a possible central sensitisation component in patients with OA, a few brief questions can elicit key features of central sensitisation. These questions include:

- How long have you have experienced pain?
- How severe is the pain?
- How frequently do you experience pain?
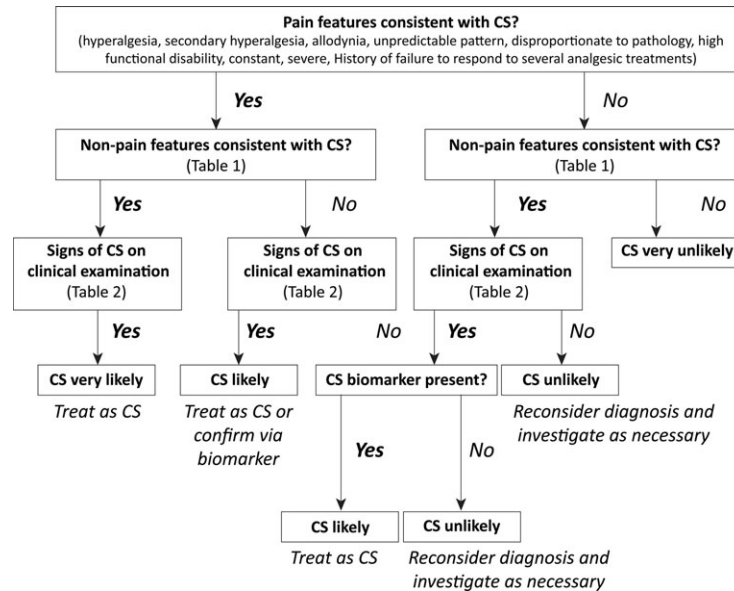- Do you have pain at rest or during sleep?

Figure 3 Diagnostic algorithm for identifying central sensitisation (CS) in patients with osteoarthrosis and related conditions

• Has there been expansion of the painful area over time?

In general, patients with central sensitisation will have had long-standing, frequent pain. The presence of repeated painful stimuli, even at low intensity, is more important than the intensity of pain in terms of eliciting 'wind-up' phenomena. In addition, pain at rest is useful for discriminating between mechanical pain and pain related to central sensitisation, which is typically not eased by rest and may occur even during sleep. In addition to these simple questions, a 38-item clinical criteria checklist used in patients with chronic low back pain has been used to identify a cluster of three symptoms and one sign that are highly predictive (sensitivity 91.8%, specificity 97.7%) of central sensitisation (Box 1) (21). Although these results were obtained in a different patient population, the features are general in nature, and it is reasonable to assume that these would also have predictive potential in patients with OA. Finally,

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Box 1 Clinical features predictive of central sensitisation (21)

• Disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple, non-specific aggravating/easing factors.
• Pain disproportionate to the nature and extent of injury or pathology.
• Diffuse/non-anatomic areas of pain/tenderness on palpation.

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several diagnostic tools such as Douleur Neuropathique en 4 Questions and Standardized Evaluation of Pain that involve interview questions and/or physical examination tests to assess the presence of neuropathic pain in general are in common use. Although these tools are not specific for detecting the presence of a central sensitisation component, positive findings can suggest the presence of the overlap between peripheral and central mechanisms that comprises neuropathic pain.

Addressing the clinical phenotype of a patient with chronic pain caused by OA with a central sensitisation component

There is evidence that, under the conditions of continuous nociceptive stimuli, Aβ fibres undergo a phenotypic switch to allow them to release substance P, whereas neurons in the superficial lamina shift to allow calcium entry, which is part of the signalling pathway that drives central sensitisation (4,5). These phenotypic transformations reflect the neuroplasticity that is a hallmark of central sensitisation. At an individual level, various pain phenotypes may emerge based on the combination of etiological, genetic and environmental factors. Characterising patients by pain phenotypes may allow individualised treatment pathways to be developed for patients with OA based on their likelihood to respond to particular treatments (31). Clinical studies have used techniques such as QST and neuroimaging to phenotype patients and allow differentiation between peripheral and central sensitisation mechanisms in OA patients

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Box 2 Clinical features that characterise a pain phenotype involving central sensitisation

- Pain at rest
- Long duration of the disease
- History of inadequate response to several analgesic medications
- Hyperalgesia
- Allodynia
- Spread of pain beyond the original area (secondary hyperalgesia)
- Inadequate coping strategy
- Insomnia
- Low mood or depression

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with neuropathic pain (19). However, simpler assessments may also be used to develop a pain phenotype and categorise patients with OA into subgroups. Clinical features that might characterise a pain phenotype involving central sensitisation are summarised in Box 2.

It is important to note that pain hypersensitivity alone is not enough to make a diagnosis of central sensitisation as peripheral sensitisation may also cause this clinical feature. Indeed, peripheral sensitisation may also have a role in maintaining central sensitisation, which further complicates the clinical picture. Again, if there is uncertainty regarding the pain phenotype and the relative importance of central sensitisation in the mechanism of chronic pain in patients with OA, clinical biomarkers may be helpful.

Addressing central sensitisation in the treatment of OA

General principles
Treatment of central sensitisation in patients with OA requires a tailored approach that takes into account the characteristic features of central sensitisation and other pain mechanisms present in each patient. Addressing central sensitisation components in patients with OA also usually requires a multimodal approach combining pharmacological and non-pharmacological treatments. If possible, pathophysiological mechanisms that maintain central sensitisation should be identified and eliminated (32). However, these may vary widely between patients and be difficult to both identify and address. Overall, the treatment of the central sensitisation component in chronic OA pain is frequently challenging (32).

Non-pharmacological approaches
Non-pharmacological therapies and strategies include patient pain education, exercise therapy, cognitive–behavioural therapy, transcutaneous electrical neural stimulation, transcranial magnetic stimulation, manual joint mobilisation ('manual therapy') and stress management/neurofeedback (Table 3) (33). In addition, interventional pain procedures such as dorsal column stimulation have been used for neuropathic pain occurring at a spinal cord level and may have potential application in intractable OA pain with a central sensitisation component (34). Use of non-pharmacological therapies typically requires a multidisciplinary approach involving relevant specialties. For some patients, these strategies can be applied as an initial step before pharmacological approaches are introduced. However, some non-pharmacological approaches, such as exercise and manual therapy, should not be applied until the patient has pain levels sufficiently low to allow these therapies. Use of non-pharmacological therapies may also open up the possibility of reducing the dose of medications required to control pain possibly by targeting different mechanisms involved in central sensitisation.

Pharmacological approaches
A variety of pharmacological treatments have been trialled in patients with neuropathic pain, including conditions that are known to involve central sensitisation. However, some of these treatments are still under investigation and are not in widespread clinical use. Several agents such as carbamazepine, gabapentin, duloxetine and pregabalin have demonstrated sufficient clinical efficacy in trials to warrant approval by regulatory bodies for specified neuropathic pain conditions, including diabetic neuropathy. There are currently no agents specifically approved for neuropathic pain in OA, although evidence has accumulated for certain agents. Paracetamol (acetaminophen) is a core first-line agent recommended by most guidelines on OA pain management (35). Although it has been shown to have mechanisms of action relevant to central sensitisation, the efficacy of paracetamol makes it only suitable for mild-to-moderate pain (35). Furthermore, the extent of this efficacy has been questioned in more recent meta-analyses (35). Pharmacological treatments that may specifically target central sensitisation in OA and have evidence for efficacy include balanced serotonin and norepinephrine-reuptake inhibitor drugs (SNRIs), calcium-channel alpha(2) delta ligands, tramadol and tapentadol (Table 4) (33,36). In addition, NMDA-receptor antagonists have also been shown to be effective for targeting central sensitisation and, clinically, certain neuropathic pain such as complex regional pain syndrome and diabetic neuropathy (37). Finally, opioids may be useful as a second-line therapy for patients with very severe pain. Response to pharmacotherapy is often

Table 3 Non-pharmacological techniques for addressing central sensitisation: rationale and practice points (33)

Technique	Rationale	Practice points
Cognitive–behavioural therapy	Increases cognitive and affective responses to pain to deactivate brain-related pain facilitatory pathways	Cognitive–behavioural therapy may be a practical method for addressing maladaptive pain cognitions including anxiety, depression and catastrophising
Exercise therapy	Time-contingent exercise (e.g. perform exercise for 5 min, regardless of pain) may deactivate brain-orchestrated pain facilitatory pathways; activates endogenous analgesia	Suggest patients exercise regularly and for set intervals rather than until pain occurs as this can facilitate 'warning signs' of damage when no damage is present
Manual therapy	Activates descending inhibitory pathways as well as having peripheral analgesic benefits	Short-term benefits; may serve as a peripheral nociceptive input in some patients
Patient pain education	Inappropriate pain beliefs and concepts (e.g. catastrophising) contribute to central sensitisation; reconceptualising pain may help reduce descending nociceptive facilitation and other mechanisms	Explaining the treatment rationale is of prime importance; 1–2 face-to-face sessions accompanied by reading material and homework is a minimal recommendation
Stress management and neurofeedback training	Reduce stress-mediated increases in central nociceptive signalling and target the cognitive–emotional component of central sensitisation	May incorporate elements from several techniques including stress management, cognitive therapy, assertiveness training and communal coping models
Transcutaneous electrical nerve stimulation	Activates descending inhibitory pathways by activating spinal μ- and δ-opioid receptors and GABA receptors	Frequently used in chronic pain; less likely to be beneficial with widespread or poorly localised pain
Transcranial magnetic stimulation	Addresses the sensory-discriminative aspects of pain and may restore descending nociceptive inhibition	Requires specialised equipment and analgesic effects are relatively short-lived (1–3 weeks)

GABA, gamma-aminobutyric acid.

heterogeneous, and patients may require a combination of medications acting on different pain mechanisms to achieve a satisfactory therapeutic effect (38).

Finally, in patients with OA, it is important that pharmacological agents provided to address the central sensitisation component do not interact

Table 4 Pharmacological agents for addressing central sensitisation in OA: key mechanisms of action (33,36)

Agent/class	Mechanisms of action
Serotonin and norepinephrine-reuptake inhibitors	Activate serotonergic descending pathways that recruit opioid peptide-containing interneurons in the dorsal horn; activate norepinephrine pathways to inhibit central nociceptive activity and alpha-2-adrenoceptors
Calcium-channel alpha(2)delta ligands	Bind to the alpha(2)delta subunit of voltage-sensitive calcium channels to decrease the release of glutamate, norepinephrine and substance P involved in central sensitisation; stimulate GABA transmission, which is decreased in central sensitisation
NMDA-receptor blockers (e.g. ketamine, dextromethorphan)	Block activity of the NMDA receptor in the dorsal horn that plays a key role in the development of central sensitisation; limits the spread of hyperalgesia and allodynia seen in central sensitisation
Tramadol	Activity at opioid μ-receptors; inhibits the reuptake of serotonin and norepinephrine
Tapentadol	Combined agonist activity at opioid μ-receptors and inhibition of norepinephrine reuptake to inhibit central nociceptive activity
Opioids	Target opioid receptors (especially μ-receptors) located at different levels of pain processing, including dorsal horn lamina, the thalamus, PAG, limbic system and cortical regions; stimulate GABA transmission, which is decreased in central sensitisation

GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; PAG, periaqueductal grey matter.

adversely with purported disease-modifying medications and other analgesics.

Serotonin-noradrenaline reuptake inhibitors

Serotonin and norepinephrine-reuptake inhibitor drugs include several agents such as duloxetine, milnacipran and venlafaxine that were initially developed as antidepressants. These agents are thought to potentiate 5-HT and norepinephrine activity in descending pain pathways resulting in pain inhibition (39).

Duloxetine has demonstrated analgesic properties in several chronic pain conditions, including neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia and chronic low back pain (39). In the United States, duloxetine is also approved for chronic musculoskeletal pain, including chronic OA pain (40). In terms of evidence for efficacy in OA pain, duloxetine has been evaluated in three separate double-blind, randomised, placebo-controlled trials in chronic OA knee pain (OA-1, (41) OA-2, (42) and OA-3 (43)). The study OA-3 also assessed the efficacy of duloxetine compared with placebo when added to non-steroidal anti-inflammatory drug therapy. All three duloxetine trials used change in pain intensity as the primary efficacy outcome variable (41–43). However, physical and emotional functioning and health-related quality of life outcomes were also assessed. The results of these trials showed that duloxetine led to statistically significant reductions in pain scores compared with placebo as early as one week after initiation of treatment (41–43). Clinically meaningful reductions favouring duloxetine were noted after 4 weeks of treatment and were maintained thereafter (39). Differences between duloxetine and placebo in other variables were less consistent. However, the results suggest that patients treated with duloxetine had greater improvements in physical functioning than patients treated with placebo and that changes in depression and anxiety had little effect on the analgesic effect of duloxetine (41–43). Finally, EuroQol: 5 Dimensions Questionnaire scores were significantly improved in duloxetine-treated patients in OA-1 (41). This evidence suggests that patients with chronic OA pain may benefit from the restoration of descending inhibition associated with central sensitisation, which plays a key role in chronic pain modulation. Reflecting this, duloxetine is included in the current Osteoarthritis Research Society International guidelines for non-surgical treatment of chronic OA pain in individuals without comorbidities and those with multiple-joint OA with relevant comorbidities (44).

Other SNRIs have undergone preliminary studies in OA pain. Milnacipran has shown antinociceptive effects in a rat model of OA pain via descending serotonergic and noradrenergic, as well as opioid, pathways (45). Venlafaxine has also shown encouraging results in a small single-blind placebo-controlled study of 18 patients with activity-limiting OA, but these results need to be confirmed in larger randomised trials (46).

Calcium-channel alpha(2)delta ligands

Calcium-channel alpha(2)delta ligands include the anticonvulsants pregabalin and gabapentin. These agents block calcium channels that are important for maintaining enhanced release of pain neurotransmitters between primary afferent fibres and second-order sensory neurons in the dorsal horn (Figure 1) (33). Calcium-channel alpha(2)delta ligands have been shown to be effective for various neuropathic pain states, including diabetic neuropathy (33). However, there is limited evidence for the effectiveness of these agents for pain in OA. One recent randomised prospective trial compared the efficacy of meloxicam, pregabalin and meloxicam + pregabalin in OA patients (47). The results of this study found that the combination of pregabalin and meloxicam was effective for pain in OA patients, whereas the single agents did not lead to significant pain relief (47). This effect was ascribed to a combination of effects on inflammation and peripheral sensitisation mechanisms (47).

Tramadol

Tramadol has been referred to as an atypical centrally acting analgesic based on its dual effects on dorsal horn neurons and descending pathways (48). Clinical studies support the use of tramadol for OA and, in separate studies, neuropathic pain (48). However, no studies to date have examined the efficacy of tramadol for specifically addressing central sensitisation in patients with OA. Treatment guidelines recommend that tramadol can be used in a similar way to weak opioids for the treatment of moderate to severe refractory pain in patients with hip or knee OA (35,48). On this basis, tramadol appears to be a reasonable choice for OA patients with a central sensitisation component. However, treatment guidelines suggest that tramadol should not be given for prolonged periods (i.e. greater than 3 months). Clinicians should also avoid prescribing tramadol to patients taking other serotonergic drugs because of the possibility of serotonin syndrome.

Tapentadol

Tapentadol is a centrally acting analgesic that demonstrates μ-opioid receptor agonism and noradrenaline reuptake inhibition that may address both nociceptive and chronic neuropathic pain mechanisms (49). In a randomised, controlled study and an open-label, continuation study, tapentadol

monotherapy reduced pain intensity and improved quality of life of patients with severe, chronic low back pain, including patients with a neuropathic pain component (radiculopathy) (36,49). This suggests that such patients may benefit from the restoration of descending inhibition associated with central sensitisation, which plays a key role in neuropathic pain modulation. Tapentadol has been shown to be effective in chronic, severe OA pain with a reduced incidence of gastrointestinal adverse effects compared with opioids (50). However, to date, tapentadol has not been recommended in OA treatment guidelines.

N-methyl-ᴅ-aspartate-receptor antagonists

Among the class of NMDA-receptor antagonists, ketamine and dextromethorphan are in current clinical use, although several other agents are also under development (33). These agents may act directly on neurochemical mechanisms involved in central sensitisation and also have the potential to enhance the effects of other analgesics (33). However, current clinically available NMDA-receptor channel blockers have a narrow therapeutic window, which possibly limit their potential use in patients with OA. Furthermore, these agents have not been studied in OA patients and the evidence base in this context is weak.

Opioids

Opioids act on opioid receptors throughout the central nervous system including those in various laminae of the dorsal horn, the thalamus, PAG, limbic system and several regions of the cortex, which are all relevant to central sensitisation mechanisms (33). Despite this, OA treatment guidelines consider strong opioids should only be used for the management of severe pain in exceptional circumstances and generally for short periods (35,44,51). Therefore, opioids should be considered a second-line treatment option to address central sensitisation when other treatments have not been effective.

Discussion

Central sensitisation is common in OA, which represents one of the most frequent causes of musculoskeletal pain worldwide. Hence, there is a wide unmet need to address central sensitisation mechanisms in OA pain, which relates to the key objective of this review article. Evidence for central sensitisation in OA comes from a variety of sources and is becoming increasingly robust. It is also clear the presence of central sensitisation predicts several negative consequences and disease features, including the possibility of comorbid conditions. Furthermore, central sensitisation is associated with pain that does

not respond to traditional pain relief strategies and treatments and is challenging to manage. A lack of systematic recommendations for the diagnosis and management of central sensitisation in OA reflects the still emerging nature of this condition and lack of linkage between research findings and clinical tools. In particular, further evidence from clinical research is required to develop validated assessment tools (e.g. questionnaires) to measure the likelihood of central sensitisation in individuals. In a similar fashion, several biomarkers to assess sensitisation mechanisms are available although evidence to confirm their suitability for clinical use is required. Until these gaps are properly addressed, we have outlined a diagnostic strategy based on a rational approach encompassing clinical history and examination and judicious use of investigational tools where there is diagnostic uncertainty. However, lack of quantitative research in this area means that this approach needs to be guided by clinical judgment. Finally, there is evidence supporting the usefulness of several non-pharmacological and pharmacological treatment modalities for central sensitisation in patients with OA. However, further research is required to define how best these can be applied in clinical practice.

Conclusion

Central sensitisation appears to be a common pathophysiological mechanism in a subgroup of patients with chronic OA pain. However, OA is only now emerging as a condition that may involve this mechanism, and there is a lack of specific guidance on clinical features, diagnosis, investigation and management of central sensitisation in this population. Central sensitisation should be suspected as the basis of characteristic chronic pain and non-painful features that have been verified in other conditions. Similarly, the diagnosis may be confirmed by careful clinical examination and judicious use of objective biomarkers. Finally, successful treatment of the challenging central sensitisation component should also follow the principles used in other chronic pain conditions. This includes the individualised and multimodal use of pharmacologic and non-pharmacologic treatment strategies as well as the judicious interventional treatment of identified pathophysiological mechanisms that maintain central sensitisation. These therapies should be applied using a multidisciplinary approach.

Author contributions

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