Pain 2

Treatment of chronic non-cancer pain

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This is the second in a **Series** of three papers about pain

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Chronic pain is a pervasive problem that affects the patient, their significant others, and society in many ways. The past decade has seen advances in our understanding of the mechanisms underlying pain and in the availability of technically advanced diagnostic procedures; however, the most notable therapeutic changes have not been the development of novel evidenced-based methods, but rather changing trends in applications and practices within the available clinical armamentarium. We provide a general overview of empirical evidence for the most commonly used interventions in the management of chronic non-cancer pain, including pharmacological, interventional, physical, psychological, rehabilitative, and alternative modalities. Overall, currently available treatments provide modest improvements in pain and minimum improvements in physical and emotional functioning. The quality of evidence is mediocre and has not improved substantially during the past decade. There is a crucial need for assessment of combination treatments, identification of indicators of treatment response, and assessment of the benefit of matching of treatments to patient characteristics.

Introduction

WHO estimates that 20% of individuals worldwide have some degree of chronic pain.[1] The presence of chronic pain has both direct health-care and associated indirect (eg, disability payments, lost productivity) costs. For example, estimates for the total cost of chronic pain exceed US$210 billion annually in the USA.[2] These large amounts are not unique to the USA. In the UK, back pain alone is estimated to cost society $26–49 billion each year.[3] For most of those affected, the presence of chronic pain compromises all aspects of their lives and the lives of their significant others (figure 1). Despite important advances in understanding of the neurophysiology of pain, the increasing availability of advanced diagnostic procedures, and the application of sophisticated therapeutic modalities and approaches, currently available treatments for chronic pain rarely result in complete resolution of symptoms. Thus, people with chronic pain will continue to live with some level of pain irrespective of the treatment or treatments they receive for the foreseeable future.

Chronic non-cancer pain is typically defined as pain lasting longer than 3 months or beyond the expected period of healing of tissue pathology.[4] Pain severity, however, is not correlated with the amount of damage and symptoms can persist long after tissue damage from an antecedent injury resolves.[4] Research suggests that chronic non-cancer pain can develop as a result of persistent stimulation of or changes to nociceptors due to localised tissue damage from an acute injury or disease (eg, osteoarthritis), or damage to the peripheral or central nervous system, or both (eg, painful diabetic neuropathy, poststroke pain, spinal cord injury), which

Key messages

- Chronic pain is a pervasive health issue that exerts a substantial social and economic burden on both the affected individual and society
- Mechanisms underlying chronic pain include a complex interaction of physiological, emotional, cognitive, social, and environmental factors
- Treatment options include pharmacological approaches; interventional techniques including nerve blocks, surgery, implantable drug-delivery systems, and spinal-cord stimulators; exercise and physical rehabilitation; psychological treatments; interdisciplinary treatment; and complementary and alternative treatments
- In view of the complex nature of chronic pain, treatment often necessitates use of a blend of different approaches
- Overall, present treatment options result in modest improvements at best, and part of chronic pain management should include dialogue with the patient about realistic expectations of pain relief, and bring focus to improvement of function

Search strategy and selection criteria

We searched Medline (between 2000, and July, 2010), Embase (2000–10), and Cochrane (2005–10) using the search terms "chronic pain" or "chronic non-cancer pain", and limited the field to "title/abstract". We focused mainly on meta-analyses, systematic reviews, and guidelines published within the past 5 years; however, we also made use of the reference lists of articles identified by this search strategy, highly regarded older publications, and the authors' personal reference lists. From this list we selected references that addressed categories of musculoskeletal (primarily osteoarthritis), neuropathic (primarily post-herpetic neuralgia and diabetic painful neuropathy), chronic widespread (primarily fibromyalgia), and low-back pain, favouring the most recent guidelines and comprehensive reviews. Four new references, published after July, 2010, were added during the peer-review process.

might not be readily detectable with currently available diagnostic technologies.[5]

Pain does not occur in a vacuum. Individuals' unique genotypes, previous learning histories, environmental and socioeconomic resources, cognitive, emotional, and behavioural factors, and physical pathology interact to mediate and moderate the experience of pain (figure 2).[6] Thus, to understand and treat patients with pain requires that consideration be given to all contributing facets. This complexity has bedevilled health-care providers, people experiencing pain, their significant others, and society since earliest recorded history. We provide a brief overview of, and evidence for the effectiveness of, the most commonly prescribed treatments for chronic non-cancer pain.

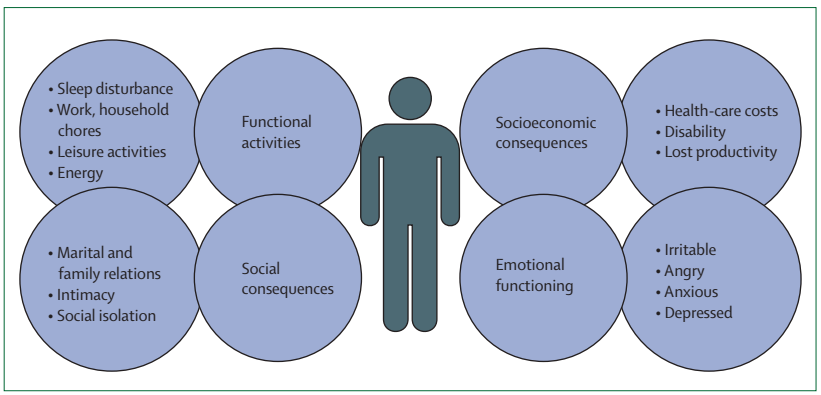

Figure 1: **The effect and burden of chronic pain**
Chronic pain affects every aspect of a patient's life, contributing to a loss of both physical and emotional function, affecting a patient's levels of activity (ability to work at home and job and engage in social and recreational pursuits); additionally, there are often serious economic consequences as a result of health-care bills and potential loss or decrease in financial income.

Treatment overview

A growing array of pharmaceutical, surgical, neuroaugmentative, somatic, behavioural, rehabilitative, and complementary and alternative treatment options are available for the management of patients with chronic pain. However, overall treatment effectiveness remains inconsistent and fairly poor. Moreover, even when treatments effectively reduce pain, they often do not produce concomitant improvements in physical and emotional functioning and overall health-related quality of life.[7]

The focus of this paper is to provide an overview of current practices and concerns in the management of patients with chronic non-cancer pain. Notably, chronic non-cancer pain is a broad category, and disorders tend to be classified on the basis of anatomy (eg, body location), cause (eg, nociceptive, neuropathic), neurophysiology, or body system involved.[4] Various classes of pain disorders have potentially distinct underlying mechanisms, and as a result drawing of overarching conclusions on any one particular treatment modality is difficult. Management options, however, overlap substantially, so we present results on the basis of therapeutic modality. We provide a contemporary survey of some of the most common pharmacological, interventional, and non-interventional treatments. A comprehensive systematic review of the effectiveness of treatments for specific diagnoses is beyond the scope of this report. We focus mainly on the categories of musculoskeletal pain (eg, osteoarthritis), neuropathic pain (eg, postherpetic neuralgia and diabetic painful neuropathy), chronic widespread pain (eg, fibromyalgia), and non-specific low-back pain on the basis of their prevalence in clinical practice and in research into treatment.

Pharmacological treatments

Background

Oral drugs have been the mainstay of treatment for pain during past centuries, and the use of drugs to treat pain has expanded exponentially in recent years, with increases in expenditures of 188% between 1996 and 2005.[7] We review evidence for classes of drugs most commonly used for treatment of chronic non-cancer pain.

Opioids

Retail sales for opioids, the most common class of drug prescribed in the USA, increased by 176% from 1997 to 2006.[8] Despite this striking escalation, their use remains controversial both with respect to efficacy and adverse physical effects and to aberrant behaviours.[9,10] A meta-analysis of 41 randomised controlled trials[11] evaluating the effectiveness of opioids for the treatment of various forms of chronic non-cancer pain, including osteoarthritis, diabetic painful neuropathy, low-back pain, and rheumatoid arthritis, concluded that on average opioids result in a small improvement in pain severity and functional improvement compared with placebo, and similar reductions in pain, but less improvement in function compared with other analgesic drugs. On the basis of similar conclusions from a systematic review of the use of opioids in osteoarthritis, Neush and colleagues[12] concluded that opioids should not be routinely used. Guidelines from both the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain[13] and the European Federation of Neurological Societies Task Force[14] recommend opioids as second-line or third-line treatment that can be considered for first-line treatment in specific clinical circumstances, such as during episodic exacerbation of severe neuropathic pain. On the basis of scarcity of evidence, opioids are not strongly recommended for use in patients with fibromyalgia in any of the three most recent evidence-based guidelines published by professional societies for the management of this disorder.[15–17]

Tramadol, a combination of a serotonin and noradrenaline reuptake inhibitor and a μ-opioid agonist, is notable because its mechanism of action is distinct from those of other opioids. Tramadol reduces pain substantially in osteoarthritis,[18] fibromyalgia,[19,20] and

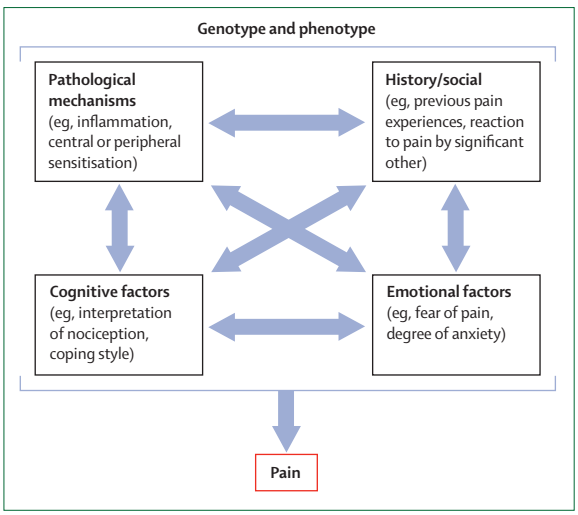

Figure 2: **Factors contributing to pain severity**
Pain severity is not accounted for solely by degree of physiological pathology, but is the result of a complex interaction among individuals' unique previous histories, any physiological abnormalities, their cognitive perceptions of nociception, emotional factors, their coping styles, and social and financial resources.

neuropathic pain.[21] There is insufficient evidence to establish whether tramadol is more effective compared with other opioids. Tapentadol, another dual-action substance that acts as both a noradrenaline reuptake inhibitor and μ-opioid agonist, was recently approved by the US Food and Drug Administration (FDA) for use in acute pain;[22] however, there is a dearth of evidence with respect to the efficacy of its use in chronic non-cancer pain.[23] Serotonin syndrome, a potentially life-threatening adverse event that can occur in patients as a result of too much serotonin in the body, is an additional side-effect to be monitored in patients taking these drugs.

Side-effects associated with opioids (eg, nausea, constipation, somnolence) contribute to attrition during randomised controlled trials and are often important enough to prevent patients from remaining on opioid treatment. In a meta-analysis of 17 studies[24] concerning efficacy of long-term opioid use for chronic non-cancer pain, 44% of patients abandon treatment 7–24 months into open-label extensions.[24] A few patients opting to remain on long-term opioid treatment can develop opioid-induced hyperalgesia, which occurs when patients taking opioids become hypersensitive to nociceptive stimuli.[25] Opioid-induced hyperalgesia is postulated to result from changes in the peripheral and central nervous system that lead to facilitation of nociceptive pathways.[25]

Aside from the physical adverse events, opioids carry a substantial risk of misuse. Studies of patients with chronic non-cancer pain taking opioids on a long-term basis suggest that as many as 45% could be engaging in aberrant drug-taking behaviours.[26] In the USA, the misuse of prescription opioids is the fastest growing form of drug misuse and is the leading cause of accidental overdose and mortality,[27] and there is increasing concern about diversion and criminal trafficking by patients and physicians. Emergency room visits involving narcotic analgesic substances increased 274% in 11 years, from 1995 to 2005, and from 1999 to 2004, the number of all poisoning deaths increased 54%,[28] whereas the number of methadone-related deaths rose 390%.[29] These concerns, as well as restricted efficacy, have resulted in some re-assessment and debate regarding practices surrounding opioid use. Manchikanti and colleagues[30] provide a detailed discussion of the complexities and complications of therapeutic use, misuse, and non-medical use of prescription opioids.

Non-steroidal anti-inflammatory drugs

The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) has been reported for patients with osteoarthritis and rheumatoid arthritis[31] and back pain.[32] NSAIDs are generally accepted to be ineffective for neuropathic pain; however, this belief is not founded on published evidence, and research is needed to establish the efficacy of NSAIDs for this class of disorders.[33] NSAIDs are not included in any of the three most recent guidelines for treatment of fibromyalgia.[15–17]

NSAID gastropathy is regarded as one of the most common serious adverse drug events affecting people in industrialised nations.[34] Selective cyclo-oxygenase (COX)-2 inhibitors have fewer gastrointestinal side-effects than do traditional NSAIDs, but they are associated with increased cardiovascular risk.[32] Careful scrutiny for the development of adverse reactions should be undertaken, particularly with long-term use. Paracetamol is a slightly weaker analgesic than NSAIDs, but is a reasonable alternative because of reduced gastrointestinal complications and low cost.[35] The widespread use of paracetamol, combined with the small margin of safety between therapeutic and toxic dose, often result in unintentional overdose.[36] On the basis of growing rates of unintentional overdose and hepatic failure associated with paracetamol, the FDA revised the drug's warning label in April, 2010.

Antidepressant drugs

Antidepressants have diverse effects that might contribute to their analgesic effect, including effects on N-methyl-D-aspartate (NMDA) and adenosine receptors, sodium channels, and serotonin, noradrenaline, and opioid systems. Meta-analyses suggest that antidepressants are superior to placebo for the treatment of chronic non-cancer pain, resulting in moderate symptom reduction.[35] Efficacy is most well researched for neuropathic pain, fibromyalgia, low-back pain, and headaches.[37] Evidence is particularly strong for use of antidepressants in neuropathic pain.[38]

Tricyclic antidepressants (TCAs), such as amitriptyline and cyclobenzaprine, have the longest track record of any antidepressants in treatment of chronic non-cancer pain. They primarily work by directly blocking the reuptake of

serotonin and noradrenaline. TCAs have important side-effect profiles including cardiovascular events (eg, hypertension, postural hypotension, arrhythmias) and falls in elderly adults; moreover, tolerability is an important issue because high doses can become toxic. A recent systematic review[37] concluded that the evidence supports use of TCAs in neuropathic pain, fibromyalgia, low-back pain, headaches, and irritable bowel syndrome.

Selective serotonin reuptake inhibitors (SSRIs) were developed to specifically target serotonin in an effort to decrease side-effects associated with the more broadly acting TCAs. Trials evaluating the efficacy of these more highly selective serotonin drugs, including fluoxetine and citalopram, are less consistent than those with dual effects on noradrenaline and serotonin; however, beneficial effects have been reported.[37,39]

Recent trials have focused on the new selective serotonin and noradrenaline reuptake inhibitors (SNRIs). These drugs target both serotonin and noradrenaline, but do not interact with adrenergic, cholinergic, or sodium channels in the way that TCAs do, thereby avoiding some of the side-effect and tolerability issues. Evidence suggests that the SNRIs duloxetine[40] and milnacipran[41] are well tolerated and effectively reduce the functional effect of fibromyalgia. Duloxetine has been recommended by the UK National Institute of Health and Clinical Excellence (NICE) as a first-line treatment for patients with neuropathic pain.[42] Additional research is needed to evaluate the efficacy of SNRIs in other pain disorders.

Anticonvulsant drugs

The primary mechanisms of action of anticonvulsant drugs include modulation of voltage-gated calcium or sodium channels, glutamate antagonism, enhancement of the γ-aminobutyric acid (GABA) inhibitory system, or a combination of these effects. The best evidence supports the efficacy of three drugs mainly used for the treatment of chronic non-cancer pain—gabapentin, pregabalin, and carbamazepine or oxcarbazepine.

Gabapentin and pregabalin act as neuromodulators by selectively binding to the $\alpha_2\delta$ subunit protein of calcium channels in various regions of the brain and the superficial dorsal horn of the spinal cord. This process inhibits the release of excitatory neurotransmitters that are important in the production of pain. There is good evidence for their effectiveness in neuropathic pain.[13,14] Pregabalin has also been shown to improve symptoms in fibromyalgia,[43] and is recommended by NICE as one of two first-line treatments for patients with neuropathic pain.[42] Evidence suggests that gabapentin results in a small net benefit in patients with low-back pain due to radiculopathy, but no evidence is available for its effectiveness in non-specific low-back pain.[44] The most common side-effects include somnolence, dizziness, fatigue, and weight gain.

Carbamazepine was one of the first anticonvulsant drugs to be tested in neuropathic pain. A recent review[45] suggests that evidence for its efficacy is mixed, with three positive and two negative trials for either carbamazepine or the newer carbamazepine derivative, oxcarbazepine.[45]

Skeletal muscle relaxants

The mechanisms of action of skeletal muscle relaxants is unclear, but could be related in part to sedative effects. Studies have not shown significant differences among this category of agents in their efficacy, adverse events, or safety. Most frequently, they are recommended as adjuvant therapy for short-term relief.[46]

Cyclobenzaprine is the best studied muscle relaxant in musculoskeletal disorders. The drug seems to have a restricted role in the treatment of chronic non-cancer pain, with the exception of fibromyalgia. In studies of fair quality it has consistently proven superior to placebo for fibromyalgia, as well as pain relief, muscle spasms, and functional status in other disorders.[47] Sedation is a common side-effect, making long-term therapy problematic.

Topical agents

Topical agents have been advocated for the treatment of chronic non-cancer pain when localised pain is present. They have the potential advantage of avoiding the systemic side-effects that are often associated with oral drugs. Capsaicin is an alkaloid derived from chilli peppers, and repeated application is thought to deplete substance P from primary afferent neurons. By comparison with placebo, topical agents effectively reduce pain in both neuropathic pain and musculoskeletal disorders including osteoarthritis.[48] Topical salicylate has also proved superior to placebo in six trials of chronic non-cancer pain.[48]

Interventional treatments

Background

Interventional pain medicine involves application of various techniques that can be used to diagnose or locate an individual's source of pain or provide therapeutic pain relief. Interventional medicine is most frequently used when a specific area of the spine is thought to be contributing to an individual's pain (ie, discogenic or sacroiliac joint pain) and there is no consensus with respect to optimum diagnostic criteria. The focus of our review is therapeutic intervention, so we will not address diagnostic uses of interventional pain medicine. We refer readers to Chou and colleagues[49] and Manchikanti and colleagues[50] for discussion and recommendations regarding diagnostic interventions for back pain. In this section, we focus on the most common therapeutic interventions, injection therapy, surgical intervention, and implantable devices, with a primary focus on low-back pain. For a more in-depth discussion of interventional therapeutic techniques for low-back pain, we refer readers to the American Pain Society (APS)[51] and the American Society of Interventional Pain Medicine[52] systematic review and evidence-based guidelines.

Injection therapy

Nerve blocks involve the delivery of various anaesthetics to visceral and peripheral nerves and muscles to interrupt nociceptive input, reduce inflammation, or destroy neurons at the source of pain. The procedures vary with respect to patient-selection criteria, location (epidural, facet joint, local site), agent, and dose. The deviations in methods make assessment of outcomes difficult. There is no consensus about technical aspects of injection therapies, and no guidelines for optimum diagnostic criteria for patient selection, frequency, number, or timing of injections.[53]

In the USA, epidural steroid injections are the most commonly performed pain management procedures;[54] however, evidence is not unequivocal for their use as long-term monotherapy.[53,55] Recent APS guidelines report that fair evidence exists for their use in patients with radiculopathy with prolapsed lumbar disc, although there is no evidence supporting their use in non-specific low-back pain or failed back surgery syndrome.[56] Facet injections are the second most commonly performed pain management procedure in the USA.[54] Luijsterburg and colleagues[57] undertook a systematic review for their use in lumbosacral radicular syndrome, and they were not clearly shown to be effective. However, Chou and colleagues[56] conclude that there is fair evidence for their use in presumed facet joint pain. With respect to intradiscal steroid injections, they report good evidence for the use of intradiscal steroid injections in presumed discogenic low-back pain, and fair evidence in radiculopathy with prolapsed lumbar disc.[56] Superficial and deep infections are a potential side-effect of injection therapies.[58] Rare but serious complications (cauda equine syndrome, septic facet joint arthritis, discitis, paraplegia, paraspinal abscesses, meningitis) have also been reported. The decision to use an injection therapy needs to balance the potential for some patients to benefit against these serious adverse events and costs.

Surgery

Chronic non-cancer pain that persists despite conservative efforts often leads to surgery. Lumbar fusion for non-radicular low-back pain with degenerative changes is one of the most rapidly increasing types of surgery. In 2001, more than 122 000 lumbar fusions were performed in the USA, a 220% increase from 1990,[59] and rates of cervical fusions rose 206% from 1992 to 2005.[60] Artificial disc replacement is one alternative to fusion surgeries. Other common surgeries include discectomy for radiculopathy with herniated lumbar disc, decompressive laminectomy for spinal stenosis, and an interspinous spacer device as an alternative to decompressive laminectomy.

In a recent systematic review[61] evaluating surgery for low-back pain, evidence was rated as fair for lumbar fusion in non-radicular low-back pain with common degenerative changes. At least one of the studies included reported a significantly greater pain reduction (33% reduction *vs* 7%) for the surgical group compared with the non-surgical group;[62] however, benefits diminished over time with as many as 41% of patients reporting no change or a worsened quality of life up to 4·5 years after surgery.[63] Evidence was regarded as good for discectomy in lumbar disc prolapse with radiculopathy, as well as laminectomy for spinal stenosis with or without degenerative spondylolisthesis. High complication rates and repeat procedures are realities of spinal surgery as well. Several studies show that significant pain can persist after spinal surgery, an estimated 30% (93 600) will result in failed back surgery syndrome,[64] and subsequent operations do not guarantee resolution of pain. In the chronic non-cancer pain population, which patients and with which characteristics are most likely to benefit from spinal surgery is unclear.

Implantable devices

Implantable devices tend only to be considered as options when oral drugs, surgery, and injection procedures have not provided adequate improvements. Spinal-cord stimulation involves the implantation of electrodes near the spine or into peripheral nerves to modulate pain processing, resulting in inhibition of nociceptive signals. The use of this technique in carefully selected patients with refractory neuropathic pain (complex regional pain syndrome [CRPS] and radicular back pain) has been shown to reduce pain, improve quality of life, reduce analgesic consumption, and allow some patients to return to work.[65] Several meta-analyses evaluating the efficacy of spinal-cord stimulation for failed back syndrome or CRPS concluded that there was moderate evidence for improvement in pain,[51,66–68] but a general need for more methodologically sound studies. The one randomised controlled trial[69] reported significant differences for pain, but not for function. Spinal-cord stimulation is also often used for low-back pain; however, in a recent systematic review, Chou and colleagues[51] concluded that there are no high-quality trials that have evaluated its use in this population.

Epidural and intrathecal drug delivery systems have been used successfully to treat some patients with intractable chronic non-cancer pain, but high costs and absence of proven effectiveness have led to substantial controversy. Bennett and co-workers[70] concluded that clinical efficacy in large-scale randomised controlled trials using intrathecal delivery of most compounds has not been shown and variations between study designs make useful comparisons of existing studies difficult. A more recent systematic review[71] concludes that, on average, moderate reductions in pain and improvements in functioning were realised for patients with chronic non-cancer pain, although long-term effectiveness is unknown. Currently, morphine and ziconotide are the only FDA-approved analgesics for long-term intrathecal infusion. However, chronic use of morphine is often

associated with loss of therapeutic effect because of tolerance and dose-limiting side-effects,[72] and ziconotide is associated with various adverse events associated with the CNS (eg, dizziness, abnormal gait) and data for its safety remain scarce.[73]

Implantation with spinal-cord stimulation or intrathecal drug delivery systems necessitates routine monitoring, replacement of the devices as needed, and refilling of drug reservoirs. All invasive interventions have the potential to create additional medical problems that need to be treated, so there is a need to balance benefits against the high costs of the procedure and long-term maintenance.[67]

Physical, rehabilitation, and psychological approaches

Although evidence suggests that exercise can effectively decrease pain and improve function, improvements are small (<30% reduction in pain and <20% improvement in function).[74] Systematic reviews also suggest that exercise intervention affects work disability status;[75,76] however, no conclusions could be made about exercise type. Moreover, patient adherence can be an impediment. Exercise treatments vary widely and are often incorporated as part of multimodal and rehabilitative treatment approaches, making assessment of the effectiveness of exercise alone a challenge.

Psychological treatments can generally be separated into theoretically-based approaches and specific techniques. The most common theoretical approaches are operant conditioning and cognitive-behavioural therapy (including acceptance-based and mindfulness-based therapy). All of these approaches emphasise patient coping, adaptation, self-management, and reduction of disability associated with symptoms, rather than elimination of physical causes of pain per se. The most commonly used psychological techniques used to achieve these goals include cognitive therapy, relaxation, and hypnosis to help patients to shift their stance from being passive, reactive, dependent, and helpless in the face of pain, to being active and resourceful in coping with their symptoms and their lives, and to replace their more typical feelings of hopelessness (panel 1).

The results of meta-analyses and systematic reviews of adult patients with chronic pain suggest that psychological treatment as a whole results in modest benefits in improvement of pain and physical and emotional functioning.[77–82] However, evidence for the long-term effects is inadequate, and evidence is somewhat contradictory for effects on vocationally relevant outcomes.[77–80] There is insufficient evidence to recommend any one therapeutic approach or modality over another. The possibility that patients with different characteristics might derive benefits from treatments with different foci and targets is reasonable to consider.[83] Psychological approaches are commonly included as components of interdisciplinary pain rehabilitation programmes (IPRPs).

***Panel 1:* Common psychological and behavioural techniques used to treat chronic non-cancer pain**

- Reconceptualisation of the patient's pain from uncontrollable to manageable
- Fostering of optimism and combating of demoralisation
- Promotion of patient feelings of success, self-control, and self-efficacy
- Encouragement of patients to attribute success to their own role
- Education in the use of specific skills such as pacing, relaxation, and problem solving
- Emphasis on active patient participation and responsibility
- Individualisation of some aspects of treatment to unique physical and psychological characteristics of the patient

***Panel 2:* Common components of an integrated interdisciplinary rehabilitation programme**

- Physical rehabilitation
- Exercise therapy
- Cognitive restructuring with an emphasis on promotion of self-management, self-efficacy, resourcefulness, and activity versus passivity, reactivity, dependency, and hopelessness
- Behavioural treatment (eg, relaxation, work to exercise quota *vs* pain)
- Vocational rehabilitation, where indicated
- Drug management as needed (preferably with reduction of opioid treatment)

Rehabilitation programmes are often thought of as a salvage approach after the alternatives described previously have proven insufficient. Thus, patients treated at IPRPs have some of the most recalcitrant problems. Although there is no single format for IPRPs, they offer an integrated approach that involves close coordination between physicians, psychologists, physical therapists, and other health-care providers. Most treatment facilities of this type have a generic concept and plan, and we present common components of an IPRP in panel 2.

The reduction of pain after treatment at IPRPs have been reported to be significant in several meta-analyses,[77,78,84] with one meta-analysis[77] reporting that the mean pain reduction for patients treated at IPRPs was 37% with a concomitant significant decrease (63%) in prescription pain treatment. Moreover, one early meta-analysis of 42 published studies[85] reported significant reductions in health-care use after treatment at IPRPs. Thomsen and colleagues[86] used social records instead of self-reports to evaluate the efficacy of an IPRP, obtaining data for disability and welfare costs for a period of 6 months before entry to a 4-month waiting list and at a 9-month follow-up after termination to evaluate the

efficacy of an IPRP. The investigators identified significant reductions in social transfers (welfare benefits, sickness benefit, and pensions). These investigators noted a 63% reduction in benefits during follow-up. The evidence for the efficacy of psychological treatments on physical functioning is more supportive for these treatments than for pharmacological and invasive treatment.[87]

The modest reductions in pain severity obtained with psychological interventions and with IPRP studies are similar to those noted with more traditional pharmacological and procedural treatment modalities.[88] Although most studies have fairly short follow-up, two meta-analyses[77,85] confirmed that the long-term effects on return to work for patients treated at an IPRP and the results were superior to those of other active treatments. Results should be interpreted with caution because not all clinics have the same patient mix, different measures might be used to assess outcomes, different programmes are not equally potent, studies are conducted in countries with diverse health-care systems, and most are not randomised controlled trials, but rather are observational studies that have relied on comparisons with waiting list, standard care, and patients who were refused insurance coverage.

Complementary and alternative medicine and other non-pharmacological approaches

Complementary and alternative medicine (CAM) includes a wide array of treatments that are not regarded as part of conventional medicine. A comprehensive review of all modalities is beyond the scope of this paper, but we address three of the most common modalities used, as well as those with the best evidence for treatment of chronic non-cancer pain. The evidence that we review is largely based on a recent systematic review[89] of CAM effectiveness for chronic non-cancer pain. We refer interested readers to this review for evidence on additional CAM modalities.

Spinal manipulation is the most commonly used CAM therapy for low-back pain. Tan and colleagues[89] concluded on the basis of two systematic reviews that spinal manipulation therapy is more effective than are sham manipulations and treatments such as bed rest and traction, but not more effective than other recommended treatments for low-back pain. Evidence for other chronic non-cancer pain disorders is scarce.

Massage is another modality commonly used by patients with chronic non-cancer pain as a supplemental treatment. Wide variations in massage techniques make generalisation from studies difficult. Tan and colleagues[89] reviewed all published evidence for massage therapy for chronic non-cancer pain and concluded that evidence supports benefit in low-back and shoulder pain, and possibly provides benefit for fibromyalgia and neck pain, but more research is needed.

Acupuncture has been used for thousands of years in the treatment of pain, although mechanisms remain unclear. Evidence supports the effectiveness of acupuncture for the treatment of chronic low-back pain,[90–93] and results are promising for the effectiveness in reduction of pain associated with fibromyalgia and neck pain.[94] There is, however, little evidence reported to support improvements in physical or emotional functioning after acupuncture treatment of patients with chronic non-cancer pain. However, acupuncture trials have typically not focused on function as an outcome.

Transcutaneous electric nerve stimulation (TENS) has been applied for diverse pain states since its introduction in the early 1970s, but there have been few large, randomised controlled trials to evaluate its effectiveness in pain management. Results from recent systematic reviews and meta-analyses draw mixed conclusions about the effectiveness of TENS in pain relief.[95,96] The methods used in TENS (eg, bandwidth, wave-form, duration) vary widely, and these factors might contribute to inconsistent results.

Conclusions

Ideally, we would include a table summarising the conclusions about treatments for chronic non-cancer pain covering all of modalities described. However, this approach is inappropriate because drawing of conclusions between the therapeutic approaches is impossible, since the meta-analyses and systematic reviews that we used vary widely in terms of diagnostic criteria used for the different conditions, outcome measures studied, criteria used to select studies for inclusion, inconsistency in some of the treatment methods, and inclusion of patients from countries with very different health and economic systems. These factors make comparison within treatments difficult and comparison across therapeutic modalities and approaches almost impossible. This situation could account for some of the inconsistency in the conclusions from meta-analyses on the same populations, with comparable treatments, and covering roughly the same time period. However, despite these concerns, a general conclusion about the treatment of chronic non-cancer pain is that the results presented are sobering. Even when significant effect sizes are reported, the clinical meaningfulness of the outcomes is not always clear. Of all treatment modalities reviewed, the best evidence for pain reduction averages roughly 30% in about half of treated patients, and these pain reductions do not always occur with concurrent improvement in function. Notably, the placebo response rate for opioid trials is around 10%, and when active placebos that mimic the side-effects of opioids are used, the response rate increases to an average across studies of 21%.[97]

These results suggest that none of the most commonly prescribed treatment regimens are, by themselves, sufficient to eliminate pain and to have a major effect on physical and emotional function in most patients with

chronic pain. This conclusion is hardly surprising in view of the complexity of chronic pain. In the absence of a cure, there is a need to maximise symptom relief so that patients are able to lead the highest quality of life possible. If there is no proven improvement in patient pain, and physical and emotional functioning, then an alternate treatment approach should be recommended. Setting of realistic expectations with patients is also crucial. Another important consideration is that treatment response is individual, and no one approach will benefit all patients. Matching of patients to particular treatments on the basis of relevant predictive characteristics would be ideal, if we had knowledge of the appropriate matching variables.[98]

A clear research agenda is apparent from our review. Sophisticated studies with creative placebo controls for non-pharmacological treatments are needed—for example, in the case of interventional techniques. Randomised controlled trials should also include alternative treatment comparisons that allow for comparative effectiveness analyses. Since none of the currently available treatments has proven to be capable of eliminating pain and restoring functioning to a high proportion of patients, attention should also be paid to the effectiveness of combination of various treatments (ie, combinations of several drugs, drugs with somatic treatments, pharmacological and psychological treatments). Trials with some combination approaches have been suggested as reasonable alternatives before more invasive procedures such as surgery.[99] Despite calls for the use of combination treatments, few studies have reported on the efficacy of combination therapy, and results showing an additive or synergistic benefit are not conclusive for any particular combination.[100,101] Finally, assessment of pain, physical and emotional functioning, patient ratings of improvement and satisfaction of events along with recording of adverse events are the recommended domains for assessment of treatment effectiveness.[102] Unfortunately, despite this recommendation, pain severity continues to be the primary outcome, particularly for pharmaceutical, surgical, and intervention studies. A great need exists for research that goes beyond asking the questions of whether a particular treatment is effective, to addressing what treatment is effective, for which patients, on what outcomes, under what circumstances, and at what cost. To achieve this aim, continual measurement of patients' core domain outcomes[90] are mandatory and should become standard of care. Clinicians and investigators need to work closely together to identify unique characteristics of treatment response (measurement-based care), to translate clinical outcomes into sustainable clinical practice (value-based care).

Contributors

DCT and DHW contributed equally to the literature search, interpretation, creation of figures, and writing of the report. AC contributed to writing of the report.

Conflicts of interest

DCT has received grants from Endo Pharmaceuticals, Ortho-McNeill Janssen, and the National Institutes of Health. He has served as a consultant to Endo Pharmaceuticals, Galderma, Pfizer, and Smith & Nephew; served on an advisory board for Eli Lilly and Pfizer; is a Special Government Employee of the US Food and Drug Administration (FDA), and serves as Co-chair of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and Associate Director of Analgesic Clinical Trials Innovations, Opportunities, and Networks (ACTION), a public-private partnership with the US FDA. HDW has received a grant from Ortho-McNeill Janssen. AC declares that he has no conflicts of interest.

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