Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have?

Jo Nijs[†], Mira Meeus, Jessica Van Oosterwijck, Nathalie Roussel, Margot De Kooning, Kelly Ickmans & Milica Matic

[†]*Artesis University College Antwerp, Antwerp, Belgium, Vrije Universiteit Brussel, Brussels, Belgium & University Hospital Brussels, Brussels, Belgium*

Introduction: Central sensitization accounts for chronic 'unexplained' pain in a wide variety of disorders, including chronic whiplash-associated disorders, temporomandibular disorders, chronic low back pain, osteoarthritis, fibromyalgia, chronic fatigue syndrome and chronic tension-type headache among others. Given the increasing evidence supporting the clinical significance of central sensitization in those with unexplained chronic pain, the awareness is growing that central sensitization should be a treatment target in these patients.

Areas covered: This article provides an overview of the treatment options available for desensitizing the CNS in patients with chronic pain due to central sensitization. It focuses on those strategies that specifically target pathophysiological mechanisms known to be involved in central sensitization. In addition, pharmacological options, rehabilitation and neurotechnology options are discussed.

Expert opinion: Acetaminophen, serotonin-reuptake inhibitor drugs, selective and balanced serototin and norepinephrine-reuptake inhibitor drugs, the serotonin precursor tryptophan, opioids, *N*-methyl-D-aspartate (NMDA)-receptor antagonists, calcium-channel alpha(2)delta (a2δ) ligands, transcranial magnetic stimulation, transcutaneous electric nerve stimulation (TENS), manual therapy and stress management each target central pain processing mechanisms in animals that – theoretically – desensitize the CNS in humans. To provide a comprehensive treatment for 'unexplained' chronic pain disorders characterized by central sensitization, it is advocated to combine the best evidence available with treatment modalities known to target central sensitization.

Keywords: chronic pain, electrotherapy, fibromyalgia, manual therapy, osteoarthritis, pharmacotherapy, rehabilitation, whiplash

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Despite extensive global research efforts, 'unexplained' chronic pain remains a challenging issue for clinicians and an emerging socioeconomic problem. It is present in many patients, including those with fibromyalgia [1], chronic whiplash [2], chronic low back pain [3], osteoarthritis [4], headache [5] and chronic fatigue syndrome [6]. An increasing amount of scientific evidence indicates that central sensitization – defined as an augmentation of the responsiveness of central neurons to input from unimodal and polymodal receptors [7] – accounts for chronic 'unexplained' pain in the majority of these patients [1,2,8-13].

10.1517/14656566.2011.547475 © 2011 Informa UK, Ltd. ISSN 1465-6566

Article highlights.

- The awareness is growing that central sensitization should be a treatment target in patients with chronic pain due to central sensitization (e.g., chronic whiplash associated disorders, temporomandibular disorders, chronic low back pain, osteoarthritis, fibromyalgia, chronic fatigue syndrome and chronic tension-type headache).
- Little is known about the effect of pharmacotherapy and other treatment strategies on the mechanism of central sensitization in humans.
- Various pharmacological and non-pharmacological treatments, with established clinical effectiveness in a variety of 'unexplained' chronic pain disorders, target mechanisms involved in central sensitization.
- A variety of drugs target those central pain-processing mechanisms in animals that, in humans, desensitize the CNS.
- Likewise, transcranial magnetic stimulation, transcutaneous electrical nerve stimulation, hands-on manual therapy, and stress management programs each target aspects of central sensitization.

This box summarizes key points contained in the article.

Central sensitization encompasses altered sensory processing in the brain [14], malfunctioning of descending antinociceptive mechanisms [6], increased activity of pain facilitatory pathways and temporal summation of second pain or wind-up [14,15]. In addition, the pain neuromatrix is overactive in cases of central sensitization and chronic pain: increased activity is present in brain areas known to be involved in acute pain sensations, such as the insula, anterior cingulate cortex and the prefrontal cortex, but not in the primary or secondary somatosensory cortex [16]. An overactive pain neuromatrix also entails brain activity in regions not involved in acute pain sensations: various brainstem nuclei, the dorsolateral frontal cortex and the parietal associated cortex [16]. Long-term potentiation of neuronal synapses in the anterior cingulate cortex [17] and decreased gamma-aminobutyric acid (GABA) neurotransmission [18] are two other mechanisms contributing to the overactive brain neuromatrix.

Besides top-down mechanisms included in the pathophysiology of central sensitization, it is important to realize that there are also bottom-up mechanisms. For example, peripheral injury and other kinds of stressor (e.g., infections) trigger the release of the pro-inflammatory cytokines and consequent activation of spinal cord glia with cyclooxygenase-2 and prostaglandin E2 expression in the CNS [19-22]. The outcome of the processes involved in central sensitization is an increased responsiveness to a variety of stimuli including mechanical pressure, chemical substances, light, sound, cold, heat and electrical stimuli. The increased sensitivity to variable stimuli results in a decreased load tolerance. Further details addressing the pathophysiology of central sensitization are explained below, together with the potential therapeutic options. For comprehensive reviews on central sensitization, the interested readers are referred to other manuscripts [1,23,24].

Central sensitization accounts for chronic 'unexplained' pain in a wide variety of disorders, including chronic whiplash-associated disorders [2,25], temporomandibular disorders [26-28], chronic low back pain [3], osteoarthritis [4], fibromyalgia [1], chronic fatigue syndrome [6,29] and chronic tension-type headache [5,30] among others. In addition, rheumatoid arthritis and migraine show features of central sensitization [31-33] but cannot be categorized as 'unexplained' pain disorders. Local musculoskeletal disorders – such as shoulder impingement syndrome [34], myofascial trigger points [35] and lateral epicondylalgia [36] – show features of segmental sensitization rather than widespread senstization. Although clinical guidelines for the recognition and assessment of central sensitization in pain patients have been provided [9], an international consensus definition or clinical criteria for central sensitization are essentially lacking. It should be noted that the present review focuses on 'unexplained' chronic pain disorders that do not fit the diagnostic criteria for neuropathic pain [37]. Hence, chronic 'unexplained' pain is defined here as non-neuropathic chronic pain due to central sensitization.

Given the increasing evidence supporting the clinical significance of central sensitization in those with chronic unexplained chronic pain [11,12,13], awareness is growing that central sensitization should be a treatment target in these patients [1,2,8,10,38]. However, little agreement regarding the treatment of central sensitization in those with unexplained chronic pain currently exists. Therefore, the present article provides an overview of the treatment options available for desensitizing the CNS in patients with chronic pain due to central sensitization. In this respect, it is important for the reader to realize that studies examining the effects of pharmacotherapy and other treatments on central sensitization are mainly animal studies' little is known about the effect of pharmacotherapy or any other treatment strategy on the mechanism of central sensitization in humans. However, a body of scientific literature in support of the clinical effectiveness of various pharmacological and non-pharmacological treatments in a variety of chronic pain disorders, characterized by central sensitization, is currently available. Whether these clinical improvements accompany amelioration of central sensitization remains to be established. The present review focuses on those strategies that specifically target pathophysiological mechanisms known to be involved in central sensitization. Besides mainly addressing pharmacological options, rehabilitation and neurotechnology options are discussed as well.

2. Pharmacotherapy potentially targeting central sensitization

Pharmacological agents such ase non-steroidal anti-inflammatory drugs and coxibs have peripheral effects, and are therefore inappropriate for the treatment of central

sensitization in patients with chronic pain [39]. However, in cases of hypersensitivity of central pain pathways, relatively minor injuries/trauma at any location are likely to sustain the process of central sensitization [1]. The analgesic effect of NSAIDs has traditionally been related to the inhibition of peripheral prostaglandin synthesis. In addition, a central action has been suggested. It is proposed that NSAIDs reduce hyperalgesia by peripheral and central mechanisms of action [40]. The peripheral mechanism would be of anti-inflammatory nature, which in turn attenuates sensitization of peripheral nociceptors, attenuates afferent nociceptive activity and thereby attenuates C-fibre-mediated central sensitization. Central effects are expected to reduce progressive tactile hypersensitivity (i.e., hyperresponsiveness to tactile stimuli), whereas the peripheral aspects of NSAIDs are expected to reduce central hyperexcitability [40]. For example, a single oral dose of ibuprofen inhibits progressive tactile hypersensitivity without reducing C-fibre-induced central sensitization by a predominant central mechanism [40]. Hence, peripherally acting anti-inflammatory drugs may be useful in shutting down peripheral sources of nociceptive input towards the CNS. However, they are unable to 'treat' the mechanism of central sensitization directly.

Several centrally acting drugs specifically target processes known to be involved in central sensitization. We aim to explain how current drugs employed in the treatment of chronic pain states interact with these processes, including the interaction of *N*-methyl-D-aspartate (NMDA)-receptor blockers such as ketamine; opioids; tricyclic antidepressants (TCAs), such as amytryptiline; selective serotonin-reuptake inhibitors (SSRIs) and selective noradrenaline-reuptake inhibitors (SNRIs) with descending pathways that link the brain with the modulation and enhancement of pain. The ability of drugs such as gabapentin/pregabalin to alter excitability is also discussed. It should also be remembered that these drugs, in particular antidepressants, might have a significant supraspinal mechanism of action that might act on the significant psychological component of pain perception, and thus allow patients to better cope with their pain [41]. These pharmacological agents are discussed below in view of treating central sensitization in those with chronic unexplained pain. It is important that the reader realizes that we do not intend to provide clinical guidelines for the treatment of central sensitization. This would be impossible given the limited scientific data available. Instead, an overview of treatment strategies known to interfere with mechanisms involved in central sensitization is presented. Hence, important issues like side effects, numbers needed to treat and numbers needed to harm are not addressed here.

2.1 Acetaminophen

Activation of the periaqueductal gray matter activates descending seretonergic and noradrenergic neurons that activate the rostral ventromedial medulla and the dorsolateral pons, respectively [42]. These brainstem centers provide powerful inhibitory action on nociceptive input at the spinal segmental level. Activation of descending nociceptive inhibition reduces nociceptive input to the CNS. Acetaminophen (paracetamol) improves peak exercise performance in healthy athletes [43]. Acetaminophen primarily acts centrally: it reinforces descending inhibitory pathways [44], namely the serotonergic descending pain pathways. In addition, acetaminophen may exert an inhibitory action on the enzyme cyclooxygenase in the CNS [45], involved in the transformation of arachnidonic acid to prostaglandins. Cyclooxygenase-2 and prostaglandin E2 expression in the CNS takes part of the mechanism of central sensitization in those with chronic pain [19,20]. Hence, in addition to its effects on descending antinociceptive pathways, its cyclooxygenase-inhibitory action might well also contribute to decreasing the hypersensitivity of the CNS.

2.2 Serotonin- and norepinephrine-reuptake inhibitors

In line with the reasoning explained for acetaminophen is the use of serotonin-reuptake inhibitor drugs, which activate serotonergic descending pathways that recruit, in part, opioid peptide-containing interneurons in the dorsal horn [46]. Relatively selective serotonin-reuptake inhibitors, like fluoxetine and clomipramine, and the serotonin precursor tryptophan, prevent stress-induced hyperalgesia in animals [47]. SNRI drugs activate noradrenergic descending pathways together with serotonergic pathways [48]. This dual control of the spinal cord by monoamine systems in the brain, whereby serotonin appears to enhance spinal processing and norepinephrine acts to inhibit activity, might be one way in which the brain can alter pain processing and may be the route by which sleep, anxiety, coping, and catastrophizing can impact on the level of pain perceived. In this context, the use of antidepressants to control pain relates to activity in these systems. Agents that block the reuptake of either or both of these neurotransmitters, such as tricyclic antidepressants (TCAs), SSRIs, and SNRIs provide benefit in the treatment of pain. Antidepressants are used to increase either serotonin or norepinephrine-mediated neurotransmission, or both. Humans studies have also shown that inhibiting both these monoamines is more effective than inhibiting just serotonin alone [49], and in this regard, the ability of norepinephrine to inhibit pain through alpha-2-adrenoceptor activation, whereas serotonin can enhance pain, is a basis for the need for increased norepinephrine levels as a determinant of efficacy of antidepressant drugs in pain [49]. Centrally acting analgesics such as duloxetine (an SNRI), have proven its efficacy in a variety of human chronic pain conditions characterized by central sensitization (e.g., fibromyalgia [50] and osteoarthritis [4]). It remains unclear whether these clinical effects can be reinforced by using some of the other treatment strategies discussed here, which have the potential of 'treating' central sensitization in those with chronic pain. The mechanism of analgesic action of TCAs is probably related to their neurohormonal

dual-reuptake inhibition, with greater norepinephrine impact. There is also some evidence that TCAs potentiate the endogenous opioid system [51].

2.3 Opioids

Opioid peptides are derived from different precursors: proopiomelanocortin, prodynorphin, and proenkephalin [52]. Enkephalins, dynorphins, and β-endorphins are the main groups of opioid peptides derived from these precursor proteins, respectively [52]. Opioids target opioid receptors (μ1, μ2, δ1, δ2, κ1, κ2, and κ3-opioid receptors), with the μ-opioid receptors as the most significant. Endogenous opioid peptide-containing neurons are located in a wide variety of CNS regions involved in pain processing: in lamina II, III, VIII and IX of the dorsal horn (i.e., presynaptic Aδ- and C-fibres, postsynaptically on interneurons and projection neurons), the thalamus, periaqueductal gray, limbic system and several regions of the cortex [39,52]. Activation of μ-opioid receptors has inhibitory effects, including presynaptic inhibition of primary nociceptive afferents and postsynaptic inhibition of projecting neurons [39]. Various opioids are available for clinical use: codeine, dextropropoxyphene, tramadol (serving as a reuptake inhibitor of serotonin and norepinephrine in addition to its opioid effects), buprenorphine, morphine, methadone, fentanyl and hydromorphone, among others.

Decreased GABA-neurotransmission appears to be an important component of central sensitization [18]. GABA-agonists like pregabalin are designed to stimulate GABA-neurotransmission, and hence theoretically facilitate opioidergic nociceptive inhibitory mechanisms. The rostral ventromedial medulla, an important brainstem centre for controlling the balance between nociceptive inhibition and nociceptive facilitation, contains both ON cells (involved in descending facilitation of nociceptive information) and OFF cells (involved in descending inhibition). Morphine is typically referred to as an opioid analgesic because it excites OFF cells (μ-opioid agonist) and suppresses ON cells (δ-opioid agonist) [53]. It causes neuronal inhibition either by blocking the release of neurotransmitters or by hyperpolarization of the cell via alterations in potassium and calcium channels [10]. Morphine produces analgesia in animals at least in part by stimulation of GABA-neurotransmission, including stimulation of GABA-A receptors [18]. Hence, morphine holds the capacity to specifically target mechanisms known to be crucial to the pathophysiology of central sensitization. Exogenous opioids such as morphine do not only target pain mechanisms, they have significant effects on human immune function as well [54]. This is in line with our current understanding of the integrated role of the immune system in the human body, including its interactions with the CNS and central pain mechanisms [19,20,21,22]. The immune system not only contributes to pain sensitivity, it also modulates opioid tolerance in humans [54].

Whether these drugs provide considerable benefits in terms of pain reduction and improved function to balance the risks associated with their use is unclear. Of particular importance to clinicians treating chronic musculoskeletal pain is opioid-induced hyperalgesia, the activation of pronociceptive pathways by exogenous opioids that results in central sensitization to pain [55]. This phenomenon results in an increase in pain sensitivity and can potentially exacerbate pre-existing pain [55]. The mechanisms and signal transduction pathways that mediate opioid-induced hyperalgesia include activation of NMDA-receptors and protein kinase C, activation of facilitatory supraspinal loops, upregulation of spinal dynorphin and apoptosis of spinal dorsal horn [56]. Opioids also have powerful positive effects on the reward and reinforcing circuits of the brain that might lead to continued drug use, even if there is no abuse or misuse [55].

There is a growing recognition that selected patients with chronic non-cancer-related pain can be given opioid drugs for prolonged periods without overt evidence of tolerance and without intolerable toxicity [57]. Many patients function better with these drugs. These observations have led to the development of consensus statements in support of cautious opioid use in carefully selected and well-monitored patients. These consensus statements have now been published by the American Pain Society, American Academy of Pain Medicine, American Society of Addiction Medicine, and the Canadian Pain Society [57].

2.4 *N*-methyl-D-aspartate receptor blockers

The *N*-methyl-D-aspartate (NMDA) receptor in the dorsal horn of the spinal cord has been demonstrated to play a role in the development of central sensitization and, separately, in the mechanisms underlying opioid analgesia and tolerance. These findings are driving new drug development and clinical studies of commercially available drugs, such as ketamine or dextromethorphan, that block this receptor. NMDA-receptor antagonists have been demonstrated to be analgesic in some settings, and the commercially available antagonists are being explored for clinical use [58]. This class of drug may offer a new and reasonably well-tolerated single therapy for chronic administration. However, the clinically available NMDA-receptor channel blockers have, at best, a narrow therapeutic window. Blockade of excitation with NMDA-receptor antagonists may limit or reduce the spread of hyperalgesia and allodynia due to sensitization and in consequence, NMDA-receptor antagonists may be seen preferentially as antihyperalgesic or anti-allodynic agents rather than as traditional analgesics [59]. Despite the presence of firm clinical evidence in support of the effectiveness of agents acting as antagonists at the NMDA-receptor complex, especially ketamine, and although some individual patients do get good pain relief in nerve-injury situations, the majority cannot achieve complete pain control. This is partly because adequate dosing is prevented by the narrow therapeutic window of the existing drugs, largely because of the widespread distribution and functionality of NMDA-receptors, meaning that the introduction of an antagonist will not only target the pathology but will also disrupt normal essential NMDA signaling within the CNS. This explains why such drugs are commonly

associated with numerous unavoidable and unacceptable side-effects. Ultimately, the broad use of NMDA-antagonists in the treatment of chronic pain will depend on strategies that increase their therapeutic window over existing drugs [41].

The therapeutic ratio therefore needs to be improved by the use of low-dose NMDA blockers in combination with another agent, more selective systemic NMDA-receptor antagonists (such as the modulation of other binding sites within the NMDA–receptor complex), or selective administration of NMDA-receptor antagonists [41,60]. An emerging principle in new pharmacological strategies for treating pain is to combine existing analgesic agents with non-toxic NMDA-receptor antagonists to enhance their analgesic effects, extend their duration and prevent tolerance to their repeated administration.

Of relevance is the crucial role that NMDA-receptor activation plays in tolerance to the analgesic effects of narcotics, dependence on narcotics and narcotic-induced thermal hyperalgesia (for a review, see [62]). Combining NMDA-receptor antagonists with opioid and even non-opioid analgesics may be a way of increasing their analgesic potency in addition to preventing tolerance and dependence. Preclinical animal studies demonstrate the practicality of the combined administration of non-toxic NMDA-receptor antagonists with various types of analgesic drugs [60].

Interestingly, recent advances in the understanding of the pharmacology of ketamine and related compounds have demonstrated that ketamine within the CNS is bound with greater affinity to agonist sites on high-affinity dopamine D2 receptors than to NMDA-receptors [62]. Findings would therefore appear to result more from their activity as a dopamine D2-receptor agonist than as an NMDA-receptor antagonist [63].

2.5 Calcium channel alpha(2)delta ligands

The molecular mechanisms of sensitization that occur in peripheral nociceptors and the dorsal horns of the spinal cord are putative targets for context-dependent drugs, that is, drugs that can discriminate between 'normal' and 'pathological' pain transmission. Among these, pregabalin and gabapentin bind to the alpha(2)delta (a2δ) subunit of voltage-sensitive Ca^{2+} channels, which sustain the enhanced release of pain transmitters at the synapses between primary afferent fibres and second-order sensory neurons under conditions of chronic pain. Gabapentin and pregabalin both bind to the a2δ subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine and substance P [64]. Pregabalin in particular represents a remarkable example of a context-dependent analgesic drug that acts at a critical step of nociceptive sensitization. Preclinical and clinical data suggest that pregabalin is more than a structural and functional analogue of gabapentin and may be effective in the treatment of nociceptive inflammatory pain that is resistant to gabapentin [65].

Gabapentin, which is readily transported into cells, is the first ligand that has been shown to modulate Ca^{2+} channel current. There is also *in vitro* evidence that gabapentin alters activity of glutamic acid decarboxylase. Such an effect may increase synthesis of GABA glutamate in neurological tissue. Because GABA receptors have been shown to mediate pre- and postsynaptic inhibition in sensory afferent fibres, it follows that gabapentin may be effective in antagonizing at least some painful sensations.

Pregabalin, a second-generation anticonvulsant, is approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia (and for adjunctive treatment of partial-onset seizures). Decreased GABA-neurotransmission appears to be an important component of central sensitization [18]. GABA-agonists like pregabalin are designed to stimulate GABA-neurotransmission, and hence theoretically facilitate opioidergic nociceptive inhibitory mechanisms. Pregabalin binds to a2δ subunit of voltage-gated calcium channels, and it reduces Ca^{2+} influx during depolarization and reduces the release of glutamate, noradrenaline and substance P [51].

2.6 Tramadol

Tramadol is a centrally acting drug that induces antinociception in animals and analgesia in humans. It is a novel analgesic agent that has some activity at μ-receptors, although the binding affinity for brain opioid receptors seems to be low [51,66]. Tramadol inhibits the reuptake of serotonin and of norepinephrine [51], and is interesting because it has non-opioid and opioid actions that can be attributed to the two isomers found in the racemic mixture [67]. Bianchi and Panerai [66] have demonstrated that tramadol is able to prevent and reverse hyperalgesic behavior without altering physiological nociception in rats. In the search for drugs that act specifically on central sensitization, Bianchi and Panerai [66] feel that tramadol deserves attention as an antihypersensitivity agent.

3. Transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation is a safe, non-invasive technique for stimulating the cerebral cortex. The short-term analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex or dorsolateral prefrontal cortex have been shown in a series of human studies using various chronic pain populations (reviewed in [68-70]) and including disorders characterized by central sensitization like fibromyalgia [71]. Repetitive transcranial magnetic stimulation is more effective in suppressing centrally than peripherally originated pain states [70]. However, discussion remains regarding the precise mechanism of action, and the clinical utility of the technique is limited by practical obstacles.

Repetitive transcranial magnetic stimulation of the motor cortex or dorsolateral prefrontal cortex in humans may specifically target some of the mechanisms involved in central sensitization. Indeed, repetitive transcranial magnetic stimulation directly targets the various structures of the human CNS involved in pain processing [68,69]. Focal somatotopical

stimulation of the motor cortex addresses the sensory-discriminative aspects of pain [69]. In addition, repetitive transcranial magnetic stimulation reverses the inhibited intracortical motor circuitry, which might restore descending nociceptive inhibition [69,72]. It might restore normal blood flow (i.e., activity) in various brain regions involved in the brain neuromatrix, including the brainstem, thalamus and the anterior cingulate cortex, which in turn restores descending nociceptive inhibition and alters the cognitive emotional component of pain [68,69,72]. However, because the diffuse analgesic effects of repetitive transcranial magnetic stimulation did not change the nociceptive flexion reflex in healthy human volunteers; Nahmias *et al.* [73] concluded that the analgesic effects might not depend on the activation of descending inhibitory systems.

Importantly, practical obstacles preclude the widespread clinical use of repetitive transcranial magnetic stimulation for those with chronic pain due to central sensitization. The analgesic effects observed in humans are too short-lived (i.e., varying between less than 1 week to 3 weeks) [69,72,75] and the availability of the equipment is limited to few specialized centers. These practical issues might by overcome by using chronic motor cortex stimulation with surgically implanted epidural electrodes. In fact, repetitive transcranial magnetic stimulation was first applied to provide a non-invasive alternative for chronic motor cortex stimulation with surgically implanted epidural electrodes, or at least to provide a non-invasive strategy capable of predicting the outcome of the implanted procedure [68,69]. Chronic motor cortex stimulation with surgically implanted epidural electrodes largely targets the same mechanisms as repetitive transcranial magnetic stimulation of the motor cortex or dorsolateral prefrontal cortex. The discussion of neurosurgery in the treatment of central sensitization is well beyond the scope of the present article.

4. Rehabilitation potentially targeting central sensitization

In addition to pharmacotherapy and transcranial magnetic stimulation, rehabilitation provides opportunities for treating central sensitization in those with chronic unexplained pain. Rehabilitation targeting central sensitization is likely to benefit from advances in (neuro)technology.

4.1 Manual therapy

Originally, manual therapy aimed at exerting peripheral effects like increasing joint range of motion, decreasing peripheral muscle tension and relieving local pain. Besides peripheral effects, manual therapy also produces central (analgesic) effects [76-78]. Manual joint mobilization exerts temporally (30 – 45 min) activation of descending anti-nociceptive pathways [42,79-81]. This was shown in animal studies [42,80,81]. A study in humans with osteoarthritis, a chronic pain disorder characterized by central sensitization, provides preliminary evidence that manual joint mobilization provides widespread analgesia [79]. Likewise, a pilot randomized, controlled clinical trial concluded that lateral glide manual therapy applied to the cervical spine may be effective in reducing sensory hyperexcitability in patients with chronic whiplash, evidenced by improvements in the nociceptive flexion reflex [38]. However, the short-term nature of the central analgesic effects of manual therapy limits is clinical utility as a treatment strategy for desensitizing the CNS. This might explain the inconclusive findings in relation to the effectiveness of manual therapy for various chronic 'unexplained' pain disorders like fibromyalgia, tension-type headache, osteoarthritis, myofascial pain syndrome and temporomandibular disorders [82]. It is tempting to speculate that repeated manual therapy treatment sessions result in long-term activation of descending anti-nociceptive pathways; future research should examine whether manual therapy has the capacity of doing so. In the absence of such evidence, manual therapy used in patients with chronic pain due to central sensitization should be adopted to the process of central sensitization. If it is not, manual therapy may serve as a peripheral source of nociceptive input to the CNS and thus will sustain the process of central sensitization [2,8]. Guidelines for the use of manual therapy in those with chronic pain due to central sensitization are presented elsewhere [2,8].

4.2 Virtual reality

Virtual reality provides a realistic, computer-generated environment. The user, in this case the patient suffering from chronic unexplained pain with central sensitization, is able to interact with that environment. For this purpose, a high-speed microprocessing computer and specialized software generates various sensory modalities including visual, auditory, tactile and motion-tracking. Virtual reality has been suggested as a desensitization therapy [83]. There is evidence to support the analgesic effects of virtual reality in humans with chronic pain [84,85] but the precise mechanism of action remains to be established. There is some (expert) agreement that virtual reality provides strong distraction [83]. According to this theory, virtual reality distracts the user's conscious attention away from simultaneous nociceptive input by replacing it with more pleasant sensory input [83]. If this is the case, then descending nociceptive inhibitory pathways might be activated during application of virtual reality, explaining its analgesic effect [83]. In line with this view, it is hypothesized that virtual reality is most effective in hypervigilant chronic pain sufferers. At present, the number of studies in humans with chronic unexplained pain is scarce; limited evidence (level 2a) supports the effectiveness of virtual reality in patients with chronic pain [86]. In addition to its analgesic effect, virtual reality provides opportunities for treating the distorted body image, as typically seen in patients with chronic pain due to central sensitization [87-91]. Indeed, virtual reality might enable motor relearning in those with chronic unexplained pain.

4.3 Improving stress tolerance and neurofeedback training

The hyperexcitability of the somatosensory system in people with chronic pain is likely to be related to the stress response

system (i.e., the hypothalamic–pituitary–adrenal axis and the autonomic nervous system). Animal studies have demonstrated that the stress response system is capable of influencing pain processing through various pathways [47,18,92-94], including the dorsal horn glucocorticoid receptors (receptors having pain inhibitory capacity) [94]. Indeed, stress triggers a switch in second-messenger signaling for pronociceptive immune mediators in primary afferent nociceptors, possibly explaining generalized pain and stress-induced symptom flares/exacerbations as typically seen in those with chronic pain due to central sensitization [92]. In addition, stress activates the dorsomedial nucleus of the hypothalamus and subsequent activation of ON-cells plus suppression of OFF-cells [93]. Together, these CNS changes result in stress-induced hyperalgesia (augmented nociceptive facilitation and suppressed nociceptive inhibition) [93]. Likewise, chronic stress (repeated forced swimming) has detrimental effects on GABA-neurotransmission both at the spinal and supraspinal level, resulting in generalized hyperalgesia and disinhibition of the hypothalamic–pituitary–adrenal axis [18]. Hence, stress-management programs target the cognitive emotional component of central sensitization. Neuro- and biofeedback training using commercially available devices provides opportunities for improving stress management programs [95,96].

Stress management is likely to address the cognitive and emotional aspects of central sensitization. 'Cognitive emotional sensitization' [97] refers to the capacity of forebrain centers of exerting powerful influences on various nuclei of the brainstem, including the nuclei identified as the origin of the descending facilitatory pathways [98]. The activity in descending pathways is not constant but can be modulated, for example by the level of vigilance, catastrophizing, depression, attention and stress [99,100]. Hence, part of the effects of cognitive behavioural therapy for chronic pain patients may be explained by its action on cognitive emotional sensitization. Improving perpetuating cognitive and emotional factors in patients with chronic pain due to central sensitization might lead to desentization, as has been shown in patients with fibromyalgia [101].

4.4 Transcutaneous electrical nerve stimulation

Transcutaneous electric nerve stimulation (TENS) is frequently used in patients with chronic pain. TENS activates large-diameter afferent fibers, which in turn activate descending nociceptive inhibitory mechanisms by activating the ventrolateral periaqueductal gray and the rostral ventromedial medulla [102,103]. Indeed, pharmacological blockade of activity in the ventrolateral periaqueductal gray and the rostral ventromedial medulla inhibits the analgesic effects of TENS in animals [102,103]. TENS primarily activates (poly)segmental inhibitory circuits [104] by activating spinal μ- and δ-opioid receptors [105] and spinal GABA(A) receptors [106], in addition to triggering GABA release [106]. In summary, TENS targets mechanisms known to be involved in central sensitization. Although modest treatment responses to TENS have been reported in humans with fibromyalgia [107,108], widespread and poorly localized chronic pain states are less likely to be suitable for treatment by TENS [104].

4.5 Cranial electrotherapy stimulation

Cranial electrotherapy stimulation is a recognized category for medical devices using microcurrent levels of electrical stimulation applied across the head via transcutaneous electrodes. Its effects are thought to result from a direct action on the brain at the level of the limbic system, the hypothalamus and the periaqueductal gray matter [109]. Hence, it intends to activate descending inhibitory pathways from the medial brainstem to the dorsal horn of the spinal cord [109], although direct evidence in support of this is currently lacking. Limited data in support of its clinical effectiveness in those with chronic pain have been provided [110-113]. These studies include patient populations like fibromyalgia that are characterized by central sensitization. Despite the fact that many (review) papers on cranial electrotherapy stimulation are written by authors affiliated to companies manufacturing cranial electrotherapy devices, given its intended action, it potentially treats central sensitization in people with chronic pain.

5. Conclusion

An overview of the treatment options for desensitizing the CNS in patients with chronic unexplained pain and central sensitization has been provided. It is concluded that acetaminophen, serotonin-reuptake inhibitor drugs, selective and balanced serototin- and norepinephrine-reuptake inhibitor drugs, the serotonin precursor tryptophan, opioids, NMDA-receptor antagonists, calcium channel a2δ ligands, transcranial magnetic stimulation, TENS, manual therapy and stress management each target central pain processing mechanisms in animals that, theoretically, desensitize the CNS in humans. However, little is known about the effect of pharmacotherapy and other treatment strategies on the mechanism of central sensitization in humans. The present overview therefore addressed pharmacological and non-pharmacological treatments with established clinical effectiveness in a variety of 'unexplained' chronic pain disorders known to be characterized by central sensitization. Still, it should be noted that vigorous uptake of medication usage in the patients described could do more harm than good. Drugs are never without side effects and this should be acknowledged by clinicians.

From the overview provided, it becomes clear that many of these treatment options target similar mechanisms. For example, morphine, gabapentin and TENS enhance GABA neurotransmission in the CNS. The majority of the treatment options discussed here aim at improving and/or activating descending nociceptive processing together with decreasing descending nociceptive facilitation, rather than targeting peripheral sources of nociceptive input. In the absence of such peripheral sources of nociceptive input, as is typically the case in patients with 'unexplained' chronic pain, a treatment targeting top-down mechanisms is required.

Future work should examine the mechanism, explaining the clinical effects of the treatment options we have for dealing with central sensitization in those with chronic unexplained pain. More specifically, examining the effects of these treatment strategies on central sensitization should be a priority for future pain studies. This can be accomplished by including outcome measures like temporal summation [14], spatial summation (or diffuse noxious inhibitory control) [6] or the nociceptive flexion reflex threshold [38] in conjunction with clinical outcomes (e.g., pain severity, pain variability) in future randomized (cross-over) clinical trials.

6. Expert opinion on combining pharmacotherapy with other treatment options for central sensitization

It is unlikely that a single drug or non-pharmacological treatment will be identified as being capable of treating such a complex mechanism as central sensitization. Indeed, central sensitization entails various interrelated processes in the CNS, including malfunctioning of descending antinociceptive mechanisms [6], increased activity of pain facilitatory pathway, an overactive pain neuromatrix [16] and long-term potentiation [17]. Heterogeneity exists in response to pharmacotherapy in those with chronic unexplained pain, including non-responders [10]. At the individual level, most people respond to two or more drugs, suggesting that several pain mechanisms have to be targeted in clinical practice [10]. Thus, instead of using a single drug, it seems more likely that the combination of different strategies, each targeting a somewhat different 'desensitizing' mechanism, will prove beneficial. The exact content of such combinations is likely to differ across patient groups (e.g., patients with osteoarthritis and fibromyalgia, two very different disorders characterized by central sensitization, will probably benefit from a different combination of treatments, even though some treatment components may overlap).

Little work has been done to examine the combined effects of treatment strategies aiming at desensitizing the CNS. Animal studies have demonstrated that high-frequency TENS in combination with morphine results in a similar reduction in mechanical hyperalgesia as high-frequency TENS alone [74]. The author suggested that a lower dose of morphine could be used in combination with TENS to decrease the side effects of systemic morphine and achieve the same degree of analgesia [74], but it remains unclear whether this also applies to humans. A randomized, controlled clinical trial revealed that repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological and conservative therapy in patients with complex regional pain syndrome type I [75]. The combined standardized pharmacological and conservative treatment was based on the best evidence available (naproxen 250 mg b.i.d., amitriptyline 50 mg q.d., and carbamazepine 200 mg b.i.d.) and a physical therapy program (kinesiotherapy plus low-impact aerobic relaxation and stretching exercises) [75].

To provide a comprehensive treatment for 'unexplained' chronic pain disorders characterized by central sensitization, combining the best evidence available with treatment modalities known to target central sensitization is advocated. For example, central sensitization contributes to the complex clinical picture of chronic whiplash-associated disorders (reviewed in [2]). Little evidence in support of any treatment strategy for patients with chronic whiplash has been provided. Combining centrally acting analgesics (e.g., duloxetine or any other SNRI) with conservative interventions (i.e., manual therapy and stress management) to target central sensitization in those with chronic whiplash associated disorders is suggested. Whether cranial electrotherapy stimulation and/or virtual reality are efficacious as add-ons to centrally acting pharmacotherapy in these patients remains to be determined. These are important questions for further work in this area. In addition to causation and effectiveness studies, dose–response studies might be of significant importance.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript. Mira Meeus is a postdoctoral research fellow of the Research Foundation Flanders (FWO). Jessica Van Oosterwijck is a research fellow of the Vrije Universiteit Brussel (OZR1596).

Bibliography

1. Vierck CJ. Mechanisms underlying development of spatial distributed chronic pain (fibromyalgia). Pain 2006;124:242-63
2. Nijs J, Van Oosterwijck J, De Hertogh W. Rehabilitation of chronic whiplash: treatment of cervical dysfunctions or chronic pain syndrome? Clin Rheumatol 2009;28:243-51
3. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50:613-23
4. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009;146:253-60
5. Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. Pain 2005;118:215-23
6. Meeus M, Nijs J, Van de Wauwer N, et al. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. Pain 2008;139:439-48
7. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd edition. Churchill Livingstone, Edinburgh; 1995. p. 13-44
8. Nijs J, Van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: application of pain neurophysiology in manual therapy practice. Man Ther 2009;14:3-12
9. Nijs J, Van Houdenhove B, Oostendorp RAB. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. Man Ther 2010;15:135-41
10. Lemming D, Sorensen J, Graven-Nielsen T, et al. The responses to pharmacological challenges and experimental pain in patients with chronic whiplash-associated pain. Clin J Pain 2005;21:412-21
11. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain 2003;104:509-17
12. Kasch H, Querama E, Flemming WB, Jensen TS. Reduced cold pressor pain tolerance in non-recovered whiplash patients: a 1-year prospective study. Eur J Pain 2005;9:561-9
13. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? A preliminary RCT. Pain 2007;129:28-34
14. Staud R, Craggs JG, Robinson ME, et al. Brain activity related to temporal summation of C-fiber evoked pain. Pain 2007;129:130-42
15. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol 2007;26:465-73
16. Seifert F, Maihofner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. Cell Mol Life Sci 2009;66:375-90
17. Zhuo M. A synaptic model for pain: long-term potentiation in the anterior cingulated cortex. Mol Cells 2007;23:259-71
18. Suarez-Roca H, Leal L, Silva JA, et al. Reduced GABA neurotransmission underlies hyperalgesia induced by repeated forced swimming stress. Behav Brain Res 2008;189:159-69
19. Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1 beta-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410:471-5
20. Bazan NG. COX-2 as a multifunctional neuronal modulator. Nat Med 2001;7:414-15
21. Watkins LR, Maier SF. Implications of immune-to-brain communication for sickness and pain. Proc Natl Acad Sci USA 1999;96:7710-13
22. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychological Rev 1998;105:83-107
23. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheumatol 2007b;36:330-56
24. Nielsen LA, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain desinhibition. Best Pract Res Clin Rheumatol 2007;21:465-80
25. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, et al. Central hypersensitivity in chronic pain after whiplash injury. Clin J Pain 2001;17:306-15
26. Maixner W, Fillingim R, Sigurdsson A, et al. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. Pain 1998;76:71-8
27. Fernandez-de-las-Penas C, Galan-del-Rio F, Fernandez-Carnero J, et al. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. J Pain 2009;10:1170-8
28. Fernandez-de-las-Penas C, Galan-del-Rio F, Ortega-Santiago R, et al. Bilateral thermal hyperalgesia in trigeminal and extra-trigeminal regions in patients with myofascial temporomandibular disorders. Exp Brain Res 2010;202:171-9
29. Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. Clin Rheumatol 2010;29:393-8
30. Langemark M, Bach FW, Jensen TS, Olesen J. Decreased nociceptive flexion reflex threshold in chronic tension-type headache. Arch Neurol 1993;50:1061-4
31. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with

widespread pain. Best Pract Res Clin Rheumatol 2007;21:481-97

32. Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D. Repeated noxious stimulation of the skin enhances cutaneous perception of migraine patients in-between attacks: clinical evidence for cutaneous sub-threshold increase in membrane excitability of central, trigeminovascular neurons. Pain 2003;104:693-700

33. Burnstein R, Yarnitsky D, Goor-Aryeh I, et al. An association between migraine and cutaneous allodynia. Ann Neurol 2000;47:614-24

34. Hidalgo-Lozano A, Fernandez-de-las-Penas C, Alonso-Blanco C, et al. Muscle trigger points and pressure pain hyperalgesia in the shoulder muscles in patients with unilateral shoulder impingement: a blinded, controlled study. Exp Brain Res 2010;202:915-25

35. Ge H-Y, Fernandez-de-las-Penas C, Madeleine P, Arendt-Nielsen L. Topographical mapping and mechanical pain sensitivity of myofascial trigger points in the infraspinatus muscle. Eur J Pain 2008;12:859-65

36. Paungmali A, O'Leary S, Sowlis T, Vicenzino B. Hypoalgesic and sympathoexcitatory effects of mobilization with movement for lateral epicondylalgia. Phys Ther 2003;83:374-83

37. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German research network on neuropathic pain (DFNS): standardized protocol and reference values. Pain 2006;123:231-43

38. Sterling M, Pedler A, Chan C, et al. Cervical lateral glide increases nociceptive flexion reflex threshold but not pressure or thermal pain thresholds in chronic whiplash associated disorders: a pilot randomised controlled trial. Man Ther 2009, doi:10.1016/j.math.2009.09.004

39. Kosek E. Medical management of pain. Chapter 12. In: Sluka K. Mechanisms and management of pain for the physical therapist. IASP press, Seattle; 2009. p. 231-55

40. Petersen KL, Brennum J, Dahl JB. Experimental evaluation of the analgesic effect of ibuprofen on primary and secondary hyperalgesia. Pain 1997;70:167-74

41. D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. Br J Anaesth 2008;101:8-16

42. Skyba DA, Radhakrishnan R, Rohlwing JJ, et al. Joint manipulation reduces hyperalgesia by activation of monoamine receptors but not opioid or GABA receptors in the spinal cord. Pain 2003;106(1-2):159-68

43. Mauger AR, Jones AM, Williams CA. Influence of acetaminophen on performance during time trial cycling. J Appl Physiol 2010;108:98-104

44. Pickering G, Esteve V, Loriot MA, et al. Acetaminophen reinforces descending inhibitory pathways. Clin Pharmacol Ther 2008;84:47-51

45. Brune K, Zeilhofer HU. Antipyretic analgesics: basic aspects. In: McMahon SB, Koltzenburg M, editors. Textbook of pain. Elsevier, Amsterdam; 2006. p. 459-69

46. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984;7:309-38

47. Quintero L, Montero M, Avila C, et al. Long-lasting delayed hyperalgesia after subchronic swimm stress. Pharmacol Biochem Behav 2000;67:449-58

48. Millan MJ. Descending control of pain. Prog Neurobiol 2002;66:355-474

49. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237-51

50. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Athritis Rheum 2004;50:2974-84

51. Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:499-511

52. Przewlocki R, Przewlocka B. Opioids in chronic pain. Eur J Pharmacol 2001;429:79-91

53. Sluka KA. Central mechanisms involved in pain processing. Chapter 3 in: Sluka KA, edition. Mechanisms and management of pain for the physical therapist. IASP Press, Seattle, USA; 2009. p. 41-72

54. Hutchinson MR, La Vincente SF, Somogyi AA. In vitro opioid induced proliferation of peripheral blood immune cells correlates with in vivo cold pressor pain tolerance in humans: a biological marker of pain tolerance. Pain 2004;110:751-5

55. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. Nat Rev Rheumatol 2010;6:191-7

56. Vanderah TW, Ossipov MH, Lai J, et al. descending facilitation and spinal dynorphin. Pain 2001;92:5-9

57. Portenoy RK. Current pharmacotherapy of chronic pain. J Pain Symptom Manage 2000;19:S16-20

58. Portenoy RK. Evolving role of NMDA-receptor antagonists in analgesia. J Pain Symptom Manage 2000;19:S1

59. Sang CN. NMDA-receptor antagonists in neuropathic pain: experimental methods to clinical trials. J Pain Symptom Manage 2000;19:S21-5

60. Price DD, Mayer DJ, Mao J, Caruso FS. NMDA-receptor antagonists and opioid receptor interactions as related to analgesia and tolerance. J Pain Symptom Manage 2000;19:S7-11

61. Mao J. NMDA and opioid receptors: their interactions in antinociception, tolerance and neuroplasticity. Brain Res Brain Res Rev 1999;30:289-304

62. Seeman P, Ko F, Tallerico T. Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. Mol Psychiatry 2005;10:877-83

63. Wood PB. A reconsideration of the relevance of systemic low-dose ketamine to the pathophysiology of fibromyalgia. J Pain 2006;7:611-14

64. Taylor CP. The biology and pharmacology of calcium channel alpha2-delta proteins Pfizer Satellite Symposium to the 2003 Society for Neuroscience Meeting; Sheraton New Orleans Hotel, New Orleans, LA November 10, 2003. CNS Drug Rev 2004;10:183-8

65. Chiechio S, Zammataro M, Caraci F, et al. Pregabalin in the treatment of chronic pain: an overview. Clin Drug Investig 2009;29:203-13

66. Bianchi M, Panerai AE. Anti-hyperalgesic effects of tramadol in the rat. Brain Res 1998;797:163-6

67. Power I, Barratt S. Analgesic agents for the postoperative period. Nonopioids. Surg Clin North Am 1999;79:275-95

68. Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in Experimentally induced and chronic neuropathic pain: a review. J Pain 2007;8:453-9

69. Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. Clin Neurophysiol 2006;36:117-24

70. Leung A, Donohue M, Xu R, et al. rTMS for suppressing neuropathic pain: a meta-analysis. J Pain 2009;10:1205-16

71. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007;130:2661-70

72. Mylius V. Pain relieving effects of repetitive transcranial magnetic stimulation of the motor cortex: what can we learn from experimentally-induced pain? Clin Neurophysiol 2010;121:807-8

73. Nahmias F, Debes C, Ciampi de Andrade D, et al. Diffuse analgesic effects of unilateral repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers. Pain 2009;147:224-32

74. Sluka KA. Systemic morphine in combination with TENS produces an increased antihyperalgesia in rats with acute inflammation. J Pain 2000;1(3):204-11

75. Picarelli H, Teixeira HJ, Ciampi de Andrade D, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional painsyndrome (CRPS) type I. J Pain 2010; In press

76. Vicenzino B, Collins D, Wright A. The initial effects of a cervical spine manipulative physiotherapy treatment on the pain and dysfunction of lateral epicondylalgia. Pain 1996;68:69-74

77. Bialosky JE, Bishop MD, Robinson ME, et al. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. Phys Ther 2009;89:1292-303

78. Bialosky JE, Bishop MD, Robinson ME, et al. The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. BMC Musculoskeletal Disorders 2008;9:19 doi10.1186/1471-2474-9-19

79. Moss P, Sluka K, Wright A. The initial effects of knee joint mobilization on osteoarthritic hyperalgesia. Manual Ther 2007;12(2):109-18

80. Sluka KA, Skyba DA, Radhakrishnan R, et al. Joint mobilization reduces hyperalgesia associated with chronic muscle and joint inflammation in rats. J Pain 2006;7(8):602-7

81. Sluka KA, Wright A. Knee joint mobilization reduces secondary mechanical hyperalgesia induced by capsaicin injection into the ankle joint. Eur J Pain 2001;5(1):81-7

82. Bronfort G, Haas M, Evans R, et al. Effectiveness of manual therapies: the UK evidence report. Chiropr Osteopathy 2010;18:3 doi:10.1186/1746-1340-18-3 Available at: http://www.chiroandosteo.com/content/18/1/3

83. Sharar SR, Miller W, Teeley A, et al. Applications of virtual reality for pain management in burn-injured patients. Expert Rev Neurother 2008;8(11):1667-74

84. Wismeijer AAJ, Vingerhoets JJM. The use of virtual reality and audiovisual eyeglass systems as adjunct analgesic techniques: a review of the literature. Ann Behav Med 2005;30:268-78

85. Gold JI, Belmont KA, Thomas DA. The neurobiology of virtual reality pain attenuation. Cyberpsychol Behav 2007;10:536-44

86. Shahrbanian S, Ma X, Korner-Bitensky N, Simmonds MJ. Scientific evidence for the effectiveness of virtual reality for pain reduction in adults with acute or chronic pain. Stud Health Technol Inform 2009;144:40-3

87. Schwoebel J, Coslett HB, Bradt J, et al. Pain and the body schema: Effects of pain severity on mental representations of movement. Neurol 2002;59:775-7

88. Fiorio M, Tinazzi M, Ionta S, et al. Mental rotation of body parts and non-corporeal objects in patients with idiopathic cervical dystonia. Neuropsychologia 2007;45:2346-54

89. McCabe CS, Haigh RC, Shenker NG, et al. Phantoms in rheumatology. Novartis Found Symp 2004;260:154-78

90. Moseley GL, Sim DF, Henry ML, Souvlis T. Experimental hand pain delays recognition of the contralateral hand—evidence that acute and chronic pain have opposite effects on information processing? Cogn Brain Res 2005;25:188-94

91. Moseley GL. I can't find it! distorted body image and tactile dysfunction in patients with chronic back pain. Pain 2008;140:239-43

92. Khaser SG, Burkham J, Dina OA, et al. Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain. J Neurosci 2008;28:5721-30

93. Martenson ME, Cetas JS, Heinrichter MM. A possible neural basis for stress-induced hyperalgesia. Pain 2009;142:236-44

94. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. Psychosom Med 2005;67:783-90

95. Nelson DV, Bennett RM, Barkhuizen A, et al. Neurotherapy of fibromyalgia? Pain Med 2010;11(6):912-19

96. Hassett AL, Radvanski DC, Vaschillo EG, et al. A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia. Appl Psychophysiol Biofeedback 2007;32(1):1-10

97. Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. Scand J Psychol 2002;43:113-21

98. Zusman M. Forebrain-mediated sensitization of central pain pathways: 'non-specific' pain and a new image for MT. Man Ther 2002;7:80-8

99. Rygh LJ, Tjolsen A, Hole K, Svendsen F. Cellular memory in spinal nociceptive

circuitry. Scand J Psychol 2002;43:153-9

100. Rivest K, Cote JN, Dumas J-P, et al. Relationships between pain thresholds, catastrophizing and gender in acute whiplash injury. Man Ther 2010;15:154-9

101. Ang DC, Chakr R, Mazzuca S, et al. Cognitive-behavioral therapy attenuates nociceptive responding in patients with fibromyalgia: a pilot study. Arthritis Care Res 2010;62:618-23

102. DeSantana JM, Da Silva LF, De Resende MA, Sluka KA. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. Neuroscience 2009;163(4):1233-41

103. Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). J Pharmacol Exp Ther 2001;298(1):257-63

104. Woolf CJ, Thompson JW. Stimulation-induced analgesia: transcutaneous electrical nerve stimulation (TENS) and vibration. Chapter 63. In: Wall PD, Melzack R, editors, Textbook of pain. 3rd edition. Churchill Livingstone, Edinburgh; 1995. p. 1191-1208

105. Sluka KA, Bailey K, Bogush J, et al. Treatment with either high or low frequency TENS reduces secondary hyperalgesia observed after injection of kaolin and carrageenan into the knee joint. Pain 1998;77:97-102

106. Maeda Y, Lisi TL, Vance CG, Sluka KA. Release of GABA and activation of GABA(A) in the spinal cord mediates the effects of TENS in rats. Brain Res 2007;1136(1):43-50

107. Lo$ame>, Norrbrink C. Pain relief in women with fibromyalgia: a cross-over study of superficial warmth stimulation and transcutaneous electrical nerve stimulation. J Rehabil Med 2009;41(7):557-62

108. Dibenedetto P, Iona LG, Zidarich V. Clinical evaluation of S-adenosyl-L-methionine versus transcutaneous electrical nerve stimulation in primary fibromyalgia. Curr Ther Res Clin Exp 1993;53(2):222-9

109. Gilula MF, Kirsch DL. Cranial electrotherapy stimulation review: a safer alternative to psychopharmaceuticals in the treatment of depression. J Neurother 2005;9(2):7-26

110. Kirsch DL, Smith RB. The use of cranial electrotherapy stimulation in the management of chronic pain: a review. NeuroRehabil 2000;14(2):85-94

111. Lichtbroun AS, Raicer MC, Smith R. The treatment of fibromyalgia with cranial electrotherapy stimulation. J Clin Rheumatol 2001;7(2):72-8

112. Cork RC, Wood P, Ming N, et al. The effect of cranial electrotherapy stimulation (CES) on pain associated with fibromyalgia. The Internet Journal of Anesthesiol 2004:8(2)

113. Gilula MF. Cranial electrotherapy stimulation and fibromyalgia. Exp Rev Med Devices 2007;4(4):489-95

Affiliation

Jo Nijs[†1,2,3], Mira Meeus[1,2], Jessica Van Oosterwijck[2,3], Nathalie Roussel[1], Margot De Kooning[1], Kelly Ickmans[2,3] & Milica Matic[4]

[†]Author for correspondence

[1]University College Antwerp, Van Aertselaerstraat 31, B-2170 Merksem, Belgium

Tel: +32 3 6418265; Fax: +32 3 641827; E-mail: Jo.Nijs@vub.ac.be

[2]Vrije Universiteit Brussel, Department of Human Physiology, Faculty of Physical Education & Physiotherapy, Belgium

[3]University Hospital Brussels, Department of Physical Medicine and Physiotherapy, Belgium

[4]University Hospital Brussels, Pain Clinic, Belgium