Pain Physician 2012; 15:E677-E686 • ISSN 2150-1149

Narrative Review

Pain in Patients with Chronic Fatigue Syndrome: Time for Specific Pain Treatment?

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Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: None.

Manuscript received: 02/28/2012
Accepted for publication: 04/24/2012

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Background: Besides chronic fatigue, patients with chronic fatigue syndrome (CFS) have debilitating widespread pain. Yet pain from CFS is often ignored by clinicians and researchers.

Objectives: To examine whether pain is a unique feature of CFS, or does it share the same underlying mechanisms as other CFS symptoms? Second, it is examined whether effective treatments for pain from CFS are currently available.

Study Design: Narrative review covering the scientific literature up through December 2011.

Setting: Several universities.

Results: From the available literature, it is concluded that musculoskeletal factors are unlikely to account for pain from CFS. Pain seems to be one out of many symptoms related to central sensitization from CFS. This idea is supported by the findings of generalized hyperalgesia (including widespread increased responsiveness to painful stimuli) and dysfunctional endogenous analgesia in response to noxious thermal stimuli. Pain catastrophizing and depression partly account for pain from CFS. Pain increases during exercise is probably due to the lack of endogenous analgesia and activation of several genes in response to exercise in CFS. There is currently no evidence in support for the efficacy of complementary medicine in the treatment of pain from CFS. Intensive education about the biology of pain from CFS (within the framework of central sensitization) has positive short-term effects for patients with CFS, and fatigue-targeting cognitive behavioral therapy appears to be effective for pain from CFS as well.

Limitations: The role of the deficient hypothalamus-pituitary-adrenal axis in relation to pain from CFS, as well as the interactions with immune (dys)functioning require further study.

Conclusion: Recent research has increased our understanding of pain from CFS, including its treatment. It is advocated to optimize current CFS treatment protocols by targeting the underlying mechanism for those patients having severe pain.

Key words: Chronic pain, chronic fatigue syndrome, fibromyalgia, central sensitization, catastrophizing, exercise, cognitive behavioral therapy.

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Chronic fatigue has been consensually put forward as the major symptom of patients with chronic fatigue syndrome (CFS). However, patients with CFS suffer from a broad spectrum of symptoms, including pain, impaired concentration, sleep disturbances, and unrefreshing sleep (1)). Pain is an additional symptom criterion in the 1994 Centers for Disease Control and Prevention criteria for the diagnosis of CFS (1)). The recent International Consensus document stresses the importance of pain

by including it in 3 out of 4 criteria (2). Pain is highly prevalent in the CFS population: up to 94% experience muscle pain, 84% have joint pain (3), and over 80% have headache (4). Cross-sectional studies have revealed that pain from CFS is associated with disability levels (5,6) and sick leave (7).

In 2007, a systematic literature review on pain from CFS was published (8). At that time, little was known about pain from CFS. The results from the systematic review, covering the scientific literature from 1972 through 2004, highlighted the clinical importance of chronic pain from CFS, and identified several etiological theories that potentially explain pain from CFS. However, only a few studies addressed the possible etiology or treatment of chronic pain from CFS. Since then, several studies have increased our understanding of pain in patients with CFS.

Given the large overlap between CFS and fibromyalgia (9,10), one may question the need for studying pain from CFS. Indeed, a large body of scientific literature regarding the etiology of chronic pain from fibromyalgia is currently available ((11,12). However, CFS and fibromyalgia are diagnostically different entities. The 1990 (13) and the 2010 (14) American College of Rheumatology criteria for the diagnosis of fibromyalgia state that patients without debilitating chronic fatigue can fulfill the diagnostic criteria for fibromyalgia. Likewise, patients with chronic fatigue but without widespread pain can comply with the 1994 Centers for Disease Control and Prevention criteria for the diagnosis of CFS (1). Patients fulfilling the CFS criteria do not necessarily comply with fibromyalgia criteria and vice versa. Hence, the diagnostic criteria for CFS and fibromyalgia select partly distinct populations with regard to pain.

In addition, patterns of functional brain activity in patients with fibromyalgia are quite different from those in patients with CFS. Compared to healthy controls, patients with CFS show significantly lower blood perfusion in the brain stem (15,16), while patients with fibromyalgia exhibited significantly lower regional cerebral blood flow in the thalamus and caudate nucleus (17). Furthermore, Substance P has been found to be elevated in cerebrospinal fluid samples of patients with fibromyalgia (18) and not in patients with CFS (19). Therefore, the knowledge on pain from fibromyalgia cannot be applied to CFS patients without further study.

An increased understanding of pain from CFS is important for several reasons. First, patients with CFS struggle to understand their illness, including the nature and meaning of "medically unexplained" symptoms like pain and fatigue. They often have a long history of negative findings from specialized biomedical examinations (e.g., imaging findings, blood analyses), which increase thoughts and helplessness with regard to their symptoms ("They cannot find anything, but my pain and fatigue are real!"). Clinicians should be able to explain to their CFS patients why they are in pain, and such an explanation should be scientifically based. Second, in order to apply appropriate treatment for pain (relief) in patients with CFS, it is crucial to understand the etiology of pain from CFS. A purely symptomatic approach is unlikely to result in clinically important improvements in a complex illness like CFS. It is important to understand whether pain is a unique, distinct feature of CFS, and if so, whether it requires a specific treatment approach. Alternatively, pain might be one out of many CFS symptoms, all sharing a similar underlying pathophysiology/psychopathology. In the latter case, specific treatment of pain from CFS would be unnecessary, so long as the underlying mechanism is addressed.

For the reasons outlined above, the following questions will be addressed: Is pain a unique feature of CFS, or does it share the same underlying mechanisms as other CFS symptoms like fatigue? Do similar cognitive and behavioral factors perpetuate pain and fatigue in patients with CFS? Which treatments are effective in reducing pain in patients with CFS?

In the first part of this narrative review, an overview of our current understanding of pain from CFS within the biopsychosocial framework is provided. In the second part, available research on the treatment of pain in patients with CFS is reviewed. The discussion section integrates both parts, translates our current understanding of pain from CFS to clinical practice, and provides a research agenda for future work in this area. This is not a systematic literature review, but to the best of the authors' knowledge, it covers the scientific literature on pain from CFS up through December 2011.

Understanding Pain in Patients with CFS

Musculoskeletal sources of nociception

Joint hypermobility is often characterized by impaired motor control in end-range movements, which might lead to recurrent micro-traumata and consequent widespread musculoskeletal pain in hypermobile patients. Even though the majority of patients with CFS (58.8%) fulfill the criteria for benign joint hypermobil-

ity syndrome, there is no association between musculoskeletal pain and joint hypermobility in CFS patients (20). Likewise, structural abnormalities in joints or muscles of patients with CFS have not been identified repeatedly (21,22). Thus, there is no evidence suggesting that peripheral musculoskeletal factors account for pain from CFS.

Nitrogen and Oxidative Stress

Nitric oxide (NO) plays a complex role in nociceptive processing (23). Although evidence exists regarding the beneficial effects of the release of small amounts of NO during inhibition of nociceptive pathways (24), excessive amounts of NO could contribute to central sensitization. Central sensitization can be broadly defined as a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways (25), which results in a pathophysiological state characterized by generalized or widespread hypersensitivity to a variety of stimuli (i.e., mechanical, thermal and chemical). NO is able to reduce the nociceptive inhibitory activity of the central nervous system, leading to central sensitization of dorsal horn neurons (26). There is one study in which NO levels were related to self-reported pain severity from CFS (27), but this finding has not yet been replicated. Controversy addressing the role of NO in CFS remains, as others were unable to find elevated levels of NO from CFS (28,29), and failed to find an association between NO levels and pain thresholds from CFS (28). Taken together, there is currently insufficient evidence to support a role for NO in relation to pain from CFS.

The inconsistent finding regarding NO might be the consequence of the indirect measuring of NO. Since its half-life in vivo in humans is only a few seconds, most of the NO is oxidized to nitrite/nitrate, and the concentrations of these anions have been used as quantitative indices of NO production. However, it is questionable whether the confounding effect of diet-derived nitrate can be totally avoided (30), and whether nitrite is not converted back to NO. Nitrite and nitrate were previously thought to be inert end products of NO metabolism. However, studies have shown that these anions can be recycled in vivo to form NO, representing an important alternative source of NO (31). So, further and more direct analysis seems warranted to further study the role of NO for pain experienced by patients with CFS.

Besides nitrogen stress, oxidative stress describes a number of chemical reactions leading to free radicals production inside the human body, which is potentially harmful for cellular integrity. Compared to healthy controls, one study found raised oxidative stress levels in patients with CFS (32). The same study revealed that oxidative stress levels in patients with CFS are associated with self-reported joint pain and postexertional malaise (32). Further study is warranted to confirm these findings in different settings, and to examine whether oxidative stress levels are different in patients with CFS as compared to other chronic pain syndromes (like fibromyalgia or rheumatoid arthritis).

Generalized Hypersensitivity

By measuring pain thresholds on both symptomatic and asymptomatic or remote places in patients and healthy controls, widespread hyperalgesia or secondary hyperalgesia can be detected. Lower pressure pain thresholds at symptomatic areas may represent primary hyperalgesia due to sensitized nociceptors within injured peripheral musculoskeletal structures. However, findings of numerous areas of hyperalgesia in sites outside and remote to the symptomatic site, together with a nonsegmental general decrease in pain thresholds, may imply a generalized hyperexcitability of central nociceptive pathways (33). A case control study identified lower pressure pain thresholds for all tested areas in patients with CFS compared with healthy controls, even at pain-free locations (34). Depression, pain hypervigilance, or pain catastrophizing did not confound the observed differences. These findings were confirmed by Ravindran et al who used dolorimetry to examine the average pressure causing pain at 18 tender points, and found that patients with CFS had lower pain thresholds than healthy controls (4). Likewise, left lateral third intercostal space tenderness was observed in 34 out of 42 (81%) patients with CFS and in none of the 20 controls (35). Studies comparing the pain thresholds patients with CFS versus those with fibromyalgia are currently unavailable.

Thermal and electrical pain threshold have been studied in CFS as well. Cold pain thresholds and tolerance levels were compared between 15 monozygotic twins with CFS and their co-twins without CFS (36). Even though pain threshold, pain tolerance and all cold pressor pain ratings seemed to differ between patients and controls, the results failed to show statistically significant differences (36). The authors themselves indicate that the small sample size requires further research (36). In addition, 2 studies compared pain thresholds to electrical stimulation of muscle tissue, skin, and subcutis between patients with CFS and

healthy controls (37,38). No difference in electrical pain thresholds of the skin and subcutis were observed, but much lower electrical pain thresholds at all sites in the muscle tissue were found in the CFS group (i.e., trapezius, deltoid ,and quadriceps muscle) (37,38). These data point towards generalized hyperexcitability of central nociceptive pathways in patients with CFS, as seen in chronic pain disorders like fibromyalgia, chronic whiplash, and osteoarthritis.

Dysfunctional Endogenous Analgesia

There is one study available that evaluated the efficacy of conditioned pain modulation (CPM, previously known as "diffuse noxious inhibitory controls") in patients with CFS (39). CPM relies on painful conditioning stimulation of one part of the body to inhibit pain in another part (40). For example, the immersion of the hand and arm in hot water (the conditioning stimulus) inhibits nociceptive input from the entire body (41). In a study of CPM in CFS, the dominant arm of the patients and healthy controls was immersed in noxious hot water (46°C), generating hyperalgesia (i.e., increased pain perception) and delayed activation of CPM in the CFS group (39). Still, this finding requires replication.

The dysfunctional endogenous analgesia in patients with CFS might be due, in part, to serotonergic abnormalities. One study showed that patients with CFS display reduced serotonin transporters in the rostral subdivision of the anterior cingulate (42). However, based on the directions of correlations with self-reported pain, the authors concluded that the reduced serotonin transporters in the rostral anterior cingulate was not related to the symptom of pain (42).

Dysfunctional Endogenous Analgesia During Exercise

In healthy individuals exercise activates endogenous analgesia, which results in higher pain thresholds during and up to 40 minutes after exercise. This mechanism is due to the release of endogenous opioids (43) and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain (44). However, exercise does not activate endogenous analgesia in patients with CFS. In fact, pain thresholds further decrease in response to exercise in patients with CFS. This was first shown in a small study of patients with CFS and healthy controls in which participants performed a graded exercise with 3 stages on a treadmill (45). Patients with CFS had decreased pain thresholds following exercise, whereas pain thresholds increased in healthy controls.

This finding was replicated in 2 larger studies using various types of exercise: 1) submaximal cycle exercise with a gradual increase of 25 W every minute until 75% of the age-predicted target heart rate was achieved (46); 6 short bouts of aerobic cycling interrupted by short recovery breaks (28); and physiologically limited (heart rate below 80% of the anaerobic heart rate, workload below 80% of the anaerobic workload) and self-paced aerobic cycling (46). All 3 studies compared patients with CFS to healthy sedentary controls. None of the 3 studies examined whether the findings were independent from the patients' expectations (i.e., whether patients anticipated that the pain thresholds would increase following exercise) or catastrophic thoughts (e.g., magnification). Nevertheless, from these studies it is concluded that none of these types of aerobic exercise were able to activate endogenous analgesia in patients with CFS who experience chronic widespread pain. Importantly, the dysfunctional endogenous analgesia in response to exercise partly explains symptom flares following exercise in CFS (46). Indeed, patients with CFS experience more pain immediately following, and 24 hours after performing either a submaximal exercise bout, or a self-paced and physiologically limited exercise bout (47).

The lack of endogenous analgesia in response to exercise is not unique to CFS. Other illness characterized by chronic pain and central sensitization, like fibromyalgia and chronic whiplash-associated disorders, show a similar inability to activate endogenous analgesia following exercise (47-49). On the other hand, dysfunctional endogenous analgesia in response to exercise is not seen in all chronic pain patients. For example, endogenous analgesia is activated normally in response to aerobic exercise in patients with chronic low back pain (28,50).

The biology of dysfunctional endogenous analgesia in response to exercise for CFS is not well understood. One study found that the gene expression in leukocytes changes dramatically in response to exercise in patients with CFS compared to healthy controls (51). More specifically, messenger RNA increases for genes that can detect changes in muscle metabolites, genes important for sympathetic nervous system processes, and immune function genes (51). Among patients with CFS, the observed increases in gene expression are correlated with self-reported symptoms of pain (51). In line with this is the finding that increases in interleukin-6

following exercise accounted for 29% of the variance in increased pain after exercise in patients with CFS (52). Although compelling, these findings require replication in other settings.

A single bout of physical activity triggers release of NO in healthy controls (53), leading to the hypothesis that dysfunctional endogenous analgesia during exercise might be due to NO release. Although the increase in NO in response to exercise is much higher in patients with CFS than in healthy controls (54), NO production is unrelated to endogenous analgesia during exercise in CFS (28).

Further work is required to study the biology of the lack of endogenous analgesia in response to exercise for CFS. Unraveling this mechanism should lead to a treatment of postexercise malaise (including postexercise pain), which is a hallmark of the illness (2) and is of particular interest in the early phases of graded exercise therapy when patients are prone to side effects due to exercise intolerance.

Pain Cognitions and Pain Behavior

The role of cognitions and behavior for CFS has been studied extensively, including the capacity to target cognitive and behavioral factors during CFS treatment (e.g., cognitive behavioral therapy for CFS). Yet few studies have examined the role of pain cognitions and pain behavior in patients with CFS. One study examined part of the "fear avoidance" model of chronic pain (55) in CFS, and found that pain-related fear of movement (or kinesophobia) was unrelated to self-reported disability or exercise performance in patients with CFS (56).

On the other hand, pain catastrophizing appears to be of importance to people with CFS. Catastrophizing, defined as a tendency to expect negative outcomes, is currently viewed as a multidimensional construct comprising elements of rumination, magnification, and helplessness (57). Pain catastrophizing (i.e. helplessness and rumination rather than magnification) predicts bodily pain in women with CFS, even after controlling for depression (58). The same study revealed that physiological exercise performance in women with CFS is related to both pain catastrophizing and pain severity, but not to depression (58). The importance of pain catastrophizing was later confirmed in a larger study showing that pain catastrophizing and depression were the main predictors for pain and functioning in patients with CFS having chronic widespread musculoskeletal pain, both at baseline (cross-sectional data analysis) and at 6 months follow-up (59). In this study, rumination was identified as the most important subscale score of the pain catastrophizing scale. Taken together, pain catastrophizing appears to be an important issue in relation to pain from CFS. This corroborates with our understanding of chronic pain in general, but contrasts with models of fatigue in patients with CFS (60) where fatigue catastrophizing appears to be of less importance.

Summary

From the available literature, it is concluded that musculoskeletal factors are unlikely to account for pain from CFS. Pain appears to be one of many symptoms of central sensitization in CFS. This assumption is supported by the findings of generalized hyperalgesia (including widespread increased responsiveness to painful stimuli) and dysfunctional endogenous analgesia in response to noxious thermal stimuli. Pain catastrophizing and depression account in part for pain in CFS. Pain made worse in response to exercise may be due to the lack of endogenous analgesia and activation of several genes in response to exercise for CFS.

Treatment of Pain in Patients with CFS

Pain Physiology Education

How should clinicians apply the science of chronic pain from CFS to practice? First, it is clear that cases where the patient is skeptical about the biopsychosocial model, and convinced that pain and related symptoms are due to an undetectable or "new" virus, are unlikely to adhere to interventions like graded activity or graded exercise therapy. Patients with "unexplained" chronic pain who are misinformed about pain, consider their pain as more threatening and demonstrate a lower pain tolerance, more catastrophic thoughts, and less adaptive coping strategies (61). Treatment adherence for active treatments is often low in these patients.

Prior to starting with treatment in these cases the gap between the perceptions of the patient and the health care professional about pain and its treatment should be closed. Therefore it is crucial to change the patient's maladaptive illness perceptions and maladaptive pain cognitions and to re-conceptualize the pain before initiating treatment. This can be accomplished by patient education about pain and central sensitization from CFS, a strategy frequently referred to as "pain (neuro)physiology education" or "pain biology education." It requires an in-depth education of altered cen-

tral nervous system processing of nociceptive and non-nociceptive input.

This approach to pain physiology education has been studied in patients with CFS using a randomized controlled trial. Compared to pacing and self-management education, pain physiology education improved the patients' understanding of pain biology, and resulted in less catastrophizing (reduced rumination about pain) (62). Practice guidelines on how to apply pain physiology education in patients with CFS are provided elsewhere (63).

It is important to realize that pain physiology education is effective for other chronic pain patients as well (e.g., chronic low back pain, fibromyalgia) (64). In addition, since pain physiology education addresses maladaptive cognitions and illness perceptions, it is conceptually similar to the educational part of cognitive behavioral therapy (CBT). The innovative aspect of pain physiology education is the use of physiology (i.e., the mechanism of central sensitization) to change perceptions and cognitions. This makes it appropriate even for CFS cases reluctant to the biopsychosocial model.

Cognitive Behavioral Therapy

CBT has been shown to be effective for improving health status and fatigue in patients with CFS (65-68). Importantly, one study found that CBT is able to improve pain severity in adolescents and adults with CFS, even though no specific emphasis was given to pain in the treatment protocol (69). This is remarkable for an intervention primarily targeting fatigue reduction and improved functioning. Changes in physical activity, changes in negative affectivity, or changes in body consciousness did not explain the decrease in pain severity in response to CBT, but the decrease in pain severity was associated with improvements in fatigue severity (69). This suggests that pain from CFS is directly related to chronic fatigue. Still, these findings require replication in other settings.

On the other hand, 2 studies found that the presence of severe pain at baseline predicts a poor response to CBT in adult patients with CFS (69,70). This suggests that the addition of a specific intervention targeting pain (e.g., centrally acting drugs like serotonergic and noradrenergic antidepressants) can potentially improve the effects of CBT for patients with CFS who have severe pain. Alternatively, one may optimize the CBT protocol for patients with CFS having severe pain. This can be done by specifically targeting maladaptive pain beliefs like pain catastrophizing, in line with CBT protocols for patients with chronic pain.

Complementary Medicine

Marshall and colleagues (71) conducted a semi-structured interview to examine the use and perceived benefit of complementary and alternative medicine and physiotherapy treatments tried by people with CFS to ease their painful symptoms. Fourteen out of 23 patients experienced pain relief in response to acupuncture, and 5 out of 18 experienced pain relief due to gentle soft tissue therapies (71). These data open new avenues for research in this area, but future work is required to examine the value of such anecdotal evidence.

Discussion

What did we learn recently about the nature of pain from CFS?

The present paper summarizes our current understanding of pain in patients with CFS. From the available research findings, it is concluded that pain from CFS is highly prevalent and debilitating. Peripheral musculoskeletal factors are unlikely to account for pain from CFS. Importantly, pain appears not to be a unique feature of CFS. Pain appears to be one out of many symptoms related to a hypersensitivity of the central nervous system (i.e., central sensitization) (72). This assumption is supported by the findings of generalized hyperalgesia (including widespread increased responsiveness to painful stimuli) and dysfunctional endogenous analgesia at rest in response to noxious thermal stimuli.

In addition, pain catastrophizing and depression partly account for pain from CFS, albeit that evidence is correlational in nature. It may well be that these constructs influence the pain experience (73), either by increasing the activity of descending pain facilitatory pathways (i.e., central nervous system pathways arising from the brain that strengthen, rather than attenuate pain), or by inhibiting activity in descending pain inhibitory pathways. This process is referred to as cognitive emotional sensitization (74), which appears to account in part for pain experienced by patients with CFS (72).

Pain increases during exercise appear to be in line with central sensitization: endogenous analgesia is absent in response to submaximal and even well-paced exercise bouts. This makes people with CFS highly vulnerable for noxious input during and following physical activity or exercise, an observation in line with the finding that genes able to detect changes in muscle metabolites are activated in response to exercise (51). Theoretically NO is able to further sensitize the central nervous system, and exercise results in a stronger

NO response in the body of patients with CFS than in healthy controls. However, its role in relation to exercise-induced pain from CFS is currently unclear.

The observations that pain catastrophizing and central sensitization partly account for pain from CFS supports the notion that pain from CFS is similar to pain from other chronic pain syndromes. Indeed, studies in clinical cohorts have revealed the important contribution of central sensitization to pain in patients with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders, and postsurgical pain (25).

What Did We Recently Learn about the Treatment of Pain from CFS?

Studies examining the effectiveness of complementary medicine for the treatment of pain from CFS are lacking. Intensive education about the biology of pain from CFS (within the framework of central sensitization) has positive short-term effects for patients with CFS; CBT appears to be effective for treating pain from CFS as well. It is suggested to include education about pain biology and central sensitization into CBT protocols for patients with CFS who have high pain levels. This might increase the effectiveness of, and the compliance with, CBT for this subgroup of the CFS population.

Research Agenda for Pain from CFS

Research has increased our understanding of pain from CFS. Yet many issues remain unresolved. Future studies should examine the role of a deficient hypothalamus pituitary adrenal-axis (75) in relation to pain from CFS, as well as the interactions with immune (dys)functioning. Given the observed association between basal salivary cortisol levels and self-reported pain in patients with CFS (76), additional studies would be warranted.

More work is required to examine the role of cognitive and emotional factors in relation to pain from CFS. Given the importance of acceptance in relation to fatigue and well-being from CFS (77,78), it seems warranted to study the impact of acceptance on pain from CFS. If acceptance will be identified as a determinant of pain from CFS, then interventions like Acceptance and Commitment Therapy might be worthwhile studying in this population. Acceptance and Commitment Therapy and CBT appear to be equally effective in the treatment of chronic pain in general (79), but have yet to be compared as treatments for CFS. In addition, it has recently been shown that CBT improves acceptance in patients with CFS (78).

Further work is required to study the psychobiology of the lack of endogenous analgesia in response to exercise for CFS, including the (mal)functioning of the brain and its neurochemistry and the role of cognitions. Unraveling this mechanism should lead to a treatment for postexercise pain, which might be crucial in improving the effectiveness of graded exercise therapy for people with CFS. In addition, it seems rational to study the role of postexercise pain related to CFS within the framework of the extended fear avoidance model of chronic pain (80). Such an extended or next generation fear avoidance model might include a motivational perspective on goals and self-regulation, as typically applied in pain management programs (80).

According to the Declaration of Montreal, access to pain management is a fundamental human right (81). Thus, access to pain management is a human right for people with CFS as well. This calls for adapting current CFS treatment protocols to account for pain as well as fatigue, especially in those having severe and widespread pain.

Still, the scientific literature on pain from CFS suggests that pain is one out of many CFS symptoms, all sharing a similar underlying mechanism (i.e., central sensitization), and that pain from CFS is similar to pain from other chronic pain syndromes. This implies that specific treatment of pain from CFS is unnecessary, as long as the underlying mechanism is addressed and pain is acknowledged by the caregiver as an important symptom. This calls for therapies targeting central sensitization in patients with CFS. In this view, it seems rational to study the impact of a pain-modified CBT protocol on the mechanism of central sensitization. Preliminary findings in patients with fibromyalgia indicate that CBT does decrease the hypersensitivity of the central nervous system (82). In line with this reasoning is the call for mediation analyses of CFS treatment studies that have used pain as an outcome measure. With respect to fatigue-based CBT, a mediation analysis revealed that a decrease in focusing on fatigue mediated the effect of CBT for CFS (83). Similar studies are required with respect to pain from CFS.

Acknowledgements

Mira Meeus is a postdoctoral research fellow at the Research Foundation Flanders (FWO). Deborah Van Cauwenbergh is a research fellow at the Artesis University College Antwerp, Belgium (PWO-G).

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