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Psychological and physical interdependence between fibromyalgia syndrome and menopause: a review of the literature

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Abstract

Background and Purpose: Fibromyalgia (FM) is a very complex chronic pain condition, characterized by widespread musculoskeletal pain, fatigue and numerous other physical and psychological symptoms, such as insomnia, morning stiffness, anxiety, depressive disorders and cognitive dysfunctions. Most women with FM are also between the ages of 40 to 55 years old, around the pre-menopausal and menopausal period. As FM, Menopause (MP) is also associated with physical and psychological symptoms, being the end of ovarian activity, whose decline produces a series of trophic, metabolic, psychological and sexual consequences, altering the homeostatic balance of the woman. The aim of the study was to investigate whether both of the treated syndromes constitute a single nosological entity, or two distinct nosological entities and the most accredited hypothesis.

Methods: Through the analysis of the scientific literature, FM and MP have been analyzed using the predicted research objective as a guiding criterion. It was considered useful to analyze the two syndromes separately and then to identify a criterion of interdependence between them. The study was conducted through the use of some keywords included in the main scientific search databases.

Results and conclusions: Our research highlight the potential menopausal influence on FM, given that the progressive depletion of ovarian activity constitutes the pathophysiological substratum of profound hormonal changes, with implications not only in terms of somatic symptoms, but also in terms of psychological distress. Furthermore, the lack of scientific evidence about psychological correlations between the two syndromes provides an interesting starting point for future research.

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1. Introduction

Fibromyalgia (FM), or fibromyalgia syndrome (SFM), is a painful and chronic condition, of unknown etiology, characterized by high prevalence in women (97%), and has an overall prevalence in the general population between 1% and 6% (Marsico & Cimmino, 2010). Until a few decades ago, the diagnosis of FM was carried out in the presence of widespread musculoskeletal pain for at least three months, in at least 11 out of the 18 specific sensitive areas

of tenderness (*tender points*). More recently, increased emphasis has been placed on extra skeletal symptoms, such as sleep architecture anomalies, fatigability, sleep disorders, problems of ideation and / or memory, conditions which contribute to the worsening of the syndrome and that influence the quality of life of these patients (Palagini et al., 2016; Wolfe et al., 2010). In particular, the main physical symptoms related to FM are: chronic widespread pain, fatigue and asthenia, headache and facial pain, chest pain, stiffness, sensation of swelling, paresthesia, sensitivity disorders, visual changes, pseudo-allergic symptoms, alterations of balance, alterations of the motility of the lower limbs, gastrointestinal disorders and genitourinary disorders (American College of Rheumatology, 2010). Furthermore, FM also presents cognitive (such as *fibro-fog*), sexual, emotional and behavioral disorders that interfere with normal daily activity (Bazzichi et al., 2013; Carmassi et al., 2017; Conversano et al., 2010, 2019; Dell'Osso et al., 2015; Glass et al., 2005; Kuchinad et al., 2007; Mease et al., 2008; Piccinni et al., 2011; Veltri et al., 2012). Several studies would show also the involvement of some personality traits with FM, such as alexithymia (Conversano et al., 2018; Marchi et al., 2019).

In fact, patients with FM often fail to satisfy even the ordinary and natural demands of family, friends and employers, perceiving their illness as a negative factor with respect to their quality of life (Breivik et al., 2006; Dell'Osso et al., 2011). At present, treatment for FM includes pharmacological and non-pharmacological therapies, although the effectiveness of both types of therapies is still debated (Atzeni et al., 2019; Conversano et al., 2019). An increasing number of scientific investigations have examined patients' experiences of illness and morbidities across a variety of chronic conditions, amongst others, diabetes (Marchini et al., 2018; Martino et al., 2019; Settineri et al., 2019a, 2019b), chronic pain (Catalano et al., 2017), stroke (Orrù et al., 2019), recidivist post-traumatic stress disorder (Dell'Osso et al., 2014), FM (Lee et al., 2017; Verbunt et al., 2008) and MP (Catalano et al., 2018; Martino et al., 2018a, 2018b) using comprehensive health-related quality of life questionnaires or other outcomes measures provided by the clinical research in order to evaluate specific domains or the burden of the diseases, which could be used for syndrome treatment and progression monitoring.

In 2001, the American Society for Reproductive (Soules et al., 2001) described the various stages of reproductive activity and the transition to MP. Each of these phases has its own characteristics and presents different individual variations, and are named as follows: menopausal transition, perimenopause, and post menopause. For the diagnosis, an amenorrhea period of six to twelve months is usually required; however, for some patients this criterion may not be adequate, therefore the blood levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) are used to distinguish MP from other forms of secondary amenorrhea (Pescetto et al., 2017). About the MP onset, De Bruin and collaborators (2001) state that heredity

determines the age variability of the onset of menopause in at least 87% of cases. The climacteric symptomatology is varied and related to the variability of the hormonal patterns that are determined in each subject, as well as to the reactivity of the different organs and apparatuses on which these modifications are reverberated and, finally, to the psychological reactions linked to the transition process from the fertile age to that which is no longer fruitful in every woman. In particular, the symptoms that are likely to be linked to menopause are: vasomotor symptoms, vaginal dryness / dyspareunia, insomnia and mood disorders (Bromberger et al., 2007; Cohen et al., 2006; Freeman et al., 2007). Estrogen deficiency also leads to a reduction in basal metabolism with consequent increase in fat mass and accumulation of adipose tissue in the abdominal area and alteration of the waist/hip ratio. This change in the distribution of body fat, from the gynoid type to the android type, in addition to increasing cardiovascular risk, can negatively affect body perception in those women who tend to link their self-esteem to their external appearance (Grimaldi et al., 2006).

Recent studies highlighted how the epidemiological, etiopathogenetic, symptomatic, and therapeutic aspects are surprisingly similar between FM and MP; this similarity could lead to the hypothesis that FM is part of the climacteric syndrome or vice-versa.

These two syndromes have been studied scientifically, among others, by Blumel and collaborators (2012), who observed that in the etiopathogenesis of both syndromes there are almost identical changes in the neurotransmitters of the autonomic nervous system and, moreover, that both seem to respond to treatment with estrogens and antidepressants. This association could suggest that changes in ovarian hormone levels, starting several years before menopause, are related to the onset of FM. Despite this similarity, however, the existence of non-climacteric patients with FM, suggests that the hormonal deficit is not the only physiopathological mechanism involved in the etiopathogenesis of this syndrome. As a result, it is likely that hormonal disorders are involved in the genesis of symptoms in most middle-aged women with FM.

The question that inspired the present work is whether both of the treated syndromes constitute a single nosological entity, or of two distinct nosological entities. The answer to this question could be very useful, since climacteric syndrome responds to treatments, whereas with FM, numerous treatments have been studied, with variable and contrasting results. Furthermore, the psychological consequences of the climacteric syndrome could play an important role in maintaining or worsening some FM related symptoms, or viceversa. Clarifying the possible interdependence between the two syndromes would also help the clinical psychologist in his

work, providing him with appropriate tools to manage the complex symptomatic corollary characterizing the FM condition.

2. Methods

2.2 Search Strategy

Our bibliographic research was carried out using the following search engines: Google Scholar and Pub Med. The search for sources was carried out using the following keywords (fibromyalgia, chronic pain, pain modulation, menopause, hormones) with different combinations using the Boolean operators AND and OR. The search field comprehended both title and abstract and time frame was set on last ten years, while research articles, book chapters and reviews were included.

3. Results

Among all the articles collected (248), those most relevant to the research topic were selected, with the following inclusion criteria: title or abstract had to contain both the syndromes in comparison, or an element among the following that could underline the overlapping symptomatology between the two (hormone related hypothesis, psychological and psycho-physiological correlations).

After the excluded articles we had a corpus of thirty-three papers; in addition to the online search criteria described above, we also hand cross-referenced the publication list referenced by each of the studies we included to ensure that no studies of significance were omitted, including also some papers dated to previous years but worthy of consideration. For the present review, forty-nine studies were identified through the combined search criteria and found to be eligible for inclusion, analysed and divided according to the following criteria, to find the link between the two syndromes. In introducing new themes, the number of articles considered will be expressed in brackets.

3.1 Hormone related evidence

3.1.1 Neuroendocrine hypothesis of FM

Epidemiological studies reveal a clear prevalence of women in chronic pain syndromes (in both intensity and frequency) especially regarding that of musculoskeletal origin, or visceral with an autoimmune etiology. Studies carried out on laboratory animals have shown that the modulation

of estrogen or androgen levels is able to modify behavioral, hormonal and neuronal responses to persistent nociceptive stimuli (Aloisi & Ceccarelli, 2001).

Recently, hypocortisolism has been reported both in patients who develop disorders due to post-traumatic stress and additionally in patients suffering from FM, chronic fatigue syndrome, and chronic pelvic pain. The development of hypocortisolism can be due to alterations of the hypothalamic-pituitary adrenal axis, due to genetic factors and stress factors, characterized by a lower availability of cortisol, and to a greater sensitivity to negative feedback of the axis and the bonding of cortisol within target cells (Heim et al., 2000). In accordance with these hypotheses, some studies show a reduction in urinary cortisol using samples of 24-hour urine from FM patients, probably due to hypersecretion of corticotropic hormone (CRH) with down regulation of CRH receptors in the pituitary gland, to glucocorticoid resistance or variations morphological at different axis levels (Dessein et al., 2000). In contrast to these observations, a hyperactivity of the HPA axis was observed in FM patients with elevated levels of cortisol, which is also associated with the degree or severity of depression; a common symptom in FM (Neeck, 2000). Furthermore, the involvement of the HPA axis has been studied to assess the stress levels induced by nociceptive stimulation. The results reported that females have corticosterone and ACTH levels higher than males and that nociceptive stimulation induces an increase in circulating levels of ACTH in females, but not in males; in contrast, corticosterone levels measured after nociceptive stimulation did not differ from controls in both genders (Pieretti et al., 1996). Since FM syndrome typically occurs in women at the beginning of menopause, an estrogen deficiency has been proposed as an associated factor (Waxman & Zatskis, 1986).

Finally, there are premenopausal women with FM, although there are no significant alterations in the levels of estradiol, progesterone or follicle-stimulating hormone (Korszun et al., 2000). Abnormalities in corticotropin-releasing hormone profiles can influence the stress response, alter the central mechanism of nociception, modify the role of other hormones mediated through the HPA axis, and induce hypofunction of the neurotransmitter systems that influence mood, motivation and somatic processes like sleep (Neeck & Crofford, 2000).

3.1.2 Somatotrophic axis

The HPA axis is closely related to the secretion of the growth hormone (GH), produced by the corticotropin release factor (CRF). Numerous studies have shown that people with FM have a deficiency in the secretion of growth hormone (GH) and insulin-like growth factor (IGF1). It is also known that, GH and IGF-1, play an important role in the regulation of body composition, lipid profile, tissue repair, cardiac and nervous function, and bone density (Martinelli et al., 2008). A significant number of studies indicate that a change in GH levels may increase energy

levels, strength, heart and cognitive function, immune response, and psychological well-being. It is also believed that over 30% of women with FM have subnormal IGF-1 levels, despite this, correlation between the research and the hypothesis has been heavily criticized due to the numerous variables in the concerned populations (Shuer, 2003).

In a double-blind, placebo-controlled study, GH was administered in 25 women who met the diagnostic criteria of the American College of Rheumathology for FM. The results showed a significant improvement in symptoms and functional capacity in conjunction with an increase in IGF-1 levels (Bennett et al., 1998). Other studies have shown a significant decrease in pain after 6/12 months of GH treatment in women with FM (Leal-Cerro et al., 2002).

Another hypothesis concerns a correlation between the HPA function and a reduction of slow-wave sleep (SWS) in FM. Several studies carried out through polysomnography, document the presence of a reduced proportion of slow-wave sleep, REM sleep and total sleep, as well as a greater number of prolonged awakenings and an electroencephalographic intrusion pattern of alpha waves (waves associated with the awakening reaction) on the delta rhythm (slow waves that characterize deep sleep) in subjects with FM when compared to control groups (Roizenblatt et al., 2001).

3.1.3 Effects of androgens (DHEA and DHEAs)

In women diagnosed with FM, in addition to pain, fatigue and depression, there is evidence of hormonal changes that occur with alterations in cortisol and adrenal glands. Furthermore, to the role of estrogens and progesterone in the psycho-neuroendocrine modulation, androgens play an important role along with that of neuroactive steroids; such as dehydroepiandrosterone (DHEA), which represents the main steroid hormone produced by the secretion of adrenal glands, also produced in the gonads and the brain, and dehydroepiandosterone sulfate (DHEAs); produced almost exclusively by the adrenal cortex. The concentration of these hormones is closely related to cognitive functions, immune patterns and the reduction of circulating cortisol (Grimaldi et al., 2006).

Since hormonal alterations are very common in MP and post-menopausal women, it could affect the symptoms of FM (Abeles et al., 2007; Gupta & Silman, 2004; Pamuk et al., 2009). Moreover, women with FM which present low levels of androgens, report changes in pain perception and increased muscle fatigue (Bradley et al., 2000; Finckh et al., 2005).

3.1.4 Hypothalamic-pituitary-gonadal axis and pain

The observation of a worsening of pain with menopause, when the levels of estrogens are low, suggested an association of these hormones with analgesia; on the other hand, even with regard

to testosterone, the sensitivity levels in certain conditions of pain in men has led to hypothesize its analgesic role (Berkley & Holdkroft, 1999).

In fact, besides the similarity on the symptomatology, there are other observations which may suggest a link between FM and disorders in ovarian function. In fertile women, the fluctuations of the ovarian hormones during the menstrual cycle seem to be associated with a mild to moderate effect on pain response; one of key features of FM (Martin, 2009). One study demonstrates that in most FM patients a worsening of symptoms is observed during the premenstrual period, i.e, in one Ovarian cycle phase with low estradiol levels (Ostensen et al., 1997). Some other researchers have also observed an increase and worsening of generalized pain, fatigue and other symptoms in women with FM during post-menopause. In the same study, the authors also identified the incidence of early menopause as significantly higher in patients with FM compared to patients with rheumatoid arthritis and healthy controls (Pamuk et al., 2009).

Although estrogens play a fundamental role in the modulation of pain, and FM patients are mainly women, their role is not yet fully understood. These hormones seem to be pronociceptive in certain experimental and antinociceptive concentrations in others (Aloisi et al., 2007; Fillingim & Maixner, 1995). Some studies reported changes in pain that post-menopausal women have experienced between the pre-menopausal periods and post-menopause. To this end, ad hoc questionnaires were used to study the socio-demographic data, clinical history, levels of subjective pain and pain familiarity. Furthermore, it has been observed that the attention paid to pain has produced a significant inhibition of wind-up phenomenon in women with FM compared to healthy men or women (Staud et al., 2003). It has also been observed that the symptoms of FM are aggravated during other events related to sex hormones, such as pregnancy or postpartum (Ostensen et al., 1997; Pamuk & Cakir, 2005).

As for the relationship between FM and MP, the influence of the age of onset of climacteric syndrome on pain and sensitivity was observed: in fact, sensitivity to pain would be higher in patients with FM with early onset of MP than in those in which it occurred later. These results document how a sharp decline or reduction in ovarian hormones can affect syndromes of chronic musculoskeletal pain, such as FM (Meriggiola, 2012).

3.1.5 Inflammatory cytokines in FM and influence of aging and menopause on FM

Several studies have recognized potential abnormalities in the inflammatory system that can contribute to the perpetuation of the symptoms of FM. The imbalance of inflammatory pro and anti-cytokines is considered a possible cause of induction and maintenance of pain in FM (Üçeyler et al., 2001).

In fact, many researchers have found high levels of circulating inflammatory cytokines and chemokines in FM patients; in particular, IL-6, IL-8, IL-10 and TNF-α (Interleukin-6, Interleukin-8, Interleukin-10, Tumor necrosis factor) (Bazzichi et al., 2007; Dowlati et al., 2010; Miller et al., 2009; Wang et al., 2008). The production or the increase of inflammatory cytokines in the animal model itself seems to represent an interesting reference to the human condition. When the laboratory mice are stimulated with lipopolysaccharide (LPS) injections in order to induce an increased interleukin-1 (il-1), they show the typical "disease behavior" which is characterized by non-specific infectious symptoms, including weakness, malaise, listlessness, hypersomnia and loss of interest in social activities. In the animal model, this behavior is protective, since the animal uses less energy in daily activities, but remains inactive in an attempt to fight the infection (Parnet et al., 2002). The syndromic constellation of women with FM appears similar to the "disease behavior" expressed by mice; but while the animals are able to regenerate following the LPS injection-induced transient change, women with FM remain in the pain behavior state (Shuer, 2003).

The differences between cytokine and chemokine levels underlying FM syndrome are taken into consideration also from the point of view of human aging, as the prevalence of the syndrome increases in older populations (Wolfe et al., 1995) and inflammatory responses change depending on the normal process of aging (Üçeyler et al., 2011; Wang et al., 2008). Several studies suggest that IL-6, IL-8 and TNF-α increase with age (Burns & Goodwin, 1997; Kiecolt-Glaser et al., 2003) and direct the inflammatory response, particularly if accompanied by stressful life situations (Kiecolt-Glaser et al, 2003). Other studies have hypothesized that the onset of MP may be the basis for age-related cytokine changes in women with FM. Indeed, some researchers have observed an increase in the rate of MP and hysterectomies in women with FM; others, have reported that the symptomatology of FM can begin or worsen with the onset of MP itself (Buskila et al., 2007).

3.2 Psychological and psychophysiological correlates

Several of the analyzed studies suggest that FM is associated with a broad spectrum of clinical manifestations and comorbidities, such as altered moods and anxiety disorders. These conditions also share some neurochemical dysfunctions, alterations of the central nervous system, and alteration of the HPA axis (Bernik et al., 2013). Furthermore, FM is also associated with fatigue, muscle stiffness, headache, sleep disorders, irritable bowel syndrome, cognitive disorders with reduction in concentration and memory loss (Marangell et al., 2011; Theadom & Cropley, 2008).

Major Depression Disorder (MDD) has been studied with particular attention in subjects with FM, considering that it has a negative impact on pain tolerance and on the patient's socio-functionality. In addition, the diagnosis of MDD is particularly complex in the FM patient due to the symptomatological similarities between the two (Okifuji et al., 2000). In the context of the monoaminergic hypothesis of depression, the mood disorder would be caused by a lack of neurotransmitters at the synaptic level; in particular, regarding deficits of serotonin (5HT), noradrenaline (NA) and dopamine (DA) (Robinson et al., 2013). As we know, at the base of FM, alteration in pain and mood modulation systems were hypothesized as common pathogenetic mechanisms (Stahl & Briley, 2004). Furthermore, serotonin and noradrenaline originate in the raphe nuclei and project the information to the spinal marrow and forebrain, exerting influence both on the processing of pain and on mood (Arnold et al., 2006; Porreca et al., 2002; Suzuki et al., 2004, 2005).

Regarding this, some studies have tried to examine the association between the state of depression and the risk of developing anxiety in a sample of middle-aged Australian women. Findings suggested that middle-aged women in perimenopause are more likely to develop symptoms of depression; postmenopausal women, on the other hand, are more likely to develop anxious symptoms. Ultimately, both perimenopause and post-menopause conditions seem to increase the risk of anxiety or depression (De Kruif et al., 2016).

3.2.1 Correlations between sexual hormones and memory function

Based on the analysis of scientific studies, a hypothesis has emerged regarding the loss of estrogen, which is typical in MP, which could mediate the existing bond between memory and sex hormones in women with FM.

Estrogen loss is also linked to the risk of developing depression or anxiety, as well as osteoporotic, cerebrovascular and cardiovascular disorders (Buckler, 2005). Moreover, a study performed by Armeni and colleagues aimed to assess the association between memory and serum levels of sex hormones (Armeni et al., 2018). The results showed that a higher frequency of cognitive symptoms (such as short-term memory problems and difficulty in remembering words or numbers) have been found during the menopausal transition (Greendale et al., 2011). Similarly, women with FM complain of numerous cognitive symptoms similar to those experienced by women in MP, also presenting difficulties with attention and concentration, working and episodic memory and verbal fluency (Shuer, 2003). Furthermore, the alteration of the gray matter in the frontal regions, whose task is that of regulating the processes of planning, as well as the control and coordination of the cognitive system, seems to play an important role in the neuropsychological aspects of the FM patient (Ceko et al., 2012; Luerding et al., 2008).

3.2.1 Morphological alterations in FM

Different pain conditions appear to be associated with different patterns of cerebral morphology alteration. Even today, it remains unclear whether the pain duration causes changes in the brain or if a certain cerebral morphology makes the subject more prone to chronic pain and pain amplification. Studies conducted using functional neuroimaging techniques have shown that in patients with FM, there is an alteration in the processing of pain, as well as anatomical and neurochemical differences compared to healthy control groups (Arnoldi et al., 2011; Ceko et al., 2012). Furthermore, patients with FM appear to have more brain activity in response to pressure and thermal stimuli in numerous brain areas: specifically, in regions involved in sensory and discriminative processes, such as the primary and secondary somatosensory cortex and in limbic systems. In FM, several anatomical sites are involved; in particular, the orbital-frontal cortex, the lateral dorsal prefrontal cortex (Apkarian et al., 2004) and the insular cortex (Kuchinad et al., 2007; Schmidit-Wilcke et al., 2005, 2008).

3.2.2 Neurotrophic hypotesis of FM

Many researchers believe that at the base of FM etiology there is the involvement of the central nervous system. Neuroplasticity allows the body to change and adapt to environmental demands mediating the synthesis of neurons in painful syndromes such as migraine headaches, rheumatoid arthritis and FM, as well as the degeneration of neurons caused by inflammatory factors (McEwen & Gianaros, 2011). The transformation that the hippocampus and amygdala undergo in the event of chronic stress is the classic example of it; the hippocampus which is also involved in the management of emotions, language and motivation, experiences a decrease in volume, its neurons lose their dendritic branches and glucocorticoid receptors diminish, preventing the hippocampus from turning off the stress reaction.

The neurotrophic hypothesis confirms that the hippocampal hypotrophy is a consequence of intense activity of the HPA axis induced by the presence of chronic stress, which determines a disproportionate increase in levels of cortisol, which stimulates the activity of both particular pro-inflammatory cytokines and of glutamate, eliciting the triggering of neurotoxicity mechanisms. This may cause a progressive degeneration of neuronal cells, particularly in the hippocampus (McEwen, 1999). In line with this hypothesis, further studies show a reduction in volume of some cerebral areas that interest, first of all, the hippocampus and also the prefrontal cortex and the nucleus accumbens (Palma & Brugnoli, 2007).

Finally, a very important role is played by the brain neurotrophic factor (BDNF) which is part of the family of neuronal growth factors. It is involved in synaptic plasticity of the central and peripheral nervous systems. Emerging data in literature suggest that it has a modulatory role on

nociceptive sensory inputs, both at a central and a peripheral level and is thought to be involved in some painful conditions such as neuropathic and inflammatory pain. In fact, some studies have confirmed a variation of the baseline levels of BDNF in FM compared to healthy controls (Laske et al., 2007).

4. Discussion and conclusions

To date, the mechanisms underlying the etiopathogenesis of FM have not been completely clarified. However, in light of recent scientific evidence, FM can be defined as a part of a broader spectrum, a continuum, which includes several factors involved in the underlying pathophysiological mechanism such as genetic factors, abnormalities of the autonomic and neuroendocrine nervous system, anomalies of the central nervous system, and environmental triggers. Moreover, the combination of several potentially responsible factors opens interesting scenarios regarding the study of the endocrine aspect and, specifically, of MP; sometimes considered as a cause and as a symptomatic or therapeutic target. The analyzed studies showed that the decreasing physiological hormone levels that alter brain neurotransmission during MP causes similar symptoms in FM, to the point that FM may be conceptualized as a part of the climacteric syndrome or that the two syndromes may be superimposed. To date, the neuroendocrine hypothesis and the neurotrophic hypothesis are the most accredited regarding the interdependence of the two syndromes; as estrogen declines, progesterones and androgens inevitably have an impact both on the biological profile, psychological and behavioral of women with FM, influencing them to be more responsive to stressful events and likely to develop symptoms such as depression or anxiety. Ultimately, since FM has a 97% rate of female onset, the researchers speculate that the hormonal sphere is capable of profoundly affecting also the patient's mood. Furthermore, polysomnography studies show that the variation in hormones levels can interfere with sleep quality and cognitive function.

This review suffers from several limitations and weaknesses. The major challenges encountered were the following: first of all, the fact of not having used a purely psychological bibliographic search database has limited the material available for the analysis with this aspect. Secondly, not many experimental studies have emerged from the research but rather dissertations on the subject were found which made the critical exposition of the results quite complex. Finally, we observed a lack of scientific evidence about psychological interrelation between the two syndromes, requiring more in-depth research.

In conclusion, the current review has confirmed an overlap in symptom manifestation of the two syndromes (FM and MP). Despite an increasing number of studies have highlighted the

interdependence between FM and MP, little importance has been given so far in the clinical practice to the investigation of the two syndromes when coexisting. For future research and in light with the new evidences provided by the recent literature, it is suggested to continue the research on the present topic by focusing on psychological and biopsychosocial perspective often neglected in the analysed literature. It would be important to understand the benefit of the symptomatologic improvement of one of the two syndromes on the other, both from a psychological and medical point of view, and to provide a reassurance to the patient who finds herself experiencing a huge corollary of symptoms at the same time.

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