



# Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine

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Chronic pain is a leading cause of disability globally and associated with enormous health-care costs. The discrepancy between the extent of tissue damage and the magnitude of pain, disability, and associated symptoms represents a diagnostic challenge for rheumatology specialists. Central sensitisation, defined as an amplification of neural signalling within the CNS that elicits pain hypersensitivity, has been investigated as a reason for this discrepancy. Features of central sensitisation have been documented in various pain conditions common in rheumatology practice, including fibromyalgia, osteoarthritis, rheumatoid arthritis, Ehlers-Danlos syndrome, upper extremity tendinopathies, headache, and spinal pain. Within individual pain conditions, there is substantial variation among patients in terms of presence and magnitude of central sensitisation, stressing the importance of individual assessment. Central sensitisation predicts poor treatment outcomes in multiple patient populations. The available evidence supports various pharmacological and non-pharmacological strategies to reduce central sensitisation and to improve patient outcomes in several conditions commonly seen in rheumatology practice. These data open up new treatment perspectives, with the possibility for precision pain medicine treatment according to pain phenotyping as a logical next step. With this view, studies suggest the possibility of matching non-pharmacological approaches, or medications, or both to the central sensitisation pain phenotypes.

## Introduction

Pain in its acute form enables us to identify potentially harmful stimuli or dangerous situations. As such, pain prevents contact with those stimuli and situations and protects damaged tissue while it heals. However, once pain evolves into a chronic state, its adaptive nature is superimposed by negative sequelae that have a massive effect on both the individual and society. Chronic pain is recognised by WHO as a disease and is one of the most prevalent diseases worldwide, leading to substantial disability and enormous societal costs.<sup>1</sup>

The frequent discrepancy between peripheral drivers of pain and the magnitude of pain and disability represents a diagnostic challenge for clinicians. Often tissue damage, inflammation, or peripheral sensitisation cannot be detected, or if detected does not suffice to explain the reported pain severity, disability, and associated symptoms. Neuroscience research—including areas such as central nociceptive processing,<sup>2</sup> neuronal plasticity,<sup>3</sup> brain alterations,<sup>4</sup> and the transition from acute to chronic pain<sup>5</sup>—has tremendously advanced our understanding of the pathophysiology of pain, and studies on CNS sensitisation (referred to as central sensitisation in this Review) provides an alternative explanation for this discrepancy. For the purpose of this Review, we define central sensitisation as an amplification of neural signalling within the CNS that elicits pain hypersensitivity.<sup>6</sup> The knowledge regarding central sensitisation, supported by findings from numerous systematic literature reviews<sup>7–15</sup> and meta-analyses,<sup>2,16–20</sup> reveals a paradigm shift in the understanding and management of pain that accounts for the role of pain modulation in the CNS. More specifically, knowledge regarding central sensitisation has initiated a shift away from considering primarily peripheral mechanisms when making patient management

decisions. For example, osteoarthritis is now regarded as a condition in which pain comes from a combination of peripheral drivers (eg, cartilage degeneration) and central mechanisms (eg, central sensitisation). Central sensitisation is reflected by a new mechanistic descriptor, nociplastic pain, that was introduced by the International Association for the Study of Pain to complement the terms nociceptive pain (pain caused by damage to non-neural tissue) and neuropathic pain (pain caused by a lesion or a disease of the nervous system). Nociplastic pain is defined as pain that arises from altered nociception with sensitisation as the major underlying mechanism.<sup>21</sup>

Meta-analyses have shown that exercise therapy,<sup>20,22</sup> manual therapy,<sup>20,22</sup> pharmacological,<sup>20</sup> and surgical<sup>20</sup> interventions are able to desensitise the CNS in patients with chronic pain. In the past 5 years, new findings have emerged from studies of central sensitisation in patients seen in rheumatology practice. These new findings include studies showing that central sensitisation predicts poor treatment outcome following procedural treatment,<sup>23</sup> rehabilitation,<sup>24</sup> and surgery,<sup>25–30</sup> studies revealing the diagnostic<sup>31,32</sup> and prognostic<sup>33,34</sup> potential of central sensitisation, and studies showing the potential of matching medications to specific pain phenotypes in rheumatology practice.<sup>35–38</sup>

This Review aims to provide an up-to-date, evidence-based summary of the latest discoveries regarding central sensitisation in patients with chronic pain, and the potential for applying these discoveries to precision medicine approaches.

## Central sensitisation in patients with rheumatic disease

Quantitative sensory testing (QST) is a collective noun for methods to assess and quantify sensory functions, often

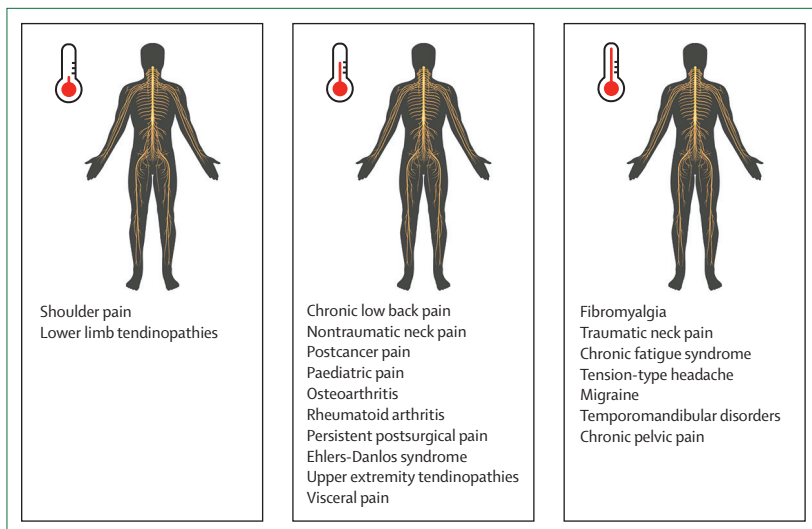
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**Figure 1:** Medical diagnoses related to central sensitisation shown on the central sensitisation continuum. The height of the thermometer reading indicates the severity of central sensitisation.

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through measuring the detection threshold of accurately calibrated sensory stimuli (eg, heat, cold, pressure, electricity, or vibration) or by rating the intensity of suprathreshold stimuli of the same sensory modalities. For an overview of terms often used in central sensitisation research, see the appendix (pp 8–9). Increased sensitivity outside the primary area of tissue injury or damage, or beyond the innervation territory of lesioned or diseased nervous structures, is a hallmark of central sensitisation. QST devices can also assess nociceptive facilitation or modulation when repeated stimuli are delivered. For example, temporal summation (ie, the increase in pain perception during repeated sensory stimulation of constant supra-threshold intensity) is commonly used to estimate facilitation, whereas conditioned pain modulation (ie, the pain inhibits pain model, reflecting the functioning of endogenous analgesic systems and defined as a decrease in pain larger than would be predicted by a small decrease in noxious stimulation) is used to assess modulation.

A growing body of evidence supports the occurrence of central sensitisation in various diseases and pain conditions commonly seen in rheumatology practice, including fibromyalgia, osteoarthritis, Ehlers-Danlos syndrome, and rheumatoid arthritis. Within individual pain conditions, there is substantial patient-to-patient variability in terms of presence and magnitude of central sensitisation, stressing the importance of individual assessment. In particular conditions (eg, fibromyalgia), features of central sensitisation occur in most patients, whereas in other conditions, these features are only present in a subset of patients, whether a majority subgroup (eg, osteoarthritis) or a minority subgroup (eg, lower limb tendinopathies; figure 1). For instance, a greater proportion of patients with fibromyalgia show high amounts of central sensitisation compared with patients with shoulder pain. This implies that high amounts of central sensitisation are

still possible in patients with shoulder pain, but occur less often.

Chronic fatigue syndrome, a condition sharing many clinical features with fibromyalgia, is also characterised by features suggestive of central sensitisation.<sup>39</sup> Although patients with rheumatoid arthritis typically suffer from an inflammatory, nociceptive pain associated with joint inflammation and destruction,<sup>40</sup> features of central sensitisation are associated with increasingly intense pain.<sup>41</sup> Nearly half of patients with rheumatoid arthritis has moderate to high amounts of pain, fatigue, pain catastrophising, and sleep disturbance, but with minimal signs of peripheral inflammation, thereby indicative of widespread pain syndrome,<sup>42</sup> whereas a third of patients also fulfil the fibromyalgia syndrome criteria.<sup>43</sup> Patients with rheumatoid arthritis without other painful comorbidities had hyperalgesia and abnormal cerebral nociceptive processing during noxious stimulation of inflamed joints, but not during stimulation of healthy tissues, thereby indicating peripheral or spinal sensitisation.<sup>44</sup> Furthermore, alterations in brain connectivity indicating central sensitisation have been documented in patients with rheumatoid arthritis.<sup>45</sup> In patients with Ehlers-Danlos syndrome, consistent findings of central sensitisation have been found, such as widespread pain,<sup>46–48</sup> generalised hyperalgesia,<sup>46,48</sup> increased temporal summation,<sup>46,47</sup> and a deficit of endogenous hypoalgesia.<sup>47</sup>

Central sensitisation is a common feature of osteoarthritis pain.<sup>12,20</sup> Compared with pain-free controls, people with osteoarthritis show increased intensity, duration, and spread of pain in response to a standardised injection of hypertonic saline, widespread sensitivity to pressure pain, cold hyperalgesia, increased temporal summation of pain, and impaired endogenous analgesia.<sup>20</sup> Neuroimaging studies have shown increased activity in the limbic system and brainstem in people with osteoarthritis,<sup>49,50</sup> both at rest and in response to standardised painful stimuli. Central sensitisation appears most common among patients with osteoarthritis with high intensity<sup>51</sup> and poorly localised pain.<sup>52</sup> Central sensitisation might partly explain the well-known discordance between pain measures and radiographic severity in osteoarthritis, because markers of central sensitisation are strongest among patients with high pain in the absence of moderate-to-severe radiographic osteoarthritis.<sup>53</sup>

Features of central sensitisation have consistently been detected in patients with chronic and recurrent low back pain, both using responses to stimulation (with pressure pain sensitivity found to be most consistently altered) and brain imaging studies.<sup>19,54</sup> In patients with chronic shoulder pain, there is sparse evidence for generalised mechanical hyperalgesia, widespread referred pain, and increased central sensitisation symptoms, whereas several studies found few features of central sensitisation.<sup>55</sup> Inconsistency among results could be attributed to the different methodologies applied or to different patient populations characterised by different degrees of

central sensitisation. In addition, most prevalent lower extremity tendinopathies (ie, patellar or Achilles tendon) are predominantly peripheral pain states,<sup>56</sup> whereas upper extremity tendinopathies (eg, supraspinatus or lateral epicondylalgia) seem to show potential signs of central sensitisation.<sup>57</sup> For more information on features of central sensitisation in various diseases and pain conditions commonly seen in rheumatology practice, see appendix (pp 1–7).

Even though features of central sensitisation can overlap across medical conditions, the same central sensitisation phenotype (eg, widespread hyperalgesia) can be driven by different underlying pathophysiological mechanisms in different patients. For example, some of the pain conditions with features of central sensitisation are characterised by peripheral inflammation (eg, rheumatoid arthritis and osteoarthritis), although inflammation in the CNS (neuroinflammation) is also a potential contributor to pain and other symptoms in rheumatological diseases. Aberrant glial activation, shown in patients with chronic non-specific low back pain, fibromyalgia, and migraine with aura, can explain the establishment, or maintenance, or both, of central sensitisation in at least a subset of patients.<sup>58,59</sup> Such heterogeneous causes of the same phenotype call for an increasingly individualised mechanistic approach to tailor treatment to individual patient pathophysiology.

### Diagnosis of central sensitisation

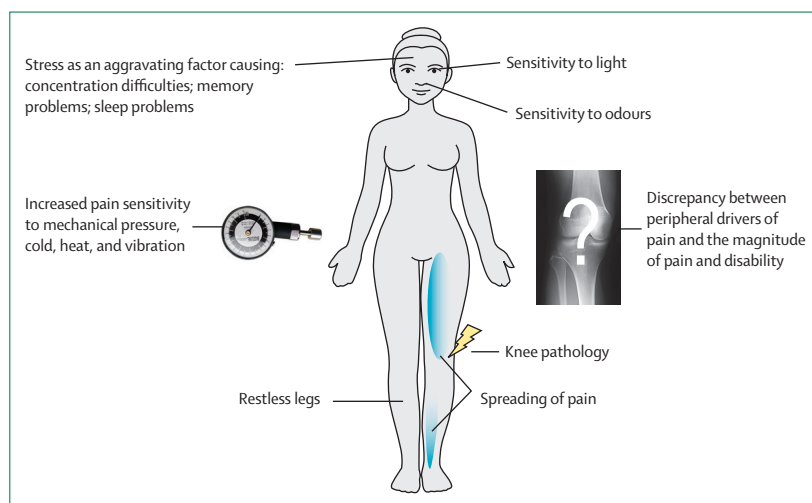
Classifying patients according to different phenotypes (ie, observable characteristics, traits, or clinical presentations without mechanistic implication) and endotypes (ie, subtypes of a disease, implying distinct pathophysiological mechanisms) is gaining attention, to better characterise diseases and to more precisely select therapeutic and management approaches. Features of central sensitisation could help to characterise patients with chronic pain using increasingly homogenous psychopathological profiles.<sup>32</sup> The European League Against Rheumatism recommendations for pain management in inflammatory arthritis and osteoarthritis state that the health professional should be able to differentiate between localised and generalised pain.<sup>60</sup>

The existing literature is characterised by tremendous variability in measures of central sensitisation. QST measures of hyperalgesia in the painful body region are not clear indicators of central sensitisation because they can also reflect peripheral sensitisation; however increased sensitivity to sensory input in non-painful and healthy body parts is generally accepted as a sign of central sensitisation. Interpretation of QST findings in individual patients has to take into account characteristics such as sex, age, ethnic or racial status, and body site of measurement—all of which have been shown by epidemiological studies<sup>61,62</sup> to influence central sensitisation. For instance, women are more sensitive to painful sensory stimuli than men, but the biological sex

influence decreases with increasing age,<sup>62</sup> and in non-traumatic neck pain remote mechanical hyperalgesia is negatively associated with age ( $R^2=25.4\%$ ,  $p=0.031$ ).<sup>61</sup> Patient-reported outcomes, such as the Central Sensitization Inventory (CSI),<sup>63</sup> have also been used to measure central sensitisation, and they are practical to use in nearly every clinical setting. By contrast with QST, which assesses responses of the sensory system to sensory input, patient-reported outcomes primarily assess symptoms considered to be related to central sensitisation (eg, unrefreshing sleep, sleep problems, sensitivity to light, spreading pain, concentration difficulties, stress as an aggravating factor, sensitivity to odours, restless legs). In the absence of consensus guidelines, clinicians are advised to consult available evidence-based recommendations to identify a predominant central sensitisation presentation in patients with musculoskeletal pain,<sup>64</sup> osteoarthritis,<sup>65</sup> and low back pain.<sup>66</sup> These recommendations include the exclusion of neuropathic pain, examining whether the pain distribution is neuroanatomically plausible, and self-reported symptoms as key indicators for clinicians to identify central sensitisation in the clinical setting (figure 2).

The PainDETECT score, a one-page questionnaire originally intended as a screening tool for the neuropathic component of pain disorders, has shown association with signs of central sensitisation in patients with osteoarthritis.<sup>67</sup> In patients with knee osteoarthritis, manual tender point count showed the strongest associations with quantitative sensory testing measures and might be the most promising proxy measure to detect pain sensitisation in these patients.<sup>68</sup> Markers of central sensitisation could potentially improve fibromyalgia diagnosis; a novel protocol based on slowly repeated evoked pain has been identified as a useful marker of central sensitisation in patients with fibromyalgia and enhances diagnostic

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See Online for appendix



**Figure 2: Clinical features of central sensitisation, shown for a patient with a knee pathology**

Increased sensitivity to sensory stimuli can be assessed using quantitative sensory testing, information about the spreading of pain obtained through history taking or a pain drawing, and information about remaining symptoms obtained through history taking, or questionnaires, or both.

accuracy of fibromyalgia beyond key clinical symptoms of the disease, such as fatigue and insomnia.<sup>31</sup>

### Central sensitisation and prognosis

Given the challenges with diagnosis of central sensitisation (ie, high variability in responses expected, absence of clear diagnostic standards, and no gold standard or reference standard), it seems appropriate to position the identification of central sensitisation as a prognostic tool. That is, measures of central sensitisation might be more useful in determining whether a favourable patient outcome is likely. Indeed, there is evidence that patients with (or at risk for) knee osteoarthritis who are pain free but have increased pain sensitivity (ie, to pressure pain and temporal summation) at baseline are twice as likely to develop incident chronic knee pain during a 2 year follow-up than patients who are less pain sensitive (OR 1.98, 95% CI 1.07–3.68).<sup>33</sup> These findings suggest that prevention or amelioration of pain sensitisation might be a novel and important approach to prevent the onset of pain related to chronic knee osteoarthritis.<sup>33</sup> In a primary care setting, symptoms of central sensitisation, as measured by the CSI, appeared to be useful as a prediction tool in patients with musculoskeletal disorders (n=150), with increasingly severe symptoms of central sensitisation predicting higher pain-related disability 3 months later (medium to large effect sizes).<sup>34</sup> Likewise, in a prospective longitudinal study (88 children and adolescents aged 10–17 years) with two study visits (at ≤1 month after pain onset and at 4 months), poorer conditioned pain modulation response (B -0.15; p=0.046) and female sex (B 3.49; p=0.003) predicted the transition from acute to chronic musculoskeletal pain.<sup>5</sup>

Study findings regarding the prognostic value of central sensitisation have been inconsistent. For example, in a prospective cohort study of 130 patients seen in primary care for acute low back pain, QST (electrical, pressure, and temperature stimulation) showed little predictive value for the development of chronic low back pain (pressure pain tolerance in the second toe adjusted OR 0.76, 95% CI 0.29–1.78; p=0.39).<sup>69,70</sup> Although results across studies are inconsistent regarding the prognostic value of QST findings as features of central sensitisation, studies using self-report measures to assess symptoms of central sensitisation all found that higher questionnaire scores were independently predictive of more persistent pain after treatment (eg, after total joint arthroplasty).<sup>71</sup> The absence of predictive ability of QST findings in some studies can be explained by the moderating effects of psychosocial and lifestyle factors, such as sleep and physical activity.<sup>72</sup> A systematic review and meta-analysis in April 2018 that included 37 studies and 3860 participants with musculoskeletal diseases concluded that baseline QST measures of central sensitisation predicted major outcomes such as pain (mean r 0.31, 95% CI 0.23–0.38; n=1057) and disability (mean r 0.30, 95% CI 0.19–0.40; n=290).<sup>73</sup> Baseline temporal summation (mean r 0.37,

95% CI 0.17–0.54) and conditioned pain modulation (mean r 0.36, 95% CI 0.20–0.50) were also associated with pain at follow-up.<sup>73</sup> For example, in 134 patients with knee osteoarthritis, higher temporal summation (OR 2.00, 95% CI 1.23–3.27) and lower pressure pain thresholds (OR 0.48, 95% CI 0.29–0.81) predicted non-response following non-pharmacological management (ie, exercise, weight loss, education).<sup>24</sup> Likewise, in 78 people with chronic lateral epicondylalgia, coexisting fibromyalgia at baseline predicted poorer pain, disability, and pressure pain threshold responses to treatment with methyl-prednisolone plus prilocaine injections for chronic lateral epicondylalgia compared with those with no coexisting fibromyalgia.<sup>23</sup>

A similar picture is seen in patients having surgery. Preoperative features of central sensitisation predict a poor outcome after surgery, as shown in patients having total knee and hip arthroplasty.<sup>25,26</sup> In one study, preoperative central sensitisation persisted 2 years after total knee arthroplasty (n=222), and patients showing preoperative central sensitisation (ie, CSI score ≥40 [scale 0–100]; 55 of 222 patients) had worse quality of life, worse functional disability, and greater dissatisfaction with treatment at 2 years after surgery.<sup>25</sup> In patients having revision for total knee arthroplasty (n=68), a CSI score of 40 or higher before revision substantially increased patient dissatisfaction with treatment after revision (OR 3.9, 95% CI 1.6–9.5; p<0.001).<sup>26</sup> A neuroimaging study provided neurobiological confirmation that a subset of patients with osteoarthritis and neuropathic-like pain (determined using PainDETECT score; n=14) had poor outcome after knee arthroplasty, characterised by increased functional connectivity between limbic areas and brainstem regions important in descending pain modulation, and increased brainstem activation associated with chronic postoperative pain.<sup>74</sup>

QST features of central sensitisation did not predict back surgery failure (defined as continued post-surgery pain or disability) at 12 months in 141 patients with chronic low back pain.<sup>75</sup> However, preoperative symptoms of central sensitisation (ie, CSI score ≥40) were associated with worse quality of life outcomes and increased length of hospital stay in 664 patients who had spinal fusion surgery.<sup>76</sup> For each 10-point increase in CSI score, the length of hospital stay increased by 6.4% (95% CI 0.4–12.6; p=0.035).<sup>76</sup> Similarly, in a prospective observational study of 17 patients with shoulder impingement syndrome, presence of either hyperalgesia or referred pain pre-operatively resulted in a substantially worse outcome (using the Oxford Shoulder Score) from subacromial decompression 3 months after surgery.<sup>77</sup> Such observations led to the development of preventive multimodal analgesia—using a combination of paracetamol, gabapentin, and celecoxib—to address the multiple pathways of acute and chronic pain by interfering with peripheral and central sensitisation, and to achieve safer and more effective perisurgical pain management with reduced opioid use. Although randomised clinical

trials exploring such multimodal analgesia are rare, a prospective observational study in 101 patients having lumbar fusion found that multimodal analgesia reduced postoperative pain (effect size  $-0.59$  to  $-1.16$ ; 28.9%–37.3% reduction on a visual analog scale) and postoperative opioid requirement (effect size from  $-0.54$  to  $-0.99$ ; 34.8%–54.2% morphine-equivalent dose reduction).<sup>78</sup>

### Can central sensitisation be treated in patients with chronic pain?

Although it is logical to target mainly the CNS to reduce central sensitisation, preclinical data suggest that nociceptive inputs arising from peripheral tissues can induce and also maintain central sensitisation.<sup>3</sup> Therefore, treatments to reduce peripheral nociception (bottom-up treatments) can potentially attenuate central sensitisation in an undetermined proportion of patients. At the group level, total hip and knee replacement led to normalisation of measures of central sensitisation at long-term follow-up.<sup>4,79</sup> This might seem contradictory to the finding that preoperative features of central sensitisation predict poor outcome following total knee and hip arthroplasty.<sup>25,26</sup> However, together these findings suggest different patient subtypes; patients showing high amounts of central sensitisation before surgery are at higher risk of poor surgical outcomes and therefore require approaches to attenuate central sensitisation (top-down treatment), whereas patients presenting few or no features of preoperative central sensitisation are more likely to benefit from joint replacement surgery. Also, within patients with preoperative central sensitisation, the mechanisms driving central sensitisation might be fundamentally different in subgroups. In some patients, central sensitisation can be maintained by peripheral input (bottom-up), and surgical removal of the source of this input normalises these patients' pain processing. By contrast, other patients are characterised by central sensitisation that is primarily central, and relatively independent of peripheral drivers, so such patients are unlikely to benefit from surgical intervention targeting peripheral sources. It is also important to highlight that there are other factors, such as pain catastrophising, that interact with central sensitisation to determine whether a postoperative outcome is positive or not.<sup>80</sup> Also, the presence of central sensitisation should not prevent health-care providers from searching for and possibly treating peripheral dysfunctions, in the context of a multifactorial disease model that considers both peripheral and central components. Unfortunately, many clinicians globally continue to focus on treating only peripheral drivers of central sensitisation, rather than adhering to a multifactorial disease model. Therefore, it is cardinal for clinicians to keep in mind that per definition, nociplastic pain implies that nociceptive input from peripheral structures is not the dominant mechanism underlying the pain experience and it should

not therefore be the main target of the treatment in those patients with predominant nociplastic components.

Among available and established pharmacological treatments, antidepressants are effective in different chronic musculoskeletal pain conditions associated with central sensitisation, such as fibromyalgia,<sup>81</sup> low back pain,<sup>82</sup> neck pain,<sup>83</sup> and knee osteoarthritis.<sup>84</sup> A systematic review found moderate to high quality evidence that the anti-convulsant gabapentin is ineffective for the treatment of low back pain or lumbar radicular pain,<sup>85</sup> whereas another systematic review found insufficient evidence to either support or refute the efficacy of gabapentin in reducing pain in patients with fibromyalgia.<sup>86</sup> Three randomised controlled trials found pregabalin to be effective in reducing pain associated with fibromyalgia.<sup>87–89</sup> A large randomised placebo-controlled trial found that for patients with fibromyalgia ( $n=750$ ), 14 weeks of pregabalin at 300 mg/day, 450 mg/day, and 600 mg/day were effective in improving sleep, Fibromyalgia Impact Questionnaire scores, and Patient Global Impression of Change scores.<sup>87</sup> Similarly, in a randomised trial of 529 patients with fibromyalgia, 8 weeks of pregabalin 450 mg/day reduced pain (change on 0–10 pain scale:  $-0.93$  pregabalin 450 mg/day  $p<0.001$ ), disturbed sleep, and fatigue compared with placebo.<sup>88</sup> 41 patients with fibromyalgia were randomly assigned in a four-period crossover study in which patients received maximally tolerated doses of placebo, pregabalin, duloxetine, and a pregabalin–duloxetine combination, each for 6 weeks.<sup>89</sup> The pregabalin–duloxetine combination was superior to either drug as monotherapy to reduce pain in patients with fibromyalgia.<sup>89</sup> Overall, it seems that anticonvulsants might be effective in relieving pain in conditions associated with central sensitisation, but their effect might not be detected in heterogeneous patient populations. It is possible that response to these medications depends on the presence and magnitude of central sensitisation, but this idea remains hypothetical.

The use of opioids for chronic non-cancer pain is a matter of considerable debate, in view of concerns about safety and scant evidence of efficacy,<sup>90</sup> such discussion is outside the scope of this Review. Although opioids might reduce indices of central sensitisation in the short term (ie, 7.5 h after medication intake),<sup>91</sup> their prolonged use (ie, for months) can lead to enhanced central sensitisation and related hyperalgesia.<sup>92</sup> Therefore, current knowledge does not support the use of opioids to treat central sensitisation and suggests that long-term use of opioids might worsen the condition of patients with established central sensitisation.

Non-pharmacological interventions can also reduce central sensitisation. A systematic review and meta-analysis studied the effect of physical therapy on temporal summation and conditioned pain modulation in patients with various chronic musculoskeletal pain conditions,<sup>22</sup> and showed that manual therapy ( $n=721$ ) significantly improved temporal summation (difference  $-0.21$ , 95% CI

−0.39 to −0.03;  $p=0.02$ ], whereas physical therapy (ie, exercise therapy;  $n=680$ ) significantly improved conditioned pain modulation (difference 0.34, 95% CI 0.12–0.56;  $p=0.003$ ), although the quantitative effect was slight. Another systematic review and meta-analysis found little evidence that pulsed electromagnetic field, transcutaneous electrical neuromuscular stimulation, electrical intramuscular stimulation, exercise programmes, and knee joint mobilisation increased localised and remote pressure pain thresholds in patients with knee pain.<sup>20</sup> Exercise produces a hypoalgesic effect and has the potential to reduce central sensitisation. Although exercise-induced hypoalgesia is robust in asymptomatic individuals, its effect is less consistent in people with musculoskeletal pain, and might be dependent on the exercise type, intensity, and duration.<sup>93</sup> Emotional states influence central pain processes;<sup>94</sup> as such, treatments to improve emotional functioning might attenuate central sensitisation. Randomised trials have established the efficacy of psychological treatments for reducing chronic pain,<sup>95</sup> and there is evidence that this effect might be mediated by mechanisms other than an effect on central sensitisation (eg, through improving self-efficacy and decreasing catastrophising thinking).<sup>95</sup> Finally, on the basis of a meta-analysis of the available literature, it was concluded that an altered dietary pattern and altered specific nutrient intake might have analgesic properties for patients with chronic pain,<sup>96</sup> although evidence comes primarily from trials in patients with osteoarthritis, and there is too little evidence supporting a positive effect on features of central sensitisation to reach conclusions.

Taken together, the available literature supports the use of pharmacological and non-pharmacological strategies to reduce central sensitisation, and consequently to improve patient outcomes. Both pharmacological and non-pharmacological strategies are supported by findings from meta-analyses, yet neither approach exerts large effects on features of central sensitisation. Trials comparing the effects of pharmacological versus non-pharmacological strategies on features of central sensitisation are absent, and therefore represent an important research priority. These treatments might be most likely to be effective in patients with particular manifestations of central sensitisation, such as widespread pain, hyperalgesia, and lowered pain thresholds. The effect size of the available treatments remains small, but these approaches are still valuable in the frame of a multimodal and comprehensive approach to chronic pain. Also, the primary outcomes of interest should always be decreased pain and improved quality of life. Future work should examine whether attenuation of central sensitisation is associated with improvements in these outcomes.

### Towards precision medicine for chronic pain in rheumatology practice

Precision medicine refers to the ability to classify patients into subgroups that differ in their susceptibility to,

biology of, or prognosis of a particular disease, or in their response to a specific treatment—and thus the ability to tailor treatment to the individual patient's characteristics.<sup>97</sup>

Studies suggest that assessment of central sensitisation might be used to improve precision pain medicine for rheumatology practices. Clinical features of central sensitisation might allow for identification of patients with knee osteoarthritis who are more likely to respond to duloxetine, a selective serotonin norepinephrine reuptake inhibitor. Post-hoc analysis of a phase 3 randomised clinical trial of 353 patients with pain due to knee osteoarthritis showed that duloxetine was effective at reducing pain in patients with three or more painful sites, but not in patients with fewer than three painful sites.<sup>35</sup> In a randomised clinical trial of 80 patients with knee osteoarthritis and evidence of central sensitisation comparing perioperative duloxetine (30 mg of duloxetine 1 day before surgery and for 6 weeks afterwards) with a control found that patients in the duloxetine group reported less pain from 2 weeks to 3 months after surgery compared with the control group.<sup>36</sup> These studies provide preliminary evidence that analgesics that act centrally might reduce the risk of chronic postoperative pain in high-risk patients who have evidence of central sensitisation before surgery. Similarly, patients with chronic low back pain and clinical features of central sensitisation responded better to duloxetine than did patients without such features.<sup>37</sup> A double-blind, randomised, crossover trial of 150 patients with chronic low back pain found that imipramine showed no overall effect on low back pain, although patients who were more sensitive to heat and cold pain had significantly more pain relief with imipramine compared with placebo.<sup>38</sup> Together, these studies suggest the possibility of personalised pain treatment in osteoarthritis and chronic low back pain, matching medications to specific pain phenotypes.

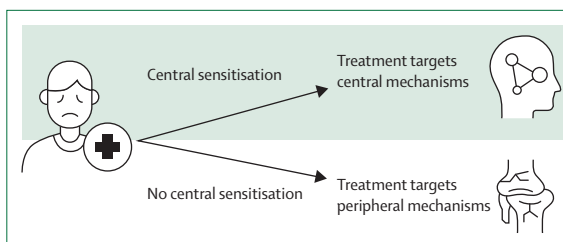
Such a precision approach to pain treatment also implies that patients not presenting with features of central sensitisation might increasingly benefit from unimodal treatment (figure 3). This idea is substantiated by an observational study showing that patients with knee osteoarthritis and stronger conditioned pain modulation (ie, increased nociceptive inhibition) before treatment responded better to the nonsteroidal anti-inflammatory drug diclofenac than did patients with weaker conditioned pain modulation, whose pain might be driven less by peripheral sensitisation and nociceptive drive from the joint and more by central sensitisation.<sup>98</sup>

Although compelling, there is a long way to go before the assessment of central sensitisation can be used to provide precision pain medicine in rheumatology practice. First, the number and relative strength of studies supporting precision pain medicine are low; prospective trials are unavailable and are therefore a research priority. Prospective trials are needed to examine matching medications to specific pain phenotypes, to confirm or refute the early findings in patients with

osteoarthritis and chronic low back pain. For the many other populations with established features of central sensitisation (appendix pp 1–7), pilot studies, or secondary analysis of available trial datasets, are needed to generate proof-of-concept for the idea of precision pain medicine. The same applies to the precision pain treatment approach that targets patients not presenting with features of central sensitisation, and whether these patients might benefit more from peripheral, bottom-up treatment.

### Matching patient education to specific pain phenotypes

The paradigm shift from peripheral to central pain mechanisms is also reflected in pain education strategies. Central sensitisation is increasingly used as an evidence-based explanation for chronic pain in rheumatology practice. Pain neuroscience education has gained worldwide interest as an innovative intervention to improve patients' pain beliefs and coping strategies. Pain neuroscience education applies the knowledge regarding central sensitisation to explain to patients that their pain is (at least partly) due to central mechanisms. In the past decade, evidence in support of pain neuroscience education for patients having chronic pain has increased, with 12 randomised clinical trials in 755 patients with osteoarthritis, chronic spinal pain, fibromyalgia, or having knee arthroplasty, and pooled effects of clinical relevance in the short term for pain (change on a scale of 0–100 was  $-5.91$ , 95% CI  $-13.75$  to  $1.93$ ), disability ( $-4.09$ , 95% CI  $-7.72$  to  $-0.45$ ) and kinesiophobia ( $-13.55$ , 95% CI  $-25.89$  to  $-1.21$ ), and in the medium term for pain ( $-6.27$ , 95% CI  $-18.97$  to  $6.44$ ), disability ( $-8.14$ , 95% CI  $-15.60$  to  $-0.68$ ) and pain catastrophising (change on a scale of 0–52 was  $-5.26$ , 95% CI  $-10.59$  to  $0.08$ ).<sup>99</sup> However, a randomised trial found that neuroscience education did not seem to add value when used with recommended first-line care for 202 patients with acute (ie, lasting less than 6 weeks) low back pain and a high risk of developing chronic low back pain.<sup>100</sup> A secondary analysis of a clinical trial revealed that pain neuroscience education was useful for improving kinesiophobia and illness beliefs in 120 patients with chronic spinal pain regardless of the presence or absence of central sensitisation, but pain neuroscience education appeared to be more effective for reducing pain catastrophising in patients with high self-reported symptoms of central sensitisation.<sup>101</sup> In line with the move towards personalised health care, it might be appropriate to use pain neuroscience education for specific pain phenotypes, but prospective trials examining whether matching education to specific pain phenotypes is beneficial are needed. Pain education is often the first step in a multimodal approach (including exercise therapy, stress management, sleep management, etc), and prospective trials should examine the effects of multimodal approaches tailored to specific pain phenotypes.



**Figure 3:** Proposed precision pain treatment approach for chronic pain in rheumatology practice, shown for a patient with a knee pathology

### Search strategy and selection criteria

We searched PubMed and Web of Science from May 1, 2020, to Aug 31, 2020, using the search terms “central sensitisation”, “chronic pain”, “nociceptive pain”, cross-referenced with search terms tailored for specific sections (eg, “diagnosis”, “treatment”, “prognostic”, “prediction”) and specific diagnosis (eg, “osteoarthritis”, “fibromyalgia”, “chronic fatigue syndrome”, “headache”, “osteoarthritis”, “Ehlers-Danlos syndrome”, “rheumatoid arthritis”, “post-surgical pain”, “low back pain”, “neck pain”, “shoulder pain”, “widespread pain”, “cancer”, “pelvic pain”, “visceral pain”, “pediatric pain”, “temporomandibular pain” and “tendinopathies”) (for search results, see appendix pp 1–6). We did not restrict search results by language, article type, or date of publication. In assessing the search results, we excluded preclinical studies, unpublished material, and conference abstracts, and prioritised for inclusion in this Review systematic reviews, meta-analyses, cohort studies, and fully powered randomised clinical trials, with special emphasis on studies published in 2015 or later.

### Conclusions

Features of central sensitisation are present in many different chronic pain conditions commonly managed in rheumatology practice, and this knowledge represents a paradigm shift in the understanding of chronic pain. Within individual pain conditions, there is substantial variability among patients in terms of presence and magnitude of central sensitisation, which stresses the importance of individual assessment. Although central sensitisation can predict poor treatment outcomes in some patient groups, there are both pharmacological and non-pharmacological treatments available that show the capacity to attenuate central sensitisation. The data in this Review open up new treatment perspectives, with the possibility for precision pain medicine treatment according to pain phenotyping in rheumatology practice as a logical next step. Within this precision-based view, studies suggest the possibility of matching non-pharmacological approaches, or medications, or both, to the central sensitisation pain phenotypes in conditions commonly seen in rheumatology practices.

#### Contributors

JN and KI developed the initial idea for the Review. JN and MC project managed the Review. All authors contributed to literature search, writing, and interpretation of the findings. JN drew figure 1 using BioRender.com.

#### Declaration of interests

EK reports personal fees from Eli Lilly and personal fees from Lundbeck, outside the submitted work. DC reports grants and personal fees from Aptinix, Eli Lilly, Samumed, Tonix, Nix Patterson on behalf of State of OK, and Lundbeck Pharmaceuticals, and Pfizer, outside the submitted

work. JN and the Vrije Universiteit Brussel received lecturing and teaching fees from various professional associations and educational organisations. SG reports grants from NIH, and personal fees from Rehab Essentials and Med Risk, outside the submitted work. All other authors declare no competing interests.

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