Fibromyalgia Symptoms Overview

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Definition

Fibromyalgia syndrome (FMS) can be conceptualized as a chronic disorder characterized by widespread musculoskeletal pain and other accompanying symptoms such as fatigue, insomnia, depression, anxiety and cognitive impairments. The etiology of FMS remains unknown, being one of the most accepted hypothesis the presence of central sensitization to pain and impairments in endogenous pain inhibitory mechanisms. The history of the development of FMS concept reveals how other symptoms -apart from pain- has become also relevant in FMS diagnosis and treatment.

The central symptom of FMS is pain. FMS patients generally report high levels of clinical pain, which are related to greater impairments in health related quality of life, cognitive abilities and disease course. Fatigue and sleeping difficulties are also common symptoms of FMS. Fatigue have shown positive associations with pain, stiffness, sleep problems, increased body mass index, FMS severity, tenderness, disability, cognitive complaints, anxiety and depression. The majority of FMS patients report poor sleep quality, take longer to fall asleep, generally wake up during the night, sleep fewer hours, and usually wake up unrefreshed. Emotional disturbances (i.e., depression, anxiety) are also frequent in FMS. In fact, depression and anxiety disorders have showed a negative impact on the clinical course and work capacity of FMS patients. Cognitive impairments are also a relevant symptom in FMS. The most common complaints among FMS patients are executive function deficits, attention problems, forgetfulness, concentration difficulties, and mental slowness. Regarding the most frequent treatments for FMS, these can be classified as non-psychological and psychological. The former includes analgesic drugs, adjuvant drugs (i.e., antidepressants, benzodiazepines, anticonvulsants, etc.), nerve blocks, electrostimulation at different levels, infiltrations, etc. The psychological therapies with the most evidence are cognitive-behavioral, acceptance and commitment therapy and mindfulness.

FMS is associated with a severe reduction of health related quality of life and psychosocial impairments. It is necessary to take all FMS symptoms and its relations into account in order to provide a more tailored and effective treatment, as well as, to improve the health related quality of life of FMS patients.

Fibromyalgia syndrome (FMS) can be conceptualized as a chronic disorder characterized by widespread musculoskeletal pain and other accompanying symptoms such as fatigue, insomnia and sleep related problems, depression, anxiety, and cognitive impairments. FMS prevalence in the general population has been estimated around 2 to 4%[1]. Prevalence data vary depending on the methods and the used diagnostic criteria[2]. Moreover, FMS has been traditionally considered more frequent in women than men[1]. However, recent studies point out that this sex difference in prevalence may be a result from biases studies[3] [4], suggesting the need of further studies in this field. Regarding the etiology of FMS, it remains unknown. One of the most accepted hypothesis is the presence of central sensitization to pain and impairments in endogenous pain inhibitory mechanisms[5] [6] [7]. See table 1 for more information. Nevertheless, other researchers have pointed out a neurological origin of FMS, based on the discovery of small fiber[8] [9] and large fiber[10] neuropathy in these patients[8]. Additionally, the involvement of idiopathic cerebrospinal pressure dysregulation in FMS pathology is still under discussion[11].

Table 1. Central sensitization to pain in Fibromyalgia Syndrome[7]

Evidences of central sensitization to pain in Fibromyalgia Syndrome	Main Authors
Decreased threshold and tolerance to pain.	Kosek 1997[12], Sorensen 1998[13], Carli 2002[14], Desmeules 2003[15], Petzke 2003[16], Reyes del Paso 2011[17].
Hyperalgesia and allodynia.	Lee 2011[18], Arkue-Barretnexea 2007[19], Woolf 2011[20], Galvez-Sánchez 2018[21].
Deficits in descending pain inhibitory pathways.	Julien 2005[22], Price 2005[23].
Supraspinal facilitation of the modulatory ascending pain pathways.	Urban 1999[24], Gebhart 2004[25].
Alterations in cerebral blood flow modulation during painful stimulation.	Duschek 2012[26], Montoro 2016[27].
Attenuated conditioned pain modulation (CPM).	Kosek 1997[12], Julien 2005[22].
Enhanced sensitization / summation to repeated heat or pressure pain.	Staud 2001[28], 2003[29], 2004[30]; de la Coba 2017[31], 2018[6].
Prolonged aftersensations after repeated mechanical and heat stimulation.	Staud 2003[29], 2007[5], 2007[32].
Deficits in pain inhibitory systems.	Henriksson 1994[33], Kosek 1997[12], Lautenbacher 1997[34]. - Reduction of serotonin and noradrenaline levels. Millan 2002[35], Russell 1992[36]. - Alterations in opioids system (opioidergic pathway). Julien 2005[22].

Higher levels of excitatory Central Nervous System (CNS) neurotransmitters, involved in enhancing wind-up and central sensitization.	- Higher concentrations of substance P. Russell 1996[37], Russell 1998[38], Schwarz 1999[39], Banic 2004[40]. - Elevations in CNS glutamate levels. Harris, 2009[41], 2010[42]; Fayed 2010[43], Banic 2004[40].
Greater neuronal activation in the neuromatrix of pain. Increased gain or "volume setting" in brain pain-processing systems.	Gracely 2002[7] Pujol 2009[44], Coghill 2003[45], Giesecke 2004[46], Gracely 2004[47].
More sensitive to pressure anywhere in their body (Note: tender points only represent regions where everyone is more tender)[48].	Kosek 1995[49], Wolfe 1997[50], Petzke 1999[51], Graven-Nielsen 2000[52].
More sensitive to other sensory stimuli such as sound.	Gerster 1984[53], Dohrenbusch 1997[54], Geisser 2008[55].

In the history of the development of FMS concept, in 1977 H.A. Smythe and H. Moldofsky[56] continued the work of P.K. Hench[57], who coined the term fibromyalgia in 1976, and proposed the first measure for evaluating the disorder. H.A. Smythe is considered the grandfather of modern fibromyalgia, among other reasons, because he was the first to conceptualized fibromyalgia exclusively as a generalized pain syndrome, accompanied by other symptoms such as fatigue, nonrestorative sleep, morning stiffness, emotional distress, and multiple tender points. In addition, H.A. Smythe and H. Moldofsky proposed diagnostic criteria based on the core symptoms previously mentioned, stablishing an important precedent regarding the relevance of other symptoms -apart from pain- in FMS. Nevertheless, it was not until 1981 that the medical community accepted FMS as a real illness[58]. This medical recognition was influenced by the research of Yunus et al.[58] who proposed the first formal set of criteria to diagnose primary fibromyalgia, in which symptoms played a more central role in fibromyalgia diagnosis. As we previous mentioned, symptoms have been a relevant issue in FMS studies since its origins.

The evolution of FMS diagnostic criteria also reveals how symptoms have been acquiring more relevance over time. In 1990, the American College of Rheumatology (ACR) proposed the first official diagnostic criteria based on pain and using the tender point examination[1]. These first criteria were widely criticized because of their limited predictive validity of clinical pain and the difficulties of applying pressure algometry in primary health care[59] [60]. Due to of this, the ACR proposed new diagnostic criteria for FMS in 2010, in which nonrestorative sleep, fatigue and cognitive complaints have nearly equal weight for diagnosis and including depression, anxiety, irritable bowel syndrome, fatigue/tiredness, muscle weakness, Raynaud's, ringing in ears, etc., as other secondary FMS symptoms. Moreover, the 2010 diagnostic criteria introduce the idea of widespread pain[61]. This interest in all FMS symptoms -not only in pain- continues in the new ACR FMS diagnostic proposals of 2011 (the modified 2010 ACR FMS diagnostic criteria)[62] and 2016[63]. Furthermore, some authors consider that the role and conceptualization of pain in FMS has evolved from the peripheral allodynia (tender points) of 1990 diagnostic criteria until the central pain perception and distress of 2016 FMS diagnostic proposal[64].

Chronic pain is a severe health problem, which has a high comorbidity with other physical and emotional alterations,

such as anxiety, depression, insomnia and cognitive deficits[65]. These symptoms are also present in FMS patients. In the following lines, we will discuss these core FMS symptoms and their relations. Moreover, we will analyze why the comprehensive assessment of all of them may be challenging.

Pain

Undoubtedly, the central feature of FMS is pain. Pain has been defined by the International Association for the Study of Pain (IASP)[66] as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage", including a subjective component and three main dimensions: the sensory-discriminative, the emotional-affective and the cognitive-evaluative. In the case of FMS pain is chronic because it is present more than 6 months. FMS patients almost always report high levels of clinical pain[67] [68] [69]. FMS patients frequently describe pain -i.e., based on pain descriptors from the McGill Pain Questionnaire (MPQ)- as throbbing, aching, exhausting, continuous, wretched, of fluctuating intensity, and with periodical exacerbations[70] [71] [72]. Traditionally, only pain intensity was routinely assessed in FMS using visual analogue scales (VAS), numeric rating scales (NRS) or specific questionnaires[73]. Nevertheless, other aspects of pain such as its location (i.e., how wide-spread it is), and its temporality (i.e., continuous vs. intermittent) are also relevant in FMS diagnosis and treatment[74]. Depression[75] [76] higher daily pain intensity[76] poor health, and lower quality of life[77] have been associated with greater pain variability, which make pain management more difficult for FMS patients and physicians.

In the same vein, pain has shown a negative impact on health related quality of life and also increases stress and negative affect, worsening the severity and course of the disease[67] [69] [78]. High levels of pain (especially its intensity and chronicity) together with the difficulties in its management, has been associated with poorer outcomes and a worse health related quality of life in FMS [67] [68] [69] [78] [79]. Several studies have reported significant associations between clinical pain and cognitive alterations in FMS[80] [81] [82] [83] [84] [85] [86] [87].

Fatigue

Fatigue[88][89][90][91][92] and sleeping difficulties (i.e., insomnia, awakening unrefreshed and daytime somnolence)[93] [94] [95] are also common symptoms of FMS. Regarding fatigue, it is conceptualized as a condition related to an exercise-induced reduction in the ability to produce force, which determines whether performance of the task can be maintained[96]. In FMS it is important to keep in mind that we are usually talking about chronic fatigue, which is a disabling, multifaceted and persistent symptom, not a circumstantial or exercise-associated problem. The concomitance of pain and fatigue in FMS is frequent, and the pathophysiology of this link is heterogeneous and not seem to have a single underlying mechanism;[97] which might be one of the reason of the high comorbidity of FMS and Chronic Fatigue Syndrome. At this regard, some authors suggest two explanatory interconnected mechanisms explaining fatigue in FMS: a failure of central motor control and the remodelling of the muscle fibres related to an altered suprasegmental control[98]. Some authors claim for a standardized nomenclature to communicate about fatigue, increase the evidence-based guidelines for fatigue assessment, and design effective treatment strategies[99], which consequently could improve the FMS diagnosis and treatment.

Fatigue in FMS patients seems to be highest in the morning[100], although more research on this issue is required[101]. Fatigue has been also associated with poorer health status in FMS, given that the lack of energy limits daily activities and reduces the ability to cope with everyday problems[88]. Pain, stiffness, sleep problems, increased body mass index, FMS impact, tenderness, disability, cognitive complaints, anxiety and depression have shown positive associations with fatigue[102] [103]. However, because of the lack of consensus and a standard protocol for assessing fatigue in FMS, the meaning of these associations should be carefully interpreted[2]. In addition, fatigue mediated in part the effect of depression, trait-anxiety and pain on health related quality of life in FMS, specifically concerning the facets of Physical Function, Physical Role, Vitality, General Health Perception and the General Physical Component[68].

Sleep Difficulties

Related to sleep difficulties, the majority of FMS patients report poor sleep quality[104] [105] [106] [107]. Patients take longer to fall asleep, generally wake up during the night, sleep fewer hours, and usually wake up unrefreshed in

comparison with healthy controls, and patients with other rheumatic diseases or other pain disorders[108] [109]. Defficient stage IV (deep sleep) has been considered as the primary sleep architecture abnormality in FMS[110]. FMS patients usually show an increased frequency of α-rhythms during non-rapid eye movement (NREM) sleep compared to controls[106] [111] [112] [113]. α EEG frequencies are frequently related to wakefulness and it has been hypothesized that this increased α activity during NREM sleep was responsible for the nonrestorative sleep pattern in FMS patients[106] [111] [112] [113]. In addition, increased sleep latency, more frequent stage shifts, and shorter total sleep time have been also observed in FMS patients[111] [114] [115] [116]. FMS patients may also experience primary sleep disorders such as obstructive sleep apnea, myoclonus, or periodic leg movements[117] [118] [119].

Regarding the relation between insomnia and other symptoms, sleep difficulties seem to increase fatigue and anxiety, increasing functional disability in FMS[69]. Furthermore, sleep disturbances and pain appear to have a bidirectional relation in FMS[93] [117] [120]. Previous researchers have also found associations between sleep problems and health related quality of life in FMS[121]. In fact, insomnia has a mediating effect on the associations between pain, trait-anxiety, depression and fatigue with Vitality and Physical Function, measured with the Short-Form Health Survey (SF-36)[68].

Sleep disturbances in FMS are associated with reductions in serotonin and endorphin levels, as well as increases in substance P and sympathetic nervous system activity[65] [69] [122],all of which might be related to the presence of central pain sensitization in FMS. Additionally, sleep problems have been associated with neuroendocrine and immune impairments in FMS, indicating the possible role of sleep difficulties not only as a consequence of the FMS, but also as a cause[69]. Furthermore, Hamilton et al. (2007)[123] pointed out that sleep might be a resource in, and moderator of, cognitive and affective responses to stress and pain in FMS patients. It is recommended to ensure basic sleep hygiene in FMS patients, including this intervention as part of an initial psychoeducational approach[124]. Moreover, improvements in sleep quality might offset the negative effects of pain on sustained attention[125].

Emotional Disturbances

Emotional disturbances (i.e., depression, anxiety) are also frequent in FMS patients. Previous researchers underscore that depressive and anxiety disorders are highly prevalent in FMS,[1] [126] [127] [128] and in consequence, a high proportion of these patients take antidepressants and anxiolytic medications, together with analgesic drugs[84] [129]. On purpose, the intake of antidepressants, anxiolytics and non-opioid medications has been related to a worse heath related quality of life in FMS[68] [129].

Depression and anxiety disorders have showed a negative impact on the clinical course and work capacity of FMS patients[78] [130]. At this regard, comorbid depression and anxiety has been associated in FMS with lower scores on health related quality of life and greater disease severity[126] [129] [131] [132] [133] [134][135], as well as with a reduction in the ability to cope with life events[92].

Trait anxiety -buy not state anxiety- has been related to current pain intensity, suggesting that anxious mood could be a predisposing factor instead of a reaction to the disease[136]. Previous studies also reported a high association between symptoms of anxiety and depression[137] [138] [139].

FMS patients with depressive symptoms usually show more sleep disturbances, sexual dysfunction, lower levels of physical function and poorer outcomes in multimodal rehabilitation[140]. Depression and pain seem to establish a vicious circle of mutual negative interaction in chronic pain,[141] including FMS[129]. Pain seems to increase the degree of depression-anxiety and then increases the perception of pain, leading to decreases in health related quality of life[142]. Negative emotional states in FMS need to be taken into account due to its negative effect in the rest of symptoms. In fact, negative affect appears to worsen symptom perception and disability by different mechanisms, including increased interoceptive attention and somatosensory and symptom amplification[143]. The assessment of depression, anxiety and affect in general should be included in the diagnostic routine of FMS in order to better understand and treat these patients.

Cognitive Impairments

Cognitive impairments are also a relevant symptom in FMS. The most common complaints among FMS patients are deficits in executive functions, forgetfulness, concentration difficulties, and/or mental slowness[84] [144] [145] [146].

Previous studies have reported that FMS patients displayed lower performance than healthy controls in tasks which assessed:

- Attention and memory functions[84] [144] [145] [146] [147] [148].

- Cognitive processing speed[85] [144] [148] [149] [150].

- Language-related skills[151] [152] [153].

- Arithmetic processing[84] [85].

- Abstract thinking[148] [154].

- Planning abilities[148] [149] [155].

- Decision making[148] [155] [156].

- Cognitive flexibility[148] [155] [157].

Cognitive deficits significantly affect the everyday life of FMS patients, which patients perceiving cognitive symptoms as one of the most worrisome and disabling symptoms of FMS[126] [158].

Regarding to the mechanisms involved in these cognitive deficits, there are different findings but more research is required. The interference effects of nociception and pain have been considered an important factor[84] [85] [146] [159] [160]. In the same vein, it has been found associations between cognitive performance and evoked pain stimulation measures and behavioral indices as pain threshold and tolerance, including pressure algometry[21] [150] [159] [161] [162] [163], contact thermode[164], and/or conditioned pain modulation[162] [163]. Affective symptoms of FMS might be additionally related to cognitive deficits[85]. Lower cognitive performance has been associated with higher pain severity, depression, anxiety, negative affect, alexithymia and pain catastrophizing, as well as lower self-esteem and positive affect[148]. Cognitive deficits have been also related to fatigue and insomnia in FMS[102] [103].

Other relevant issues regarding symptoms of Fibromyalgia Syndrome

There are also other great variety of symptoms that usually accompany FMS, for instance dizziness and vertigo[165], increased urinary frequency[166], temporomandibular symptoms[167], intolerance cold[168], alteration of bowel habits[169], tension headaches[168], morning stiffness, abdominal pain, hypersensitivity to heat, cold and stress[170], corneal sensitivity and complaints of ocular discomfort and pain[171], and hearing loss[172], among others.

Previous studies have shown some factors which worsen FMS symptoms and might be associated with disease exacerbations. Some of the most relevant factors are stress and negative life events, emotional distress, weather changes, cold, periods of exacerbated insomnia, and physical exercise. By contrast, rest, relaxation, social support and warmth are considered relief factors by the majority of FMS patients[104] [173].

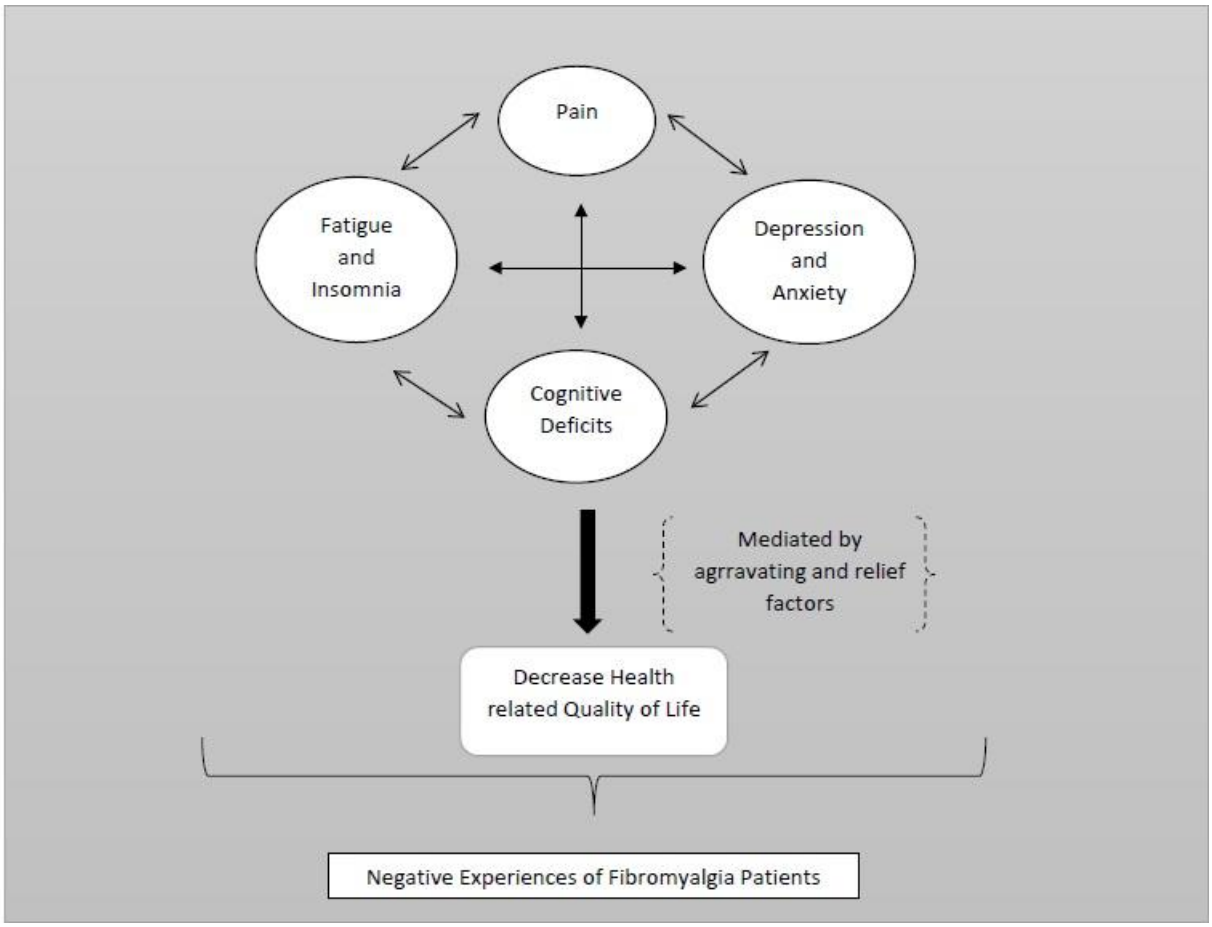
Another relevant issue is related to the complex nature of FMS symptoms, because pain and the majority of FMS symptoms do not have a clear origin, provoking discomfort in FMS patients and a lack of social support and/or medical and social acceptance[2] [174]. Moreover, these symptoms are always present in the majority of patients and exhibit a high variability (i.e., their intensity changes from day to day and within the day) which make their treatment and prevention more difficult[175] [176] [177] [178]. The current available evidence points out a complex picture, in which clinical and emotional symptoms affected each other and have a reciprocal mutual enhancing influence in FMS[68] [129].

Due to the symptomatology and characteristics of FMS, this illness is associated with a severe reduction of health

related quality of life and psychosocial impairments[68] [126] [129] [130] [142] [179]. In fact, FMS considerably reduces perceived functioning in physical, psychological, and social spheres, and has a negative impact on personal relationships, parenting, work, daily activities, mental health and social life[180] [181].

Therefore, it is necessary to take all FMS symptoms and its relations into account in order to provide a more tailored and effective treatment, as well as, to improve the health related quality of life of FMS patients. See Figure 1 for more details.

Figure 1. Fibromyalgia Syndrome Symptoms' and its associations.



Fibromyalgia Syndrome Treatment

Regarding the most frequent treatments for FMS, these can be classified as non-psychological and psychological. The former includes analgesic drugs (steroidal and non-steroidal anti-inflammatory drugs, minor opiates, major opiates, non-opiate analgesic, etc.), adjuvant drugs (which are not analgesics but enhance their action: antidepressants, benzodiazepines, anticonvulsants, etc.), nerve blocks, electrostimulation at different levels, infiltrations, etc. Additionally, it is recommended not include opiates in the treatment and avoid patients become poly pharmacies[2]. Among the non-psychological treatments are also physiotherapy and occupational therapy[182].

The psychological therapies with the most evidence are cognitive-behavioral, acceptance and commitment therapy and mindfulness[183]. The psychological treatments also encompass biofeedback, relaxation, alternative therapies (i.e., yoga, acupuncture, Pilates, mindfulness), visual imagery techniques, hypnosis and sexual therapies[65] [184]. Furthermore, it is advisable to use patient-reported outcomes (PROs) in FMS to get a better understanding of the disease[74]. PROs have been defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." PRO tools enable assessment of patient–reported health status for physical, mental, and social well-being (PROs)[185].

Conclusions

In short, FMS is defined as a chronic disorder characterized by widespread musculoskeletal pain and other

accompanying symptoms such as fatigue, insomnia, depression, anxiety and cognitive impairments. The etiology of FMS remains unknown, being one of the most accepted hypothesis the presence of central sensitization to pain and impairments in endogenous pain inhibitory mechanisms.

The central symptom of FMS is pain. FMS patients generally report high levels of clinical pain, which are related to greater impairments in health related quality of life, cognitive abilities and disease course. Fatigue and sleeping difficulties are also common symptoms of FMS. Fatigue have shown positive associations with pain, stiffness, sleep problems, increased body mass index, FMS severity, tenderness, disability, cognitive complaints, anxiety and depression. The majority of FMS patients report poor sleep quality, take longer to fall asleep, generally wake up during the night, sleep fewer hours, and usually wake up unrefreshed. Emotional disturbances (i.e., depression, anxiety) are also frequent in FMS. Depression and anxiety disorders have showed a negative impact on the clinical course and work capacity of FMS patients. Cognitive impairments are also a relevant symptom in FMS. The most common complaints among FMS patients are executive function deficits, attention problems, forgetfulness, concentration difficulties, and mental slowness. Treatments for FMS can be classified as non-psychological and psychological. The former includes analgesic drugs, adjuvant drugs (i.e., antidepressants, benzodiazepines, anticonvulsants, etc.), nerve blocks, electrostimulation at different levels, infiltrations, etc. The psychological therapies with the most evidence are cognitive-behavioral, acceptance and commitment therapy and mindfulness.

To sum up, FMS is associated with a severe reduction of health related quality of life and psychosocial impairments. It is necessary to take all FMS symptoms and its relations into account in order to provide a more tailored and effective treatment, as well as, to improve the health related quality of life of FMS patients.

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Keywords

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