



## Chronic Pain 1

## Chronic pain: an update on burden, best practices, and new advances

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See [Comment](#) page 2029This is the first in a [Series](#) of three papers about chronic pain

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Chronic pain exerts an enormous personal and economic burden, affecting more than 30% of people worldwide according to some studies. Unlike acute pain, which carries survival value, chronic pain might be best considered to be a disease, with treatment (eg, to be active despite the pain) and psychological (eg, pain acceptance and optimism as goals) implications. Pain can be categorised as nociceptive (from tissue injury), neuropathic (from nerve injury), or nociplastic (from a sensitised nervous system), all of which affect work-up and treatment decisions at every level; however, in practice there is considerable overlap in the different types of pain mechanisms within and between patients, so many experts consider pain classification as a continuum. The biopsychosocial model of pain presents physical symptoms as the denouement of a dynamic interaction between biological, psychological, and social factors. Although it is widely known that pain can cause psychological distress and sleep problems, many medical practitioners do not realise that these associations are bidirectional. While predisposing factors and consequences of chronic pain are well known, the flipside is that factors promoting resilience, such as emotional support systems and good health, can promote healing and reduce pain chronification. Quality of life indicators and neuroplastic changes might also be reversible with adequate pain management. Clinical trials and guidelines typically recommend a personalised multimodal, interdisciplinary treatment approach, which might include pharmacotherapy, psychotherapy, integrative treatments, and invasive procedures.

## Introduction

It is difficult to overestimate the burden of chronic pain, which is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.<sup>1</sup> Pain is the main reason why people seek medical care, with three of the top ten reasons being osteoarthritis, back pain, and headaches.<sup>2</sup> Among the four leading causes of years lost to disability, three of these (back pain, musculoskeletal disorders, and neck pain) are chronic pain conditions.<sup>3</sup> Prevalence rates of chronic pain vary between 11% and 40%, with a study by the US Centers for Disease Control and

Prevention (CDC) estimating the point prevalence at 20·4%.<sup>4</sup> A systematic review comprising studies done in the UK reported a pooled chronic pain prevalence rate of 43·5%, with the rate of moderate-to-severe disabling pain ranging from 10·4% to 14·3%.<sup>5</sup> A large-scale 4-year longitudinal study, also done in the UK, found the annual incidence rate for chronic pain to be 8·3%, with a recovery rate of 5·4%.<sup>6</sup>

This paper is the first in a Series of three papers about chronic pain, and aims to provide an overview of chronic pain for a non-specialty audience, with emphasis on best practices and selected advances. The areas covered include epidemiology, the classification of pain, overarching models, and management, with the other articles focusing on nociplastic pain<sup>7</sup> and neuromodulation,<sup>8</sup> two areas that have witnessed substantial advances in the past several years but have not been adequately addressed in the general medicine literature.

Not all people are affected by chronic pain equally. Data from the CDC found higher prevalence rates in women, individuals from lower socioeconomic backgrounds, military veterans, and people residing in rural areas.<sup>4</sup> Regarding race and ethnicity, studies are mixed, with some reporting the highest rates among non-Hispanic White people than any other group,<sup>4</sup> whereas most have reported a higher prevalence in racial and ethnic minorities, such as African American people and indigenous populations.<sup>9</sup> Explanations for racial differences include enhanced physiological pain sensitivity, cultural differences, and reduced access to care. When controlling for income amount and adverse life events, differences in prevalence are attenuated, but not eliminated.<sup>10</sup> The prevalence of chronic pain and

## Search strategy and selection criteria

From January to July, 2020, we searched databases on MEDLINE, Embase, Ovid, and Google using the key words “chronic pain”, “neuropathic pain”, “non-neuropathic pain”, “nociceptive pain”, “inflammatory pain”, “diffuse pain”, and “nociplastic pain”, cross-referenced with key words tailored for individual sections (eg, “cost-effectiveness”, “biopsychosocial”, “cancer”, etc) There were no restrictions on article types, date of publication, or language. For the pain management section, key words were chosen on the basis of the treatment(s) and conditions evaluated (eg, “gabapentin” and “neuropathic pain”). For this section, we prioritised systematic reviews, meta-analyses and large, randomised trials, but did not exclude any data sources including publicly available government documents.

associated disability is higher in low-income countries than in high-income countries.<sup>11</sup>

The economic costs of chronic pain are substantial. A report by the Institute of Medicine, released in 2010, estimated that chronic pain afflicts approximately one in three Americans, costing between US\$560 and US\$635 billion per year in medical costs and lost productivity.<sup>10</sup> This estimate did not include the cost of care for institutionalised individuals (such as prisoners or nursing home patients), military personnel, and children, or the costs associated with caregiving. A newer report found the average cost per year for one of the 15.4% of Australian people living with chronic pain to be AU\$22 588–\$42 979, when non-financial costs were considered.<sup>12</sup>

### Chronic pain as a disease model

Acute pain is an unpleasant, dynamic psychophysiological process, usually in response to tissue trauma and related inflammatory processes; thus, this pain possesses a survival value and plays a role in healing. However, once the acute danger period has passed, the pain no longer becomes a necessity, but a burden—a disease unto itself.<sup>13</sup> Although there is no clear threshold of when acute pain becomes chronic, it is generally accepted that pain persisting beyond the expected healing period (3 months according to International Classification of Diseases, 11th edition criteria)<sup>14</sup> is pathological.

In contrast to acute pain, chronic pain contains little evolutionary benefit. In viewing chronic pain as a disease, patients and providers might shift their expectations from eradicating the problem to controlling it (ie, functional and emotional restoration). Consistent with other diseases, chronic pain is associated with unique, and sometimes disease-specific, alterations in the peripheral nervous system and CNS, along with many quality of life decrements.<sup>13,15</sup> The predisposing factors and consequences of chronic pain are well known, but the flipside is that factors promoting resiliency, such as emotional support systems and good health, can promote healing and reduce pain chronicification.<sup>13</sup> Similar to other diseases, there is evidence that quality of life indicators and neuroplastic changes might be reversible with adequate pain management.<sup>16</sup>

### Biopsychosocial model and consequences of chronic pain

The biopsychosocial model postulates pain and disability as multidimensional, dynamic interactions among biological, psychological, and social factors that reciprocally influence each other (figure 1).<sup>17</sup> It is generally accepted that characteristics such as depression, anxiety, poor sleep, and adverse social conditions can be the result of chronic pain, but it is less commonly known that these factors also predispose individuals to chronic pain. Psychological factors associated with the development of chronic pain include depression, anxiety, post-traumatic stress, poor coping skills, and catastrophisation, among

others. Sociocultural factors that are associated with chronic pain include low educational attainment, culture, and poor social support.<sup>18</sup> Contributing biological factors include genetics, age, sex, sleep, hormones, and endogenous opiate systems (figure 1).<sup>17,19</sup>

As a leading cause of disability, chronic pain interferes with an individual's ability to work and can lead to financial ramifications, including homelessness; in studies evaluating chronic pain in the undomiciled, the prevalence ranges from 47% to 63%.<sup>20,21</sup> Chronic pain affects relationships and self-esteem, and is associated with higher divorce and suicide rates, and an increased risk of substance abuse.<sup>22–24</sup> When controlling for other variables, chronic pain is associated with a reduced life expectancy.<sup>25</sup>

Chronic pain affects biological processes in dynamic ways. Pain might affect survival rates in patients with cancer, with one meta-analysis, which included over 10 000 patients, finding a mean survival time of 27 months in individuals with severe pain versus 71 months in those without pain.<sup>26</sup> Although it is well established that individuals with abnormal pain processing are prone to chronic pain, it is less well known that a history of pain predicts persistent pain after injury.<sup>27</sup>

In acute pain, peripheral mechanisms predominate though central sensitisation and immune system

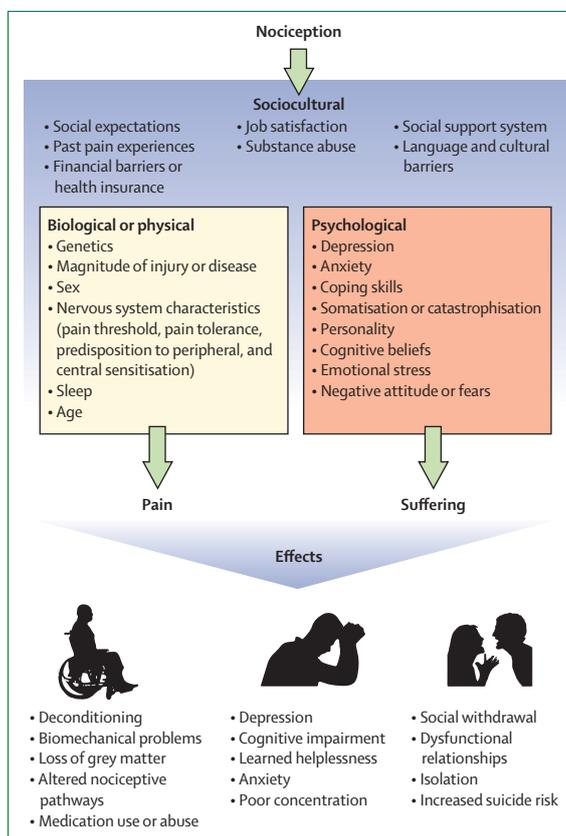


Figure 1: Biopsychosocial model of pain showing the complex interaction between chronic pain and biological, psychological, and social factors

activation, and epigenetic modulation can also contribute.<sup>28</sup> Yet unlike most acute pain, chronic pain is associated with deleterious pathophysiological and anatomical changes, including peripheral and central sensitisation, the development of new neural connections, and pathology-specific brain alterations.<sup>14,29</sup> Some of these changes might be elicited and maintained not only by nociception, but also by psychosocial factors. Examples of the protean effects chronic pain has on biological processes include the suppression of cell-mediated immunity and humoral immunity, alterations in gene expression, transformation of nerves that generally transmit non-pain signals into nerves that express substance P and excite nociceptive spinal neurons (a phenotypic switch), and decreases in grey brain matter.<sup>29-32</sup> Most of these changes are at least partly reversible with effective treatment.<sup>15,33</sup>

### Classification of pain and its importance

The categorisation of pain influences prognosis, work-up, and treatment at all stages, with implications for

the provision of services (payer authorisation) and prevalence estimates. For example, in patients with back pain, in addition to red flags, which include severe or progressive neurological deficits (present in some patients with neuropathic pain), imaging is recommended when considering an invasive procedure, such as surgery or a cervical epidural steroid injection, which are more effective for neuropathic than non-neuropathic pain.<sup>34</sup>

The IASP defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”.<sup>1</sup> This definition acknowledges that pain can occur in the absence of identifiable tissue damage, such as in fibromyalgia. As pain is always subjective, a patient’s report of pain should be accepted at face value in the absence of evidence to the contrary, although physicians might consider other means (eg, facial expressions, imaging) to evaluate pain and identify causes (figure 2; table 1). Table 1 describes the three main categories of chronic pain: nociceptive, neuropathic, and nociplastic.

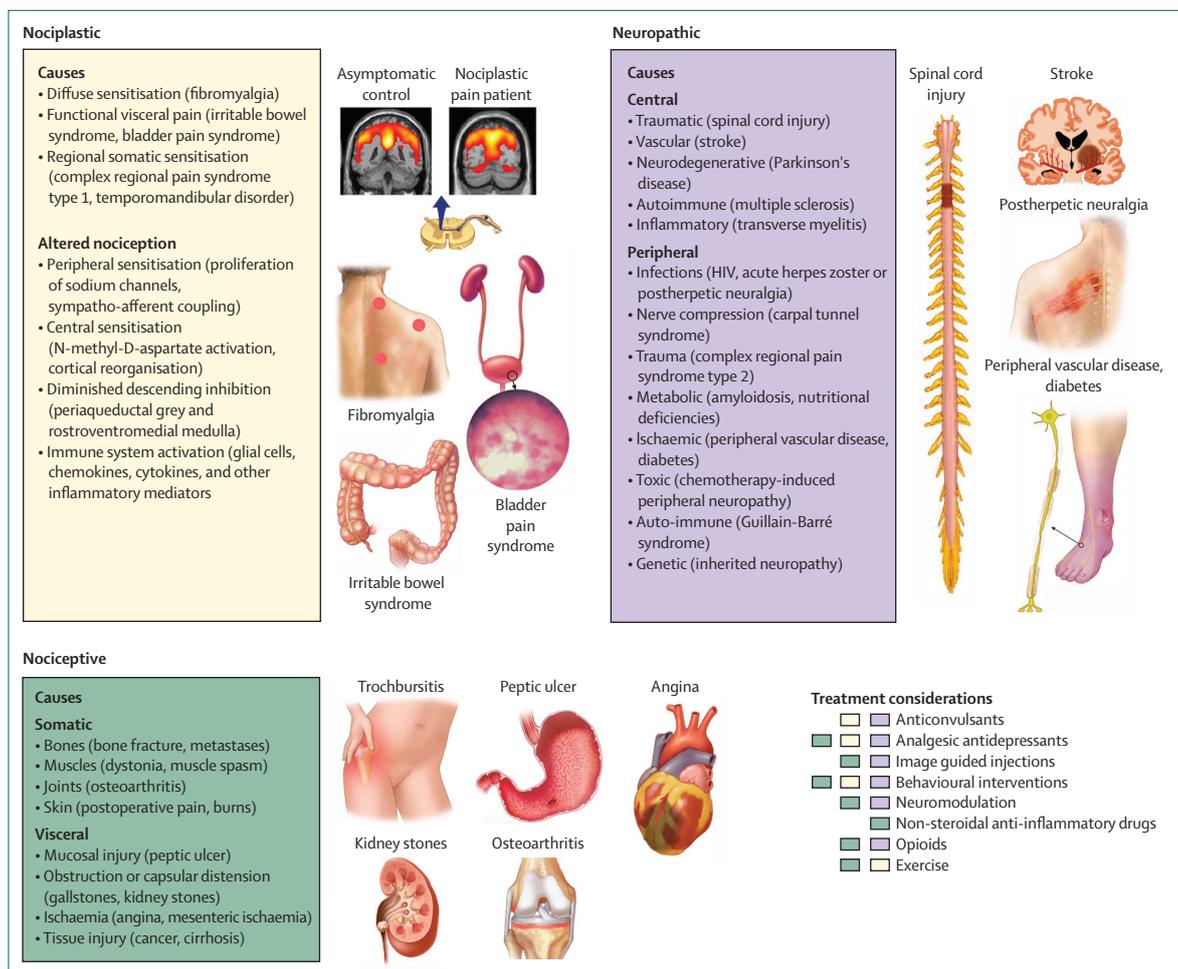


Figure 2: Illustrative drawing showing the various manifestations of neuropathic, nociceptive, and nociplastic pain, along with treatment considerations

### Nociceptive pain

Nociceptive pain results from activity in neural pathways, secondary to actual stimuli or stimuli that might potentially damage tissue. Nociceptive pain is the most common form of chronic pain, encompassing arthritis and most forms of spinal pain (table 1).<sup>35</sup>

### Neuropathic pain

Neuropathic pain is defined by the IASP as pain caused by damage or disease affecting the somatosensory

nervous system.<sup>36</sup> Compared with nociceptive pain, neuropathic pain is typically associated with sensory abnormalities, such as numbness and allodynia, more prominent pain paroxysms and, depending on the nerve(s) affected, neurological findings (table 1). Typical descriptors for nociceptive pain include terms such as aching and throbbing, whereas neuropathic pain is generally described with adjectives such as lancinating and shooting. Approximately 15–25% of chronic pain is neuropathic, with the most common conditions including

	Nociceptive pain	Neuropathic pain	Nociplastic pain
Causes	Tissue or potential tissue damage	Disease or injury affecting the nervous system	Maladaptive changes that affect nociceptive processing and modulation without objective evidence of tissue or nerve damage
Examples and mechanisms	Degenerative changes that occur via normal wear and tear (degenerative disc disease, facet arthropathy, primary osteoarthritis), trauma (eg, burns, muscle tears, traumatic arthritis), muscle spasm, visceral pathology (eg, ulcers, renal stones, pancreatitis)	Nerve or nerve root compression (eg, radiculopathy, carpal tunnel syndrome), toxins (eg, chemotherapy), metabolic (eg, liver disease, diabetes), ischaemia (eg, peripheral vascular disease, diabetes), trauma (eg, postsurgical pain), infectious (eg, shingles, HIV), inflammatory (eg, acute and chronic inflammatory demyelinating polyradiculoneuropathy), hereditary (eg, Charcot-Marie Tooth)	Central sensitisation, wind-up, glial and chronic immune system activation, disturbed response to psychosocial stressors, reduced central inhibition. Examples include bladder pain syndrome, fibromyalgia, irritable bowel syndrome, temporomandibular disorder, some tension-type headaches and non-specific back pain
Descriptors	Throbbing, aching, pressure-like	Lancinating, shooting, electrical-like, stabbing	Similar to neuropathic pain; visceral pain (eg, interstitial cystitis, irritable bowel syndrome), might be described as diffuse, gnawing, aching, sharp
Sensory deficits	Infrequent and, if present, in non-dermatomal or non-nerve distribution	Frequent (eg, numbness, tingling, pricking)	Not uncommon, in non-dermatomal and non-nerve distribution
Motor deficits	Might have pain-induced weakness	Neurological weakness might be present if motor nerve affected; dystonia or spasticity may be associated with CNS lesions, and sometimes peripheral lesions (eg, complex regional pain syndrome type 2, other forms of peripheral nerve trauma)	Generalised fatigue common; weakness might be related to deconditioning
Hypersensitivity	Uncommon except for hypersensitivity in the immediate area of an acute injury	Pain frequently evoked with non-painful (allodynia) or painful (exaggerated response) stimuli	Common, often diffuse; hyperalgesia and sensitivity to mechanical stressors more common than allodynia
Pain pattern	Distal radiation less common; proximal radiation frequent around area of anatomical structure	Distal radiation common in a nerve or nerve root (dermatomal) distribution	Diffuse spread not confined to an anatomical referral pattern; patients often have multiple nociplastic conditions
Precipitating or relieving factors	Exacerbations less common and often associated with activity	Exacerbations common and unpredictable	Common, often related to psychosocial stress
Autonomic signs	Uncommon	Colour changes, temperature changes, swelling, or sudomotor (sweating) activity, or a combination, occur in a third to half of patients	Sympathetic nervous system hyperactivity common in diffuse pain (fibromyalgia) and visceral pain conditions (irritable bowel syndrome)
Accompanying symptoms	Higher rates of psychopathology including depression and anxiety than controls	Greater psychological distress and concomitant disability than observed in nociceptive pain	Psychological distress affects most individuals. Cognitive symptoms, insomnia, and fatigue are common. Gastrointestinal complaints and sensitivity to other sensory stimuli often occur. Association with multiple sensitivity reactions to chemicals
Concomitant conditions	Higher rates of psychopathology, insomnia, obesity, other pain conditions, cognitive impairment, hypertension, and cardiovascular disease	Higher rates of psychopathology, insomnia, cognitive impairment (eg, dementia), and hypertension and cardiovascular disease. Many diseases that cause neuropathic pain result from conditions that can lead to pain and other symptoms (diabetes, rheumatoid arthritis, lupus, coeliac disease, HIV, and other infections). Severe neuropathy can result in autonomic symptoms (eg, gastroparesis, dizziness, and syncope)	Similar to nociceptive pain. Nociplastic conditions have high co-prevalence rates with each other, and with other chronic pain conditions such as spine pain, arthritis and headaches, cataplexy, and psychiatric conditions such as post-traumatic stress and eating disorders
Effective non-opioid pharmacological treatments	Non-steroidal anti-inflammatory drugs (topical and systemic), muscle relaxants (more effective for acute and subacute spinal pain), serotonin–norepinephrine reuptake inhibitors and tricyclic antidepressants, disease modifying anti-rheumatic drugs (inflammatory arthritis), nerve growth factor inhibitors (anticipated approval), tramadol	Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors, gabapentinoids, high concentration capsaicin patch (regional pain), lidocaine patch (regional pain), tramadol	Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors, gabapentinoids, ketamine infusions

Table 1: Distinguishing features of neuropathic, nociceptive, and nociplastic pain

diabetic neuropathy, postherpetic neuralgia, and radiculopathy.<sup>29</sup> Several instruments have been validated for the classification of chronic pain, although physician designation is the reference standard.<sup>37</sup> As opposed to many forms of nociceptive pain and acute nerve injury, chronic neuropathic pain is always maladaptive. Although the association between pain intensity and disability is weak, compared with similar degrees of nociceptive pain, neuropathic pain might be associated with greater decrements in quality of life.<sup>38,39</sup>

### Nociplastic pain

Nociplastic pain is pain that arises from the abnormal processing of pain signals without any clear evidence of tissue damage or discrete pathology involving the somatosensory system.<sup>7</sup> Previously known as functional pain syndromes, these conditions include pain states such as fibromyalgia, irritable bowel syndrome, and possibly non-specific back pain (table 1). The pathophysiological mechanisms that cause these disorders primarily involve augmented sensory processing and diminished inhibitory pathways (see the article on nociplastic pain in this series). With few exceptions, procedural interventions are associated with poorer outcomes in individuals with nociplastic pain than in patients with nociceptive (eg, from joint injections) or neuropathic (eg, from epidural steroid injections) pain.<sup>40</sup>

### Mixed pain and pain classification as a continuum

There is growing recognition that many pain conditions, especially those involving cancer and spine pain, have a mixed pain phenotype (ie, do not fall neatly into one category), with one large study estimating the prevalence of mixed pain among patients with chronic pain in primary care and orthopaedic settings to be more than 50%.<sup>41,42</sup> It is important to recognise that similar to conditions such as a headache, many experts consider the types of pain to occupy different points on a continuum, as the main distinction between neuropathic and non-neuropathic pain is the absence of transduction with neuropathic pain (ie, there are no distinct pain pathways). This framework might explain why non-steroidal anti-inflammatory drugs (NSAIDs), though considered more effective in nociceptive pain, might sometimes improve neuropathic pain, and pre-emptive membrane stabilisers might decrease or prevent postsurgical pain.<sup>43,44</sup> Although the concept of mixed pain is increasingly recognised by clinicians and researchers, the term itself is absent in IASP terminology and most major textbooks.

### Cancer versus non-cancer pain and patients who recover from cancer

Many guidelines on pain management, including the CDC guidelines on opioids,<sup>45</sup> assert that cancer should be considered separately from other chronic pain

conditions, and is subject to different recommendations. Yet, as the US Food and Drug Administration has asserted (FDA-2012-P-0818),<sup>46</sup> the mechanisms and pathways for cancer and non-cancer pain are identical; there is no pathophysiological reason why cancer and non-cancer pain should be treated differently, because patients suffer from both conditions; and compared with acute pain, where inhibitory mechanisms are not maximised, there is less nociceptive signalling.<sup>47</sup> Rather, the distinctions between cancer and non-cancer pain revolve around existential issues such as uncertainty and prognosis. Although the sensory-discriminative (ie, somatosensory perception, including pain intensity and location) aspects of cancer and non-cancer pain might be similar, cancer pain might be associated with more pronounced affective–motivational and cognitive–evaluative components.<sup>48</sup>

The 5-year survival rate for all cancer types is approximately two-thirds<sup>49</sup> and, according to one study, up to 40% of patients with chronic pain seen at pain centres affiliated with cancer hospitals are patients who have survived cancer.<sup>50</sup> Patients who have survived cancer might experience nociceptive, nociplastic, and non-neuropathic pain related to treatment (surgery, chemotherapy, radiation), tumour burden, natural processes, and psychological precipitators.<sup>51</sup> In patients who have recovered from cancer who have chronic pain, treatment should be similar to other patients, tailored to unique considerations.

## Pain management

### Best practices

Published guidelines for chronic pain vary depending on whether they refer to the treatment of symptoms (neuropathic pain or back pain) or a condition (knee osteoarthritis), the perspective of the authors (eg, guidelines on knee osteoarthritis differ between surgical and non-surgical specialties),<sup>52,53</sup> and the methods of development. Although mechanism-based pain treatment is optimal, identifying the mechanisms behind the pain can be challenging or impossible in clinical practice, so treatment is typically symptom-based or disease-based.<sup>54</sup> For many patients, the goals of therapy should be tailored towards an improved quality of life, which might be more realistic than meaningful pain reduction. In 2019, the US Department of Health and Human Services published a document on pain management best practices, summarised in the panel.<sup>55</sup>

Pain is a dynamic consequence of a host of biological, psychological, and social factors; hence, guidelines have recommended interdisciplinary treatment, which ideally makes use of a personalised approach with a shared-decision model.<sup>10,56</sup> The stepped care model, proposed by the US Veterans Health Administration, advocates for beginning care with the least resource-intensive services and progressing to specialty care and less conservative approaches via a patient-centred,

biopsychosocial framework.<sup>57</sup> A multimodal approach should include self-care, which might consist of weight loss if appropriate; a healthy lifestyle, including exercise, good nutrition, and proper sleep hygiene; smoking cessation; and ergonomic modifications when indicated. Other treatments in such a framework can include opioid and non-opioid pharmacological therapies, psychological therapies, integrative treatments, and procedures. Although most guidelines advocate a flexible (personalised) multimodal approach,<sup>55–57</sup> some have been more restrained with their recommendations; for instance, advocating for anti-depressants as the only pharmacological therapy.<sup>58</sup>

### Exercise and psychotherapy

Exercise is perhaps the most commonly recommended self-management strategy, and might improve sleep (as poor sleep increases pain sensitivity), facilitate weight loss, stimulate endorphin secretion, and reverse deconditioning. A review of 21 Cochrane reviews containing 381 primary studies and 37 143 participants concluded that exercise is more beneficial for function (strong evidence for a small effect) than pain relief (conflicting evidence for a small effect), and more beneficial for musculoskeletal and diffuse pain phenotypes than for neuropathic pain, although it has been successfully used across the pain spectrum.<sup>59</sup> There is no strong evidence that any one exercise regimen is more beneficial than others, so a comprehensive programme should be tailored to individual needs (eg, low-level aerobic exercise for fibromyalgia; strength training for back pain associated with deconditioning; flexibility training for arthritis and trigger points; balance training for patients with pain-induced weakness at risk for falls).<sup>60</sup>

The most common psychologically based intervention for chronic pain is cognitive behavioural therapy (CBT), which involves restructuring maladaptive beliefs, attitudes, and behaviours that contribute to disease burden. Practitioners should recognise that, although CBT is typically administered by psychologists, it ideally involves a multidisciplinary framework, and any practitioner might use CBT principles to guide patient interactions and facilitate beneficial behavioural changes. CBT has been evaluated across the spectrum of pain disorders as a stand-alone treatment and in combination with other therapies. A systematic review evaluating psychological therapies for chronic pain (excluding headaches) found that CBT, but not behavioural therapy, provides small benefit in the short term when compared with usual treatment, but not when compared with an active control (table 2).<sup>61</sup> A strong therapeutic relationship is crucial for maximising the effect of CBT, with the best candidates being motivated, educated individuals with clearcut goals and comorbid mood or anxiety disorders, or both, that amplify pain.

### Panel: Best practices for pain management

- Development of a treatment plan that includes establishing a diagnosis, and measurable outcomes that focus on improvements in aspects such as quality of life
- Emphasis on an individualised, patient-centred approach
- Use of a multidisciplinary approach, which might include restorative therapies (eg, physical therapy, exercise), pharmacotherapy, procedural interventions, behavioural treatments, and complementary and integrative therapies
  - Safer and less invasive treatments including self-care (weight loss, exercise) should be used before more invasive treatments
  - Treatment should be tailored to the diagnosis and patient (eg, non-steroidal anti-inflammatory drugs for nociceptive pain; younger patients (<30 years old) are more likely to develop tolerance to and be harmed by opioids)
- Care should be based on the biopsychosocial model
- Consideration of the needs of some populations that are confronted with unique challenges associated with pain, including children, older people (≥65 years), racial and ethnic minorities, and military personnel
- Address barriers to access to care (eg, financial issues, stigma)

### Non-opioid pharmacological management

Neuropathic and non-neuropathic pain are treated with various classes of non-opioid medications.

For neuropathic pain, analgesic antidepressants and antiepileptic drugs are first-line medications based on many placebo-controlled trials that are of moderate and high quality. Among the different antidepressant drug classes, tricyclic antidepressants (eg, nortriptyline hydrochloride and amitriptyline hydrochloride; with the number needed-to-treat [NNT] being 3·6 [95% CI 3·0–4·4] for 50% relief) and serotonin norepinephrine reuptake inhibitors (eg, duloxetine hydrochloride and venlafaxine hydrochloride; NNT 6·4 [95% CI 5·2–8·4]) are indicated for neuropathic pain.<sup>75,76</sup> Antiepileptic drugs, particularly gabapentin and pregabalin, have proven their efficacy in treating several neuropathic pain conditions, including postherpetic neuralgia, diabetic peripheral neuropathy, and spinal cord injury (NNT range 2·9–7·7).<sup>75,76</sup> Topical lidocaine (NNT=4·4) and capsaicin at high concentrations (NNT=10·6) can reduce the evoked (allodynia) and spontaneous pain that frequently accompany neuropathic conditions.<sup>76–78</sup> Compounded pain creams that contain medications that act via the CNS (eg, ketamine hydrochloride, gabapentinoids) dilute peripherally acting ingredients that might be effective when applied topically, and were shown in a large placebo-controlled trial to be ineffective for neuropathic, non-neuropathic, and mixed pain.<sup>79</sup>

For non-neuropathic pain, topical and oral NSAIDs are considered first-line treatments for osteoarthritis and other

	Reference	Treatment definitions	Study selection	Control treatment	Patients and conditions	Results	Comments or limitations
<b>Psychological treatment</b>							
CBT: a psychosocial intervention focused on challenging and changing maladaptive cognitive distortions and behaviours, improving emotional regulation, and the development of personal coping strategies	Williams et al (2020) <sup>61</sup>	CBT: Methods of cognitive appraisal which assess, test, and revise maladaptive beliefs; involvement of strategies of emotional regulation and exposure; behavioral activation; and skills in problem-solving and motivation	59 RCTs	Active comparator; treatment as usual	5869; with non-malignant pain excluding headache	CBT had a very small benefit for pain, small benefit for disability, and no benefit for distress compared with the active comparator at end of treatment; no benefit for pain or disability at 6 months; compared with treatment as usual, CBT had a small benefit for pain, disability, and distress at end of treatment; at 6 months, a very small benefit for pain and a small benefit for disability and distress were maintained	Treatment results decrease over time after treatment; some evidence based on previous studies for a decrease in health-care use; predominantly moderate quality of evidence
Behavioural therapy: manipulation of external environment and physiological internal environment to effect behavioural change	Williams et al (2020) <sup>61</sup>	Behavioural therapy: identification and reduction of disabling behaviors contingent on pain, or that are strengthened by the short-term benefits of avoidance	8 RCTs	Active comparator; treatment as usual	452; with non-malignant pain excluding headache	No evidence at any time point for benefit compared with active comparator or treatment as usual for any outcome measure	Evidence ranged from very low to moderate quality; results differed from some other reviews
ACT: contextually focused psychotherapy that aims to increase patients' ability to engage in values-based, positive behaviours	Hughes et al (2017) <sup>62</sup>	Explicit use of both an acceptance and commitment component	11 RCTs (10 valid for meta-analysis)	Active comparator; wait list or treatment as usual	836; with chronic pain	ACT did not reduce pain intensity compared with active treatment but had a small effect compared with no treatment	Small effects that decline with better study quality and over time; very low quality evidence; concerns with generalisation, treatment heterogeneity, and other sources of bias
Mindfulness therapy: a subtype of CBT defined as moment-to-moment awareness of one's experience without judgment	Hilton et al (2017) <sup>63</sup>	Mindfulness meditation either as adjuvant or monotherapy	38 RCTs (30 valid for meta-analysis)	Treatment as usual; passive control education and support groups	3536; with fibromyalgia, musculoskeletal pain, back pain, arthritis, migraine, headache, and irritable bowel syndrome	Mindfulness reduced pain compared with mixed control groups but the higher-quality studies had a smaller effect	Unclear effects on pain but possible short-term effects on anxiety and function; most reviews were of poor or fair quality; similar limitations to CBT
Biofeedback: a process whereby electronic monitoring of a normally automatic bodily function is used to train someone to acquire voluntary control of that function	Sielski et al (2017) <sup>64</sup>	Biofeedback of any kind for at least 25% of the total treatment time as either stand-alone therapy or adjunctive to psychotherapy	21 studies	Active comparator; wait list; no treatment	1062; with back pain	Small-to-medium reduction of pain intensity lasting 8 months	Might work best in conjunction with other types of therapy; heterogeneity in definitions of biofeedback; requires substantial resources
<b>Physiological treatment</b>							
Massage: the manipulation of body tissues for the purpose of improving function in the nervous, muscular, and circulatory systems	Furlan et al (2015) <sup>65</sup>	Soft-tissue manipulation with the use of hands or a mechanical device	25 RCTs	Active comparator (TENS, manipulation, traction, physical therapy, etc); or inactive controls (wait list, no treatment, sham massage)	3096; with non-specific low back pain	Massage reduced pain but not function compared with active and inactive controls, primarily in the short term	High risk of bias, especially for blinding; substantial heterogeneity

(Table 2 continues on next page)

inflammatory chronic conditions (eg, tendonitis), and shorter courses of oral NSAIDs are widely used to treat back pain.<sup>80</sup> Unlike NSAIDs, acetaminophen (paracetamol) is devoid of anti-inflammatory effects, and one systematic review found no evidence for efficacy in patients with

persistent back pain, and only clinically insignificant benefit in the short term for osteoarthritis.<sup>81</sup> By some metrics, skeletal muscles make up the largest organ systems in the body and, although muscle relaxants have been shown to be effective for acute spinal pain, little

	Reference	Treatment definitions	Study selection	Control treatment	Patients and conditions	Results	Comments or limitations
(Continued from previous page)							
Yoga: an originally Hindu practice that includes breathing exercises, meditation, and assuming various bodily postures to improve physical and mental wellbeing	Wieland et al (2017) <sup>66</sup>	Primarily Iyengar, Hatha, and Viniyoga forms of yoga	12 RCTs	Exercise controls; non-exercise control (education); yoga added to exercise or not added	1080; with non-specific low back pain	Yoga reduced pain compared with both exercise and non-exercise controls; both effects were statistically significant but only the comparison with non-exercise controls was clinically significant and based on a single study	Little evidence for an effect beyond regular exercise; all studies poorly or not blinded; treatment preference (bias) for yoga (ie, enrolled patients who sought out yoga) probably affected the results
Tai Chi: a meditative exercise using slow, focused, circular movements, and deep breathing	Hall et al (2017) <sup>67</sup>	All styles of Tai Chi	15 RCTs (8 included in meta-analysis)	Active comparator (exercise, physical therapy, multidisciplinary therapy); no treatment (usual care, attention control, wait list)	Approximately 900 included in short-term pain analyses; musculoskeletal pain	Tai Chi reduced pain compared with no treatment or usual care in short term; low-quality evidence that Tai Chi might be better than stretching and education for disability reduction	Minimal evidence for superiority to other treatments; studies limited to a small size, patient preference bias, overall poor methodology, and substantial variation in performance (eg, different styles and durations)
<b>Complementary and alternative treatment</b>							
Acupuncture: an originally Chinese therapy for treating disease or relieving pain by inserting needles along specific pathways or meridians	Paley and Johnson (2019) <sup>68</sup>	Inserting fine needles into the skin at specific points	177 reviews	Sham acupuncture	Chronic pain	Mixed evidence for active acupuncture being more effective than sham acupuncture	High heterogeneity in patient population and performance (eg, type of acupuncture, point prescription, and duration), low power, inadequate controls, and a high risk of bias complicating the meta-analyses; overall quality of primary studies was poor; other reviews have found benefit for sham acupuncture over no treatment
Acupuncture	Vickers et al (2018) <sup>69</sup>	Insertion and stimulation of needles at specific points on the body to facilitate recovery of health	39 RCTs	Sham acupuncture; or no acupuncture	20 827; with non-specific musculoskeletal pain; osteoarthritis; headache; or shoulder pain	Acupuncture relieved pain compared with sham and no-acupuncture control; treatment effects might persist up to a year	Acupuncture has small effects on specific types of pain but the effect is highly dependent on the choice of control treatment; the same limitations apply as noted above
Chiropractic: a system of integrative medicine based on the diagnosis and manipulative treatment of misalignments of joints, especially in the spine, which are thought to cause other disorders by affecting nerves, muscles, and organs	Coulter et al (2018) <sup>70</sup>	Interventions with a therapist involving manipulation, mobilisation, or both	51 trials (9 in meta-analysis)	Active comparator (exercise, physical therapy); sham treatment; no chiropractic	11 76 for meta-analysis; with chronic non-specific low back pain	Manipulation reduced pain and disability more than active comparators; mobilisation reduced pain but not disability compared with active comparators	Some evidence that manipulation and mobilisation have small effects for non-specific low back pain; studies comparing chiropractic with sham treatment were too few and too heterogeneous for meta-analysis; although risk of bias was not considered serious, only 12% of studies were high quality; high heterogeneity in patient selection and performance

(Table 2 continues on next page)

	Reference	Treatment definitions	Study selection	Control treatment	Patients and conditions	Results	Comments or limitations
(Continued from previous page)							
Chiropractic	Coulter (2019) <sup>71</sup>	Interventions with a therapist involving manipulation, mobilisation, or both	47 trials (6 in meta-analysis)	Active comparator (exercise, physical therapy); sham treatment; no chiropractic	4460 for meta-analysis; with chronic non-specific neck pain	Manipulation reduced pain and disability more than active comparators; mobilisation reduced pain but not disability compared with active comparators	37 studies evaluated chiropractic as unimodal therapy, which does not reflect clinical practice; few studies evaluated quality of life; high heterogeneity in patient selection and performance; slightly less than half of studies were deemed to be high quality
Dietary supplements: product ingested to supplement the diet, which might include vitamins, minerals, herbs and other botanicals, amino acids, and other substances	Liu et al (2018) <sup>72</sup>	Any dietary supplement for hand, hip, or knee osteoarthritis where efficacy and safety was investigated	69 RCTs	Placebo	11 586; with hand, hip, and knee osteoarthritis	Among 20 supplements, the most widely used (eg, glucosamine and chondroitin) did not result in clinically significant effects on pain and function; only green-lipped mussel extract and undenatured type II collagen had clinically important effects on pain in the intermediate term; no supplements were identified with clinically important effects in the long term	Overall methodological quality was poor with only 10% of patients having a low risk of bias; although the overall analysis showed evidence for a meaningful effect at short-term follow-up, there was no effect at long-term follow-up; most studies were industry sponsored
Music: clinical use of musical interventions to improve quality of life	Garza-Villarreal et al (2017) <sup>73</sup>	Any type of patient or researcher-chosen music (adjuvant)	14 RCTs	Standard care with or without active control (eg, reading, conversation)	1178; with cancer pain, fibromyalgia, osteoarthritis, multiple sclerosis, non-malignant pain	Music relieved pain compared with usual care, less compared with an active control; self-chosen music had largest effect	High heterogeneity regarding patients, delivery (patient vs provider), length of intervention, and type of music; effect for depression greater than for pain or anxiety; high risk of bias for blinding
TENS: placement of small electrodes to deliver electrical impulses across the skin to relieve pain	Gibson et al (2019) <sup>74</sup>	TENS delivered through the skin via a perceptible sensation excluding a current delivered percutaneously	9 Cochrane reviews, including 51 unique RCTs	Sham; usual care or no treatment; active intervention with or without TENS; different types of TENS or stimulation	2895; with rheumatoid arthritis, neuropathic pain, cancer, phantom pain, fibromyalgia, low back pain, osteoarthritis, neck pain, spinal cord injury	Results were mixed or inconclusive regarding whether TENS improved pain or function compared with sham or no treatment	Unable to conclude with any confidence that TENS is beneficial or harmful because of low-quality evidence; risk of inadequate blinding is particularly high; few studies reported secondary outcome measures (function, quality of life); reviews reporting benefit (knee osteoarthritis) contained a high risk of bias

ACT=acceptance and commitment therapy. CBT=cognitive behavioural therapy. RCT=randomised controlled trial. TENS=transcutaneous electrical nerve stimulation.

**Table 2: Systemic reviews evaluating psychological, physiological, complementary, and alternative treatments for pain**

evidence exists for chronic back or neck pain.<sup>82</sup> Among the various muscle relaxants, there is scant evidence for the efficacy of benzodiazepines,<sup>82</sup> which can cause physical dependence and increase the risk of opioid-related complications.<sup>83</sup> Despite specific indications for neuropathic pain, analgesic antidepressants (eg, nortriptyline hydrochloride, amitriptyline hydrochloride, duloxetine hydrochloride, milnacipran hydrochloride) and anti-epileptic drugs (eg, gabapentin, pregabalin) have established efficacy for fibromyalgia,<sup>84</sup> and analgesic antidepressants are effective for low back pain.<sup>82</sup> Because antidepressants act predominantly by enhancing

descending modulatory systems,<sup>85</sup> they are more versatile analgesic agents than most other first-line agents for neuropathic pain. The treatment of nociplastic pain is covered in another article in this Series, but in general the evidence for non-opioid medications (antidepressants, gabapentinoids) is similar to that for neuropathic pain.

### Opioids

Opioids are the reference standard for acute pain, although new evidence suggests that around 6% of individuals who are given opioids after surgery will be on chronic opioid therapy, with baseline risk factors

(eg, a history of substance abuse, a pre-existing pain condition) having a greater effect on long-term use than the surgery.<sup>86</sup>

Currently, opioids are no longer considered to be a first-line treatment for any form of chronic pain, and many guidelines do not recommend them at all in some populations (eg, young individuals with non-cancer pain).<sup>87</sup> Risks notwithstanding (see below), what is not always appreciated is that opioids are among the most efficacious drugs for chronic pain associated with nervous or non-nervous tissue injury in the short and intermediate terms. Although it was previously asserted that neuropathic pain was less responsive to opioids than nociceptive pain, one systematic review found no evidence for a difference in their effectiveness stratified by pain classification.<sup>88</sup> For nociplastic pain, the evidence supporting the use of opioids is less robust, and there are several pathophysiological reasons why opioids might be less effective. These include high endogenous concentrations of opioids in fibromyalgia and diffuse pain (which might cause hyperalgesia), a high prevalence of opioid-induced bowel dysfunction (which might be higher than 50%) for abdominal disorders, and a greater risk for the development of opioid-induced hyperalgesia syndromes (eg, gastrointestinal, facial) than for nociceptive and neuropathic conditions, which might exacerbate nociplastic pain.<sup>89–91</sup> Opioid antagonists have even been shown to be efficacious for nociplastic pain.<sup>92</sup>

Critics assert there is little evidence for the long-term benefit of opioids, but this criticism extends to non-opioid analgesics, as the absence of long-term placebo-controlled trials extending beyond 12–16 weeks stems from regulatory requirements and ethical concerns. Although many people develop side-effects and tolerance that limit any long-term benefit with opioids, systematic reviews do provide some evidence for long-term functional improvement.<sup>93</sup> Two things that distinguish opioids from non-opioids are that most opioids have been approved for general conditions rather than disease-specific pain conditions (ie, moderate-to-severe pain), and that the risk for side-effects increases over time.

Sustained-release opioids are indicated for use for chronic pain severe enough to require opioid treatment daily, around the clock, in the long term, and for which alternative treatment options are inadequate. Although initially touted as having a lower risk for abuse and providing superior relief for individuals with constant pain than short-acting opioids, the CDC found no evidence to support these claims.<sup>45</sup> However, a review by the US Agency for Healthcare Research Quality found that immediate-release (ie, transmucosal delivery) opioids were better than oral opioids for breakthrough pain.<sup>94</sup> Although the CDC guidelines reported mixed results regarding the relative risk of overdose with sustained-release or long-acting opioids,<sup>45</sup> two large database reviews found that patients taking long-acting methadone (compared with sustained-release opioids), or initiating therapy with sustained-release opioids,

were more likely to overdose.<sup>95,96</sup> Currently, the CDC recommends sustained-release and long-acting opioids only in individuals who are opioid-tolerant.<sup>45</sup>

### Opioid risks

Misuse, abuse, and addiction are major concerns with opioids, with addiction rates ranging from less than 1% to more than 25%, depending on the definition of addiction, the population studied, and the rigour with which patients are selected for therapy.<sup>97</sup> Rates of abuse and misuse are higher than for addiction, with misuse estimated at between 20% and 30%.<sup>98</sup> However, in carefully selected populations, the rate of addiction is less than 8%.<sup>99</sup> Risk stratification tools have been advocated to improve selection, but one review found that most tools were validated using low-quality studies, and many do not want to discriminate patients at a high risk for addiction from patients at a low risk, or account for patient subterfuge.<sup>100</sup> Risk factors for opioid abuse include young age (<30 years old), substance abuse and smoking history, psychological stress, trauma, pre-existing legal problems, poor social support, and disease-related factors, such as unclear cause of the pain.<sup>100</sup> Recently, some experts have called for predictive modelling, which could include phenotyping, genotyping, psychological screening, improved risk stratification, and prognostic testing to identify candidates for opioid therapy.<sup>101</sup> In addition to abuse and addiction, the lesser-known risks of chronic opioid therapy include immunosuppression, sleep apnoea, osteoporosis, hormonal changes including reduced fertility and sexual dysfunction, and an increased risk of myocardial infarction.<sup>102</sup>

### Non-surgical interventional treatment

Non-surgical procedural interventions have surged substantially in the past 2 decades, only to taper off amidst increased scrutiny. Minimally invasive procedures might be used for neuropathic pain (epidural steroid injections [ESI]), nociceptive pain (radiofrequency ablation [RFA]), mixed pain disorders (eg, spinal cord stimulation for post-laminectomy syndrome, coeliac plexus neurolysis for pancreatic cancer), and even some nociplastic pain conditions (eg, steroid injections for temporomandibular disorders), though they tend to be less effective for individuals whose primary pathology is central sensitisation.<sup>40</sup> Such procedures might be used for diagnostic (eg, facet blocks) and therapeutic purposes, and to facilitate other treatments (eg, sympathetic blocks to enable physical therapy for complex regional pain syndrome). The ideal candidates for procedures are those with a pathology consistent with neuroanatomical pain distribution patterns, and individuals without psychopathology, secondary gain, and lower degrees of disease burden (eg, those taking opioids, and with high baseline disability scores). Randomised studies have found that injections done as part of a multimodal

approach are more effective than those done as stand-alone therapy.<sup>103</sup>

Guidelines recommend intra-articular steroid injections for osteoarthritis that affects large and medium joints,<sup>53</sup> although repeated injections have been shown to reduce cartilage volume.<sup>104</sup> In individuals with lumbar radicular pain from disc pathology, a Cochrane review evaluating epidural steroid injections that included 25 randomised controlled studies found evidence for only small benefits in the short term for pain and function compared with the placebo.<sup>105</sup> However, randomised trials allowing for multiple injections have found evidence for long-term (>12 months) improvement.<sup>106</sup> There is less evidence supporting ESI for spinal stenosis than for a herniated disc, and only low-quality evidence supporting ESI for non-radicular pain.<sup>107</sup> For neck pain related to disc herniation, stenosis, discogenic pain, and a history of surgery, moderate evidence supports ESI for long-term improvements in pain and function.<sup>108</sup> Among different routes, randomised studies have found transforaminal epidural injections to be more efficacious than interlaminar injections, albeit with greater risks.<sup>109</sup>

RFA is frequently made use of to treat non-neuropathic pain, being a common treatment for facet and sacroiliac joint pain, and knee osteoarthritis. It is most commonly used when targeted nerve fibres supplying nociceptive information are contained within nerves devoid of  $\alpha$  (motor) or  $\alpha$ - $\beta$  (light touch, resulting in numbness) fibres. RFA of the cervical and lumbar facet joints, sacroiliac joint, and knee might be associated with modest pain relief in the long term, but clinical outcomes are highly dependent on careful patient selection and meticulous technique, with otherwise high-quality studies that have used lax recruitment criteria or ablation strategies resulting in small lesions, yielding negative or mixed results.<sup>53,110–113</sup>

### Surgical treatment

Large joint pain and spine-related pain are common indications for surgery. Knee and hip osteoarthritis are frequent indications for joint replacement, but up to 38% of individuals experience persistent pain after arthroplasty (total knee and hip arthroplasty).<sup>114</sup> Predictors of persistent pain after total knee or hip arthroplasty include depression and anxiety, pain catastrophising, high amounts of pre-surgical pain, baseline opioid therapy, and chronic pain involving multiple body regions.<sup>115</sup> Despite the influence of these factors on outcome, pre-surgical pain coping skills training, exercise, or education have little effect on long-term pain and functional outcomes.<sup>116</sup>

A broad range of operative techniques are used to treat lumbar and cervical spine pain, including spine decompression, discectomy, fusion, and disc arthroplasty, with the clinical outcomes of these treatments being mixed. In a systematic review that included 19 randomised

controlled trials, low-quality evidence supported surgical decompression for lumbar disc herniation compared with non-operative treatment for improvements in pain at 6-month follow-up and function at 1-year follow-up.<sup>117</sup> For lumbar discogenic pain, no significant differences in disability scores were observed between patients randomised to receive spine fusion or behavioural-based rehabilitation.<sup>118</sup> Spine decompression with or without fusion for lumbar stenosis is associated with improvements in pain, functionality, and quality of life for 2–4 years after surgery compared with conservative management.<sup>119</sup> However, one systematic review reported low-quality evidence for functional improvements at 2-year follow-up after spine decompression, compared with non-surgical management.<sup>120</sup>

For neck pain with and without radiculopathy or myelopathy, low-quality evidence showed no significant differences between surgery and conservative care (rehabilitation or physiotherapy).<sup>121</sup> For individuals with degenerative cervical myelopathy, non-surgical compared with surgical management resulted in similar functional outcomes, although patients managed non-surgically had higher rates of admission and treatment in hospital for spinal cord injury.<sup>122</sup> Two surgical options for cervical disc disease, including herniation, are anterior cervical discectomy, with or without fusion, and disc arthroplasty. In a randomised, double-blind trial, 109 patients with a single-level herniated cervical disc were allocated to receive disc arthroplasty, anterior cervical discectomy and fusion, or discectomy alone.<sup>123</sup> At 2-year follow-up, no significant differences were observed in neck pain, arm pain, or quality of life.<sup>123</sup>

Neurostimulation, including spinal cord, motor cortex, and deep brain stimulation, provides pain relief through the electrical modulation of the nervous system. The most widely used neurostimulation technique is spinal cord stimulation, which involves percutaneous placement of electrodes in the epidural space. Systematic reviews support the use of spinal cord stimulation for various chronic neuropathic pain conditions, such as complex regional pain syndrome and post-laminectomy syndrome,<sup>124</sup> and spinal cord stimulation might be associated with significant reductions in opioid consumption,<sup>125</sup> although most studies evaluated did not use blinding. Although conventional spinal cord stimulation generates paraesthesia within the painful areas, newer systems including dorsal root ganglion, burst, and high-frequency devices, might provide better pain relief, for some patients without paresthesias.<sup>126</sup> For more information on neuromodulation, please see the third article in this Series.<sup>8</sup>

Intrathecal drug delivery systems directly administer drugs spinally, allowing substantial dose reduction (eg, 300:1 oral to intrathecal morphine ratio) and a lower incidence of some side-effects (eg, gastrointestinal). Indications for intrathecal drug delivery systems include spasticity (baclofen), failed spine surgery, complex

	Comments	Issues
Efficacy for interventional procedures	Interventional procedures such as epidural steroid injections, radiofrequency ablation, and neuromodulation are difficult to blind in placebo-controlled trials	Facilitating blinding and equipoise (eg, the injection of LA and steroids epidurally instead of into soft tissue, injecting LA and steroids around nerve-targeted ablation, injecting LA around the pedicles [location for facet joint nerve blocks] for vertebral augmentation) can preclude the use of true placebos; treatments that involve obvious physical effects (eg, psychomimetic effects for ketamine infusions, Horner's syndrome for stellate ganglion blocks) and alterations in perception (eg, conventional neuromodulation) might be difficult to blind; ethical issues surrounding the performance of sham procedures that carry physical risks; reimbursement considerations for expensive sham procedures
Comparative and cost-effectiveness studies	Particularly important from patient and societal perspectives for expensive, high-risk procedures	Randomised, comparative-effectiveness studies are unlikely to be funded by device manufacturers; both cost-effectiveness and comparative-effectiveness studies are subject to strong bias (financial incentives, different expectations, unequal experience, etc); registries and big data analytics might provide objective information
Predictive modelling	Can involve genotyping and phenotyping	Might be especially important for high-risk and high-cost treatments; registries and other sources of big data can be helpful in identifying responders, but randomised trials might be needed to establish which treatments benefit which patients
Precision medicine	Personalised approach to treatment that considers genes, lifestyle, and environment	Might combine genomics, big data analytics, and population health; personalised medicine is already used for conditions without widely accepted treatment algorithms in a multidisciplinary context; might be particularly useful for risky (eg, opioids) and costly (eg, biological drugs) therapies
Biomarkers, including neuroimaging	Biomarkers and other psychophysical and anatomical measurements are surrogates for conditions with subjective outcomes	There is a poor correlation between imaging findings and chronic pain; molecular biomarkers such as cytokines are not surrogates for pain, but rather for other physiological processes, such as inflammation; many objective markers (eg, activity amounts, facial expressions, quantitative sensory testing) are dependent on effort and subject to manipulation; includes functional and chemical brain imaging that might someday be used to identify susceptible patients, and help objectify the measurement of pain and pain treatment response
Preventing pain chronification	Research centred on planned, high-risk surgeries but also the early identification of at-risk individuals	Multimodal regimens might include efforts aimed at the preoperative (pre-emptive analgesia, psychotherapy), surgical period (operative and anaesthetic techniques), and postoperative periods (aggressive regimens that might include, but are not focused on, opioids); field is ripe for personalised medicine; preventive strategies in asymptomatic individuals (eg, exercise) have yielded mixed results
Regenerative medicine	Most auspicious for chronic degenerative conditions such as osteoarthritis and neurological injuries	Might involve autologous, non-autologous, or synthetic treatments; can involve substantial risks (eg, carcinogenesis, immunosuppression, invasive injections) and costs; raises ethical issues for treatments involving fetal tissue
Gene therapy	Might target specific chronic pain mechanisms in a tissue-specific manner, such as restoring the normal channel (voltage-gated sodium and potassium channels), molecular (anti-pro-inflammatory cytokines), or receptor (opioid) function	Might be more effective for diseases characterised by specific mutations and trauma (eg, sickle cell disease, diabetes, spinal cord injury) than for symptoms (eg, back or abdominal pain); might involve viral or lipid vectors, chemical transfection or physical transfer (eg, injection, electroporation); can act via multiple avenues (psychological predisposing factors, pain tolerance and threshold, response to treatment); side-effects might include cancer, induced immune response, nausea, or vomiting
Psychotherapy	Might reduce maladaptive thoughts, improve coping skills, and reduce physiological nociception via the modulation of pain amplifying mechanisms (eg, sympathetic nervous system activation, anxiety)	Remote psychological interventions (telemedicine, web-based techniques) can improve access to care; screening and psychological interventions might be used in individuals at high risk to prevent the chronification of pain; might be used to refine the selection of surgical and chronic opioid therapy candidates
Mechanisms underlying placebo effects	Might reveal basic interactions in pain mechanisms and optimise clinical testing	Clarification of a possible increasing placebo effect in some countries might help phase 3 trials to show efficacy for new pain medications; might vary according to pain condition and treatment (ie, higher for procedures than pills); evidence suggests that a strong, empathic provider-patient relationship might be more important than expectations

LA=local anaesthetic.

**Table 3: Promising areas of pain research**

regional pain syndrome, and cancer.<sup>127</sup> Medications frequently infused, alone or in combination, include opioids, local anaesthetics (bupivacaine), clonidine, and ziconotide.<sup>127</sup>

### Integrative treatments

Integrative medicine combines complementary and alternative treatments with psychological and physiological interventions in a holistic approach to health (table 2).<sup>61–74</sup> According to a survey in 2007, nearly 4 in 10 American adults used complementary (in addition to traditional medicine) and alternative (in lieu of traditional medicine) treatments, with pain being the most common indication.<sup>128</sup> Subsequent studies have shown that the rates of alternative treatments such as acupuncture continue to increase, and that there is a sex and cultural component to the use of such treatments (eg, use is more prevalent in White

people, women, and in those with higher educational levels).<sup>129</sup> Although many treatments seem promising with small effects that are observed for pain and quality of life, the methodological quality of studies is typically poor. Inherent problems in doing these studies include inadequate comparators, difficulty with blinding, and the high placebo response rates associated with pain therapies that patients need to seek out and pay for, and which often require multiple hands-on sessions.

### Future avenues for research

Table 3 describes promising future research areas, ranging from advances in research methodologies, identifying neurobiological mechanisms, and emerging therapies. Evaluating pain treatments, particularly invasive ones, is challenging on multiple fronts. An important question concerns the optimum control

comparator (ie, using invasive placebos, and whether or not true placebos are even possible for some interventions),<sup>130</sup> For example, controlled studies evaluating epidural steroid injections have typically used epidural non-steroids as a sham, although a meta-analysis found that more than half of the short-term effects from epidural injections stem not from the steroid, but from the injectate itself.<sup>131</sup> Regarding RFA, vertebral augmentation, and joint injections, the same concerns hold true.<sup>132</sup>

Regenerative (eg, stem cells) and biological therapies (eg, nerve growth factor inhibitors) have generated intense interest, especially for traumatic injuries and degenerative conditions. The conceptual appeal of regenerative medicine is that it uses naturally occurring substances, thereby reducing the likelihood of adverse reactions, particularly when autologous tissue is involved. A systematic review based on low-quality studies found some evidence for regenerative therapies in disc degeneration and little evidence for facet and sacroiliac joint pain.<sup>133</sup>

A crucial area of research is identifying the factors that cause the transition of acute to chronic pain, and preventing its development. This line of research involves elucidating how risk factors for chronic pain neurophysiologically influence pain perception, spinal cord processing, and the interpretation and modulation of pain in the brain.<sup>134</sup> Advances in behavioural neuroscience, physiologically augmented functional neuroimaging techniques, and genome-wide association studies are enhancing the individualisation of clinical phenotypes that might drive development of targeted mitigation strategies.<sup>44,135</sup> Perioperatively, these strategies might involve individualised psychological therapies targeting those with pre-existing psychopathology; strategically used regional anaesthetic techniques such as epidural analgesia, which might prevent persistent pain after high-risk operations (eg, limb amputation); preemptive analgesics such as gabapentinoids, N-methyl-D-aspartate inhibitors (ketamine),  $\alpha$ -2 agonists, and antidepressants; and rehabilitative interventions to build preoperative resilience, improve postoperative pain management, and promote recovery.<sup>44,136</sup> The field of epigenetics is expanding knowledge about how individual experience and the environment lead to changes in gene expression that can alter function in CNS regions implicated in pain chronification.<sup>137</sup>

Another research priority involves the identification of biomarkers that can objectively quantify pain, identify individuals at risk for chronic pain after injury, and predict outcomes. Biomarkers have been categorised as diagnostic, prognostic, or predictive, quantifying susceptibility or risk, and serving as surrogate endpoints. Some studies have focused on several categories including functional and neurochemical (which can measure alterations in central opioid and dopaminergic systems) imaging, molecular (eg, genomic), psychophysical (eg, quantitative sensory testing), and behavioural (eg, facial expressions) indicators. Perhaps the most promising of these is neuroimaging,

which might have improved specificity with the use of modern tools such as multivariate pattern analysis and machine learning. Neuroimaging has been touted as a tool to assess risk, identify true nociceptive correlates (which might be useful in cases involving litigation and disability assessment) and mechanisms of pain, improve patient selection in research studies, and objectify outcomes.<sup>138</sup> The main disadvantage of neuroimaging is that it runs counter to the widely held belief that pain is always subjective; for example, the anticipation of the development or maintenance of pain might be difficult to distinguish from actual nociception. Discovering new biomarkers and refining existing ones is a key priority of the National Institutes for Health Federal Pain Research Strategy.<sup>139</sup>

Finally, predictive modelling based on large-scale databases and multi-centre clinical trials might be used to identify treatment candidates, stratify outcomes by practitioner, and establish long-term outcomes. Predictive modelling can also be used to favourably modify cost-effectiveness, and establish personalised treatment algorithms.

#### Contributors

SPC was responsible for the concept and outline, drafting of the manuscript, and producing the tables and figures. LV drafted the manuscript and tables. WMH drafted the manuscript, tables, and figures.

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