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Fibromyalgia: From treatment to rehabilitation

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Abstract

Fibromyalgia is a clinical syndrome of chronic widespread pain and reduced pain thresholds to palpation. The pathophysiology remains unknown, but there is increasing evidence that peripheral and central sensitization cause an amplification of sensory impulses that may alter pain perception in fibromyalgia patients. Interventions to treat fibromyalgia should aim at different targets simultaneously in order to reduce peripheral and central sensitization. There are both pharmacologic and non-pharmacologic approaches with evidence for effectiveness in the treatment of fibromyalgia and its associated symptoms. Evidence from randomized trials and meta-analyses shows that partial and short-term improvements in fibromyalgia symptoms can be achieved with low doses of antidepressants and with physical activity such as aerobic and strengthening exercises. A multidimensional approach which emphasizes education and integration of exercise and cognitive behavior therapy improves quality of life and reduces pain, fatigue and depressive symptoms when measured on a short term basis. More recently, trials have shown the neuromodulators gabapentin and pregabalin to be effective in reducing pain and improving quality of sleep in fibromyalgia. In addition, small trials of noninvasive brain stimulation have also shown benefits in reducing pain in fibromyalgia. It is essential to keep in mind that some important clinical conditions can mimic and overlap with fibromyalgia and should always be ruled out by a complete history, physical examination and appropriate laboratory testing.

Keywords

Fibromyalgia syndrome; Chronic Pain; Disability; Treatment; Rehabilitation

Introduction

Fibromyalgia is a clinical syndrome of chronic widespread pain and reduced pain thresholds to palpation. Because of the relatively high prevalence (White et al., 1999; Lindell et al.,

Conflict of interest statement

None

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2000; Senna et al., 2004), number of comorbidities, degree of disability and global severity, there is a significant burden of disease for this condition (Wolfe et al., 1997). Due to its clinical importance, there are a relatively large number of studies being performed to help us understand the mechanisms underlying fibromyalgia. With new findings showing the critical importance of central nervous system (CNS) changes in fibromyalgia, the goal of this article is to present an evidence based treatment and rehabilitation update based which is based on the current knowledge and understanding of fibromyalgia.

Diagnostic Criteria

Despite being subjective in nature, the diagnosis of fibromyalgia (Wolfe et al., 1990) seems to correlate with neuroimaging evidence showing increased brain activation responses (Gracely et al., 2002; Giesecke et al., 2004; Pujol et al., 2009). In fact, 4kg/cm² is the amount of pressure needed to detect differences between brain activation in fibromyalgia patients and those in healthy controls (Pujol et al., 2009). As novel biomarkers, neuroimaging results might be helpful in developing new rehabilitation approaches.

Many conditions can mimic and overlap with fibromyalgia. These include hypothyroidism, tendonitis, ankylosing spondylitis, lupus erythematosus, dermatomyositis, rheumatoid arthritis and osteoarthritis. This overlapping leads to an important question of whether these conditions can result in similar changes in the peripheral and central nervous system as compared to patients with fibromyalgia only. If this is the case, then perhaps a common treatment could be effective in conditions where symptoms of fibromyalgia are seen along with these other diagnosis. Nevertheless, it is crucial to perform all steps to rule out these comorbidities as they can affect response to treatment.

Current pathophysiology overview – the basis for treatment and rehabilitation

Contemporary pain management has shifted from symptom control to management based on the pathophysiological mechanisms of pain (Woolf, 2004). Even though the full pathophysiology remains unknown, there is increasing evidence that peripheral (Staud et al., 2003; Staud, 2006; Staud, 2007; Staud and Spaeth, 2008) and central sensitization at the spinal cord, brainstem and cortical levels result in an amplification of sensory impulses that may alter pain perception (Desmeules et al., 2003; Giesecke et al., 2004; Price and Stoud, 2005; Meeus and Nijs, 2007; Staud and Spaeth, 2008).

A clear understanding of the complex mechanisms involved in pain generation, modulation, amplification and perpetuation is important as the basis of a comprehensive therapeutic program for the treatment and rehabilitation of fibromyalgia patients. Recently, it has been recognized that persistent and intense nociceptive sensory information generated by the peripheral tissues can lead to neuroplastic changes in the CNS (Staud, 2006; Staud and Spaeth, 2008). These changes include an increased excitability of dorsal horn neurons producing pain hypersensitivity, temporal summation of pain and wind-up after-sensations.

Together, these neurophysiological changes suggest that pain induces, and is partially maintained by, a state of central sensitization (Woolf and Salter, 2000) in which an increased transmission of nociceptive information allows normally non-noxious input to be amplified and perceived as noxious stimuli. Also, peripheral nociceptive input may initiate and maintain central sensitization (Staud et al., 2003; Staud, 2006; Abeles et al., 2007; Lawson, 2008). It has already been suggested that for fibromyalgia patients, nociceptor systems in the muscles and bones undergo a sensitization of vanilloid receptors, acid-sensing ion channel receptors, and purino-receptors (Staud and Smitherman, 2002; Staud, 2006).

Tissue mediators of inflammation as well as nerve growth factors can excite these receptors and cause extensive changes in pain sensitivity (Staud and Smitherman, 2002). It is currently known that peripheral acid-sensing ion channels (ASIC1a) create acid microenvironments (Nagae et al., 2006). Also, elevated ASIC1a activity is required for the development and maintenance of central sensitization (Nagae et al., 2006; Duan et al., 2007). In fact, Shah et al. (2005) found that active myofascial trigger points present lower pressure pain thresholds when compared to people with no pain or the presence of only latent trigger points. They also demonstrated the distinct in-vivo biochemical milieu of muscle with significantly elevated levels of substance P, calcitonin gene-related peptide (CGRP), bradykinin, tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), serotonin, and norepinephrine in the vicinity of active myofascial trigger points at the upper trapezius muscle. Overall, pH was significantly lower in the active trigger points.

There is also a large body of evidence demonstrating the role of the CNS in the pathophysiology of fibromyalgia. First, non-REM sleep is altered in patients with fibromyalgia (Moldofsky et al., 1975) and is associated with the severity of their symptoms (Moldofsky and Scarisbrick, 1976). The association between the lack of non-REM sleep and the symptoms of fibromyalgia might be linked to an abnormality in serotonergic transmission. Indeed, it has been shown that p-chlorophenylalanine (PCPA), a centrally acting serotonin synthesis inhibitor, can induce symptoms similar to fibromyalgia (Sicuteri et al., 1972). Second, the association of depression and fibromyalgia is well described (Gruber et al., 1996), and some hypothesize that a similar pathophysiologic phenomenon might underlie both conditions (Arnold et al., 2000). Third, several studies have shown that tricyclic antidepressants and other antidepressants are associated with an improvement of symptoms in fibromyalgia, including pain (Arnold et al., 2000). In fact, tricyclics have also been demonstrated to be efficacious in pain relief in other pain syndromes (Frank et al., 1988). Finally, neuroimaging studies have shown that, compared to healthy controls, patients with fibromyalgia have a change in regional cerebral blood flow to certain pain-related structures including the thalamic nuclei (Mountz, et al., 1995; Kwiatak et al., 2000). A transcranial magnetic stimulation (TMS) study showed motor cortex excitability changes in the excitatory and inhibitory systems in patients with fibromyalgia (compared to healthy controls) that are similar to changes found in patients with other chronic pain disorders, such as rheumatoid arthritis (Salerno et al., 2000).

Because of the peripheral and central nervous system sensitization, continuous pain in patients with fibromyalgia leads to additional neuroplastic changes that can sustain pain and, therefore, maintain a continuous cycle that is responsible for the chronic and refractory condition of this disease. It is then reasonable to assume that patients with longer disease duration will have greater and more refractory pain. Therefore, it is important to determine the degree of CNS changes in patients with fibromyalgia as to better guide interventions for this condition.

In this context, the diagnosis of central and peripheral sensitization is very important because spinal cord neurons that normally would only be activated by noxious stimuli are now activated by normally non noxious stimuli, a phenomenon widely known as allodynia (Hoheisel et al., 1993). This explains why after central sensitization is established; only minimum peripheral input is needed for the maintenance of the chronic disabling and painful condition (Staud and Spaeth, 2008). The same rationale can be applied to poor sleep, psychological distress and other trigger factors for the recurrence of fibromyalgia symptoms.

It is important to note that other chronic conditions, such as irritable bowel syndrome, temporomandibular disorders, chronic non specific low back pain, and migraine share the

same clinical characteristics (Staud and Spaeth, 2008) and possibly a similar pathophysiological basis that needs to be further investigated.

Finding the best treatment target

Interventions to treat fibromyalgia should aim for different targets simultaneously. Indeed, CNS models associated with chronic pain are helpful to understand fibromyalgia at the central nervous system level and might be used in fibromyalgia to develop effective targets for this condition. In this model, the neural network that characterizes perceptions of pain and pain behavior processing is comprised of pathways linking the thalamus, cortical areas, and limbic system. Therefore, three important areas associated with fibromyalgia include (a) areas associated with somatosensory processing including different levels from nociceptors, spinal cord to thalamus and parietal cortex; (b) areas involved in affective emotional processing; (c) areas involved in executive processing. Therefore, activity in these areas is critical for sustaining chronic pain in fibromyalgia.

The model also provides a framework for the development and evaluation of the effects of behavioral and other interventions for pain management. Therefore using this model, we can observe how different approaches can be used and propose targets for the different approaches in fibromyalgia.

Treatment and Rehabilitation rationale

Once peripheral and central sensitizations are present, the rationale for treatment approaches should also target the CNS structures rather than using local anti-inflammatory agents alone. Therefore, treatment and rehabilitation of fibromyalgia is based on the concept that pain is primarily related to central sensitization (Goldenberg, 2007). In fact, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids were the mainly prescribed medications for fibromyalgia patients in the past (Wolfe et al., 1997). Available evidence-based guidelines recommend that NSAIDs, corticosteroids and opioids should not be used in fibromyalgia patients as first line medications, due to their lack of effectiveness. This scenario has changed in the recent years, and now the most common medications prescribed are antidepressants, opioids and NSAIDs as well as the combination of antidepressants and opioids, antidepressants and neuromodulators and sedatives and opioids (Berger et al., 2007).

Current management of fibromyalgia has shifted from a classic biomedical approach to a rehabilitation model approach to improve health status and overall health related quality of life (Lawson, 2008).

Treatment and Rehabilitation Evidence Based Update

Because a specific mechanism underlying the symptoms in fibromyalgia is not yet known, treatment for fibromyalgia is based on controlling the variety of symptoms; thus requiring the integration of both pharmacologic and non-pharmacologic approaches in a multimodality fashion that should be tailored according to an individual patient's needs. With this approach, two main components of treatment are usually adopted. First, pain control is managed by the use of pharmacologic and physical interventions aimed to reduce peripheral and central sensitization. Second, the treatment of fibromyalgia-associated symptoms is combined with strategies to manage the dysfunctional sleep, fatigue, mood disorders, cognitive dysfunction, headache, migraine, irritable bowel and bladder syndromes, and other fibromyalgia associated disorders.

Because fibromyalgia is a condition associated with significant changes in brain areas associated with affective and emotional processing, it is important to avoid amplification of symptoms by continuous activation of this area. It is therefore critical to initiate a program of education as one of the main foundations of treatment. Care providers should explain the validity of the illness, despite unrevealing laboratory and imaging tests. It also needs to be underscored to patients that fibromyalgia is a chronic entity with no curative interventions available at the present time. Despite its chronicity and no cure, symptoms can be controlled promoting quality of life and functional recovery. There are periods of relapse and recurrence of symptoms, which are usually triggered by physical and emotional distress. Early identification of symptom recurrence and self-management strategies should be used as much as possible. Instructions to reduce caffeine and other stimulant intake may help reduce sleep disturbances (Crofford and Appleton, 2000).

Regarding specific treatments for this condition, there is no clear consensus on the treatment of choice for any single type of intervention (Burckhardt, 2002; Morris et al., 2005). Evidence from randomized trials and meta-analyses shows that partial and short-term improvements in fibromyalgia symptoms can be achieved with low doses of antidepressants, physical activity such as aerobic and strengthening exercises, relaxation techniques and behavioral therapies (Goldenberg et al., 2004; Buckhardt et al., 2005; Carville et al., 2008).

Pharmacological approaches

Standard treatment typically involves the chronic use of medications with the goal of pain control via central modulation. The aim is to reduce afferent nociceptive transmission at the dorsal horn of the spinal cord or to increase the activity of the descending inhibitory pain systems. These pharmacological approaches have a more diffuse effect that can also influence cognitive (executive) and affective processing areas.

Tricyclic antidepressants, serotonin/norepinephrine-reuptake inhibitors (Uçeyler et al., 2008; Hauser et al., 2009c), neuromodulators (Hauser et al., 2009b) and tramadol have all been shown to decrease pain in fibromyalgia. The combination of tricyclic antidepressants and tramadol can also lower the seizure threshold. Amitriptyline, selective serotonin or noradrenalin reuptake inhibitors, and 5-HT₃ receptor antagonists (Müller et al., 2006; Seidel et al., 2007) were associated with larger effect sizes and higher number needed to harm (Carville et al., 2008). The most commonly used neuromodulators are gabapentin and pregabalin. Both produce selective modulation of the calcium channel alpha-2-delta ligands and decrease the release of several nociceptive neurotransmitters such as glutamate, norepinephrine and substance P (Hauser et al., 2009b).

Non steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are not effective for the treatment of fibromyalgia (Goldenberg et al., 2004; Buckhardt et al., 2005; Carville et al., 2008). Although simple analgesics can reduce pain to some extent, these drugs are of limited help. Such medications can be useful in the case of comorbid conditions such as tendonitis, bursitis or if other peripheral pain generators are present. In the past, NSAIDs and opioids were the most commonly prescribed medications for fibromyalgia patients (Wolfe et al., 1997) and in fact might have led to detrimental effects. Opioids can be used judiciously, as in any other chronic pain state, but not as a first line medication. Strong opioids (oxycodone and morphine) should be avoided (Goldenberg et al., 2004; Buckhardt et al., 2005; Carville et al., 2008). Tramadol, however, reduces pain and improves functional outcomes in patients with fibromyalgia (Goldenberg et al., 2004; Buckhardt et al., 2005; Furlan et al., 2006; Carville et al., 2008).

Non pharmacological approaches

Therapeutic Exercises

There is scientific evidence suggesting that controlled and supervised aerobic exercise performed on a graded treadmill, such as walking or jogging, in a training range of 60 to 75% of maximum heart rate adjusted for age (210 minus age), for at least 20 minutes duration, at least three days a week for 6 consecutive weeks, reduces fibromyalgia symptoms and is effective for the treatment of fibromyalgia (Sim and Adams, 2002; Mannerkorpi et al., 2007; Busch et al., 2008; Carville et al., 2008). Individualized aerobic fitness programs can improve cardiovascular fitness and deconditioning. Post exertional pain may be avoided by starting the exercise training just below the full aerobic capacity while increasing frequency, duration and intensity as soon as tolerated (Buckhardt et al., 2005). Progression should be slow and gradual. Low impact aerobic physical activities such as walking, swimming and heated pool activities are the best options (Carville et al., 2008). Exercises should be performed on a regular basis. The main challenge is adherence to a long term exercise program.

Strengthening exercises should be performed two to three times per week, with a minimum of one set of 8 to 12 repetitions of each exercise, starting at an intensity of 40 to 60% weight resistance of one maximum repetition, defined as the maximum load that can be lifted fully one time only. Progression should be pursued over time. Any type of muscle strengthening exercise can be applied; however, moderate to heavy progressive resistance exercises of the hip extensors, abductors and adductors; knee extensors and flexors as well as trunk and upper extremity flexors and extensors are most commonly assessed in the literature (Busch et al., 2008).

The mechanisms by which exercises exert therapeutic effects are still not clear. There are different mechanisms which are potentially responsible for the improvement of symptoms in fibromyalgia. It seems that that exercise improves plasticity efficiently, as indexed by an increase in BDNF. It is therefore conceivable that this increase can promote activity restoration in other areas associated with low levels of activity such as areas involved in executive processing. In addition, it has been shown that exercise might decrease and regulate somatosensory processing through increased afferent input.

Electrical stimulation

In the context of brain dysfunction, techniques of neuromodulation are proving beneficial as an approach for the treatment of both chronic pain and fibromyalgia. In fact, several studies have shown that motor cortex stimulation with epidural electrodes or with repetitive transcranial magnetic stimulation (rTMS) is effective in reducing pain in patients with refractory central pain (Tsubokawa et al., 1991; Brown and Barbaro, 2003; Lefaucheur et al., 2004; Pleger et al., 2004; Khedr et al., 2005; Nuti et al., 2005). Response rates are in the range of 40–80%. Indeed, a recent meta-analysis showed that invasive and noninvasive techniques of motor cortex stimulation are associated with significant improvements in pain (Lima and Fregni, 2008). The rationale for motor cortex stimulation is based on evidence showing significant thalamic (and thus somatosensory) dysfunction in chronic pain and significant changes in thalamic activity with motor cortex stimulation (Garcia-Larrea et al., 1999). Among the techniques of noninvasive brain stimulation, transcranial direct current stimulation (tDCS) is a viable option.

During tDCS, low amplitude direct currents are applied via scalp electrodes and penetrate the skull to enter the brain. Although there is substantial shunting of current in the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential, as

shown by two recent modeling studies (Miranda et al., 2006; Wagner et al., 2007) and thus influences the level of excitability and modulates the firing rate of individual neurons. When tDCS is applied for a sufficient duration, cortical function can be altered beyond the stimulation period (Nitsche and Paulus, 2001), and the direction of the cortical excitability changes will depend on the current orientation.

Interestingly, tDCS has shown to be a powerful technique for pain treatment. Preliminary studies have assessed its effects in patients with spinal cord injury (Fregni et al., 2006a) and in patients with fibromyalgia (Fregni et al., 2006b). In the first study, patients with chronic pain due to spinal cord injury (n=17) were randomized to receive sham or active tDCS of the primary motor cortex (2mA, 20min for 5 consecutive days). There was significant improvement in pain after active anodal stimulation of the motor cortex, but not after sham stimulation (Fregni et al., 2006a). In addition, there was a significant cumulative analgesic effect and the peak of pain reduction on a visual analogue scale was achieved after the last session of stimulation. Two weeks after the termination of stimulation, patients in the active tDCS group still showed a trend to have less pain compared to baseline (Fregni et al., 2006a). In a subsequent study, thirty-two fibromyalgia patients were randomized to receive sham stimulation or real tDCS with the anode centered over the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC) (2 mA for 20 minutes on 5 consecutive days). A blinded evaluator rated the patient's pain, using the visual analog scale for pain, the clinician's global impression, the patient's global assessment, and the number of tender points. The results showed that active anodal tDCS of the primary motor cortex induced significantly greater pain improvement compared with sham stimulation or stimulation of the DLPFC. Importantly, the effects of five sessions of tDCS lasted for at least two weeks after the end of stimulation (Fregni et al., 2006b). Another potential use of tDCS is in combination with drugs. A recent study has shown that the combination of tDCS with cycloseride, a NMDA agonist, leads to an enhancement of analgesic effects (Antal et al., 2008).

One important issue is the stimulation target. As brain stimulation offers the possibility to target focal brain areas it is therefore possible to focalize treatment on specific neural networks. Therefore it is possible to target areas associated with somatosensory processing such as the primary motor cortex and somatosensory cortex or with affective emotional processing such as prefrontal areas. Both approaches have been used for fibromyalgia; however, there is still insufficient data to draw any definitive conclusions. For instance, when using tDCS, it appears that M1 stimulation is a better target as compared to DLPFC. However, using transcranial magnetic stimulation, both targets have been used with relative success. Another important issue is the combination of other approaches with brain stimulation as there may be a beneficial interaction effect.

Acupuncture

Benefits from acupuncture are less well-documented for fibromyalgia patients, and results are still controversial (Deluze et al., 1992; Assefi et al., 2005; Martin et al., 2006; Mathew and Ernst, 2007; Targino et al., 2008). Despite emerging neuroimaging evidence demonstrating that acupuncture can modulate and decrease neuronal activity at several CNS structures (Hui et al., 2005; Dhond et al., 2007; Napadow et al., 2007), clinical benefits seem to be of small magnitude and of short duration (Mathew and Ernst, 2007). Acupuncture recruits a wide network of brain regions including the primary somatosensory (SI), second somatosensory (SII), anterior cingulate (ACC), prefrontal (PFC) and insular cortices, amygdala, hippocampus, hypothalamus, periaqueductal gray and the cerebellum (Hui et al., 2005; Dhond et al., 2007; Napadow et al., 2007), which are similar to the structures usually involved in chronic pain states. Acupuncture may be valuable in reducing the number of

tender points lower than 4kg/cm² and the mean pressure pain threshold over the 18 classic tender points when added to usual treatment (Targino et al., 2008).

Injections

Treatment of concomitant myofascial pain, along with instruction in relaxation techniques, may benefit some patients with an associated myofascial pain component (Staud, 2006).

Cognitive Behavior Therapy

Associated psychological and psychiatric comorbidities are common in patients with fibromyalgia and account for 25 to 70% of the patients. Among all available psychosocial techniques, cognitive behavioral therapies have the highest efficacy as a complimentary approach with fibromyalgia patients, and should be associated with education and exercise therapy in a multicomponent approach (Hauser et al., 2009a). The main objective is to modify negative behaviors into positive attitudes. The goals of the educational programs are to provide patients with information about active self management of pain, the importance of physical activities and relaxation techniques, pain coping skills and individual strategies for behavioural change (Foster et al., 2007; van Koulil et al., 2007). As an isolated intervention, educational programs did not influence pain and disability in fibromyalgia patients (van Koulil et al., 2007). However, when associated with other psychological and exercise therapies in a multicomponent approach, educational programs were capable of reducing pain and improving quality of life (Hauser et al., 2009a).

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