

**REVIEW**

# Fibromyalgia, sleep disturbance and menopause: Is there a relationship? A literature review

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**Abstract**

**Introduction:** Fibromyalgia (FM) symptoms worsen in a significant portion of patients with the onset of menopause. Some patients report that their symptoms begin after menopause, suggesting a relationship between these entities. Sleep disturbance is a common condition in FM and menopause, and it is associated with chronic pain.

**Methods/Objectives:** Several electronic databases were searched, from the first available year to April 2018 to evaluate the publications that assessed the effects of menopause and sleep disturbance on the appearance or worsening of FM and the role of hormone therapy for these patients.

**Results:** The results are summarized in three tables. The objective sleep patterns of FM patients included high sleep latency, frequent arousals and intrusion of alpha wave sleep and NREM (non-rapid eye movement) sleep in delta sleep. Poor sleep during menopause is more frequent in late perimenopause and surgical menopause, and may be related to vasomotor symptoms or not. Hormone therapy exerted a positive effect on subjective sleep quality of symptomatic menopausal women. Studies have shown a high association between FM and early and surgical menopause. Raloxifene exerted a positive effect on pain and sleep in FM patients; however one study that analyzed the effects of transdermal estrogen therapy found no improvement in subjective and objective parameters of pain.

**Conclusion:** Further studies are needed to elucidate the nature of the association between menopause, sleep and persistent pain syndromes, such as FM, showing the role of hormone therapy in prospective placebo-controlled trials.

**KEYWORDS**

climacteric, fibromyalgia, hormone replacement therapy, menopause, sleep wake disorder

## 1 | INTRODUCTION

Fibromyalgia (FM), which is characterized by the presence of persistent and widespread pain associated with multiple clinical symptoms such as sleep disturbance, fatigue, cognitive dysfunction, and depression, is one of the commonest diagnoses in rheumatologic

outpatient clinics.<sup>1</sup> The understanding of FM has changed from a predominantly peripheral musculoskeletal pathology to a centralized pain state, a maladaptive pain amplification through a variety of different mechanisms. This does not deny the contribution of peripheral nociceptive mechanisms, but these individuals feel more pain than would normally be expected based on the degree of



nociceptive input.<sup>2</sup> Recent studies have shown that FM is influenced by both genetics and epigenetics, and it is triggered by environmental factors, stress, and physical or emotional trauma.<sup>3,4</sup> FM has a prevalence of 2%-8%, and this variation depends on the diagnostic criteria used (American College of Rheumatology [ACR] criteria, 1990 or 2010 or 2010 revised).<sup>1</sup> Brazil has an estimated prevalence rate of 2.5%-4.4%,<sup>5,6</sup> and there is evidence of greater prevalence of FM among midlife women, suggesting a possible role of the decrease in hormone levels in developing or worsening FM symptoms.<sup>1</sup>

Poor sleep has been reported in almost 90% of subjects with FM. Sleep and FM exhibit a reciprocal relationship, so quality of sleep worsens with the severity of FM symptoms.<sup>7</sup> Studies have demonstrated that deprivation of some stages of NREM (non-rapid eye movement) sleep can lead to painful musculoskeletal symptoms and intense muscular tenderness.<sup>8</sup>

Women are more susceptible to sleep disturbance than men, and this disturbance intensifies after the 5th decade.<sup>9</sup> However, the literature does not clarify if such sleep alterations are related to hormonal changes, age, psychosocial stressors or symptoms accompanying menopause, such as hot flashes. These symptoms can initiate, promote, or worsen sleep disturbance in this stage of life.<sup>10</sup> Certain drugs used for menopause can be an option for the treatment of these sleep disturbances.<sup>11</sup>

To date, no review has clarified the relation between FM, menopause, sleep, and hormone therapy (HT). Therefore, this review aimed to evaluate publications that observed the effects of menopause and sleep disturbance in establishing or aggravating FM, as well as the role of HT for these patients. This review also compared the methodologies of these studies, examined the diagnostic criteria used, evaluated quality of sleep (subjective or objective) pain intensity, and quality of life, and determined the role of the aforementioned menopause symptoms.

## 2 | METHODOLOGY

This research was performed via searching the principal databases PubMed, Scopus, Web of Science, and BVS-Biblioteca Virtual em Saúde (Health Virtual Library). Original research reports (up to April 2018) that correlated FM and sleep disturbances with climacteric and menopause were searched. The following keywords were used: "fibromyalgia", "sleep", "sleep wake disorders", "insomnia", "climacteric", "perimenopause", "menopause", "hormone therapy" and "estrogen replacement therapy".

First, 290 articles were obtained and analyzed. After thoroughly reading the titles and abstracts, we excluded the studies that contained other non-related research subjects, editorials, conferences, and all that were repeated in different databases.

After the first selection a total of 39 articles were included in this review.

Some papers focused on assessing the effects of hormonal alterations on symptom intensity of patients with FM. Others assessed subjective or objective sleep quality in patients with FM, through

questionnaires, polysomnography (PSG), or actigraphy (AG), to determine predictors of poor sleep. The lack of consistency among the parameters used by the different investigators in their evaluations was noteworthy. Roughly, the papers could be grouped into three main lines of analysis: "FM and sleep disturbance", "sleep disturbance and menopause" and "FM and menopause".

## 3 | RESULTS

### 3.1 | Fibromyalgia and sleep disturbance

The relationship between FM and sleep disorders is well established. Even before FM was recognized as a clinical condition by the World Health Organization, sleep disturbance was associated with widespread pain and fatigue, the classical triad of symptoms that characterized FM, with great specificity and sensitivity.<sup>12</sup> In the 2010 research, which gave rise to the ACR revised diagnostic criteria of FM, the presence of non-restorative sleep was the second most important factor to differentiate FM from the control cases, and widespread pain was determined to be the principal symptom in the diagnosis of FM.<sup>13</sup> Despite these findings, the studies were not design to properly clarify the nature of this association.

The studies that evaluated sleep and FM are listed in Table 1.

### 3.2 | Discussion

Seven studies were selected for this topic, and all made an objective evaluation of sleep through PSG. However, the obtained results were divergent, which may be due to variations in methodology. Klerman et al<sup>14</sup> evaluated changes in circadian rhythm markers in patients with FM compared with healthy controls. They used PSG but did not describe their findings. Their results suggested that changes in circadian rhythm are not associated with pain, fatigue, subjective sleep disturbance, or cognitive disturbances.

In 2001, Roizemblatt<sup>15</sup> analyzed the characteristics of different alpha sleep patterns in patients with FM using PSG. Different patterns of alpha wave intrusion in the NREM phases of sleep were found, and painful symptoms of FM and poor subjective quality of sleep were correlated. In 2015, Rosenfeld also evaluated PSG and quantitative electroencephalogram (qEEG) in FM patients, to measure the delta and alpha events frequency power, during NREM sleep. The D/A ratio was calculated by dividing total delta events (D) by total alpha events (A) for each patient's entire NREM sleep time to produce a single number. He found significant differences in the qEEG ratio of delta to alpha frequency power, which was 95% specific for FM, when  $\leq 1$ , compared to a control population. He also found obstructive sleep apnea in 45% of the participants and conclude that PSG with EEG should be performed on those with severe symptoms to properly diagnose breathing sleep disorders and quantify D/A, which was considered a trusted marker of FM.<sup>16</sup>

Unlike Roizemblatt, Chervin could not identify alpha intrusions in NREM sleep. In his study, PSG measures showed nonspecific evidence of mild sleep disturbance, such as increased number of shifts

**TABLE 1** Summary of the studies that analyzed fibromyalgia and sleep

Author	Dx FM	Objectives	Participants	Methodology	Results	Comments
Roizenblatt et al <sup>15</sup> /2001 - <i>Arthritis and Rheumatism</i>	ACR-1990	Characterize the patterns of alpha EEG sleep and their associations with pain and sleep in FM patients	40 FM and 43 HC post menopausal	Pain and QS QT BDI PSG: TST, SL, SE, %SS (TST); SWS; AI.	FM > % 1 N-REM S = FM > αAtS 2 N-REM S and SWS; FM < SQS and > pain FM > α phasic/tonic pattern than HC 72% FM painful symptoms worse after sleep and > number of tender points	Evaluations of sleep by EEG can help to identify the sleep α intrusions in ♀ with severe symptoms. These findings may be useful in selecting appropriate therapeutic modalities.
Klerman et al <sup>14</sup> - 2001 - <i>Journal of Clinical Endocrinology and Metabolism</i>	ACR-1990	Assess the cortisol level, melatonin level and CBT in FM compared with HC	10 FM and 12 HC -pre-menopausal	Self-rated pain scores Interview from DSM-IV FIQ AT 3 weeks/ PSG 3 nights. Cortisol, melatonin level and CBT	FIQ > FM Cortisol/melatonin level and CBT were similar in both FM > pain and stiffness	Results suggest that abnormalities in circadian phase do not contribute to the pathophysiology of fibromyalgia
Landis et al <sup>18</sup> - 2003 - <i>Brain, Behavior and Immunity</i>	ACR-1990	Compare pain, psychic variables, SQ, and indicators of immune system functioning in midlife women with FM	33 FM and 37 HC	BDI R SCL-90 POMS & SS PSG 2 nights T lymphocytes and natural killer cell activity Urine cortisol	FM: < pain threshold, > number of tender points, > psychic stress > Depression Index, < SQS FM < SE; > SL and < % NREM 2 S % Lymphocytes T and natural killer similar	Showed minimal alterations of immune system and absence of relation with FM symptoms and natural killer lymphocytes function. * more studies are needed
Chervin et al <sup>17</sup> - 2009	ACR-1990	Explore physiologic differences, between FM associated with disturbed sleep, daytime sleepiness, fatigue, or pain	15 FM and 15 HC	SD McGill PQ and GBS CES-D SSE PSG 3 nights Urine cortisol HRV AAT	FM > pain, fatigue and depression FM > McGill and GBS Index FM > CES-D scores PSG unspecific alterations: > n. SS αSP in SWS does not differ from HC FM > HRV	New approaches are needed, with junction analysis of HRV. These could bring consistent physiological measures that would distinguish sleep from FM from HC
Diaz-Piedra <sup>20</sup> - 2015 - <i>Sleep Medicine</i>	ACR-2010	Assess SQ predictors in FM, with emphasis in PSG, pain, depression and anxiety	60 FM, 39 HC	PSQI, ESS, HADS, McGill PQ. PSG: 2 nights	FM > PSQI, ESS > 10; FM > anxiety and depression indexes FM < SE, and > %NREM 1 S; > W% SQ	Multidisciplinary treatments would be more effective in improving SQ I-CBT would be more effective than AD in FM patients.

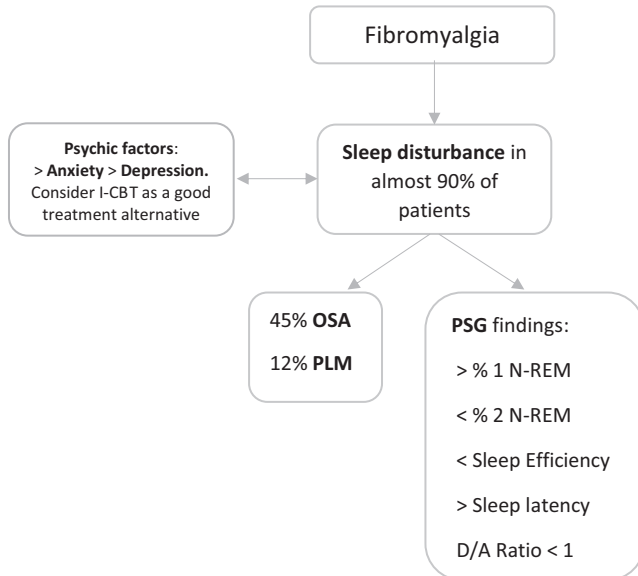
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TABLE 1 (Continued)

Author	Dx FM	Objectives	Participants	Methodology	Results	Comments
Rosenfeld <sup>16</sup> - 2015 - <i>Journal of Clinical Neurophysiology</i>	ACR-1990	Characterize the PSG and qEEG features of FM and compared with a control sleep disorder population	133 FM and 252 without FM	ESS PSG - 1 night	FM - 45% OSA and 17% AHI > 15 FM > TST PSG measures: SE, WASO, AHI, RDI, PLM (12%), D/A < in FM, with good specificity	PSG can be used to diagnose respiratory sleep disorders in FM, also to quantify the D/A relationship, that can be a reliable marker for FM
Bugra, Çetin <sup>19</sup> - 2018 - <i>Psychiatry Research</i>	ACR-2010	Investigate sleep structure in FM in order to shed light on the etiology of disordered sleep in FM patients.	17 FM patients Using amitriptyline, gabapentin, pregabalin, venlafaxine	PSG 1 night PSQI, ESS, FIQ, VAS, PHQ-SADS IL-1, IL6, FNT alpha Evaluate the treatment response	> IL6 levels related to > % N1S > Level of IL6 related to > AI Ttm:> SQS and improve psychiatric and clinical variables > IL6 levels:>VAS > latency REM	Pain, psychiatric and clinical variables and IL6 levels improve after treatment. Limitations: short sample, first night effect PSG. Different drugs can produce different effects on pain and symptoms

Abbreviations: ACR, American College of Rheumatology; AD, antidepressants; AHI, apnea/hypopnea index; AT, actigraphy; AAT, auditory arousal threshold;  $\alpha$ At S2 NREM, alpha activity stage 2 non-REM sleep; AI, Arousal Index;  $\alpha$ SP, alpha sleep patterns; BDI, Beck Depression Inventory; CBT, core body temperature; CES-D, Center for Epidemiological Studies Depression Scale; DSM IV, Diagnostic and Statistical Manual of Mental Disorders; Dx, diagnostic; EEG, electroencephalogram; FIQ, Fibromyalgia Impact Questionnaire; GBS, Gracely Box Scale; HADS, Hospital Anxiety and Depression Scale; HC, healthy control; HRV, heart rate variability; I-CBT, insomnia cognitive-behavioral therapy; McGill, McGill Pain Questionnaire; PHQ-SADS, Patient Health Questionnaire-somatic, anxiety, and depressive symptoms; PLM, periodic limb movements; POMS, 65-item Profile of Mood States; PSG, polysomnography; QT, questionnaires; RDI, Respiratory Distress Index; R-SCL90, revised 90-item symptom checklist; SD, sleep diary; SL, sleep latency; SE, sleep efficiency; SQ, sleep quality; SQS, subjective quality of sleep; SSE, Stanford Sleepless Scale; SWS, slow wave sleep; TST, total sleep time; Ttm, treatment; VAS, Visual analog scale; W%, number of awakenings; WASO, wake after sleep onset; %1N-REMS, percentage of stage 1 non-REM sleep; %SS, percentage shifts of sleep; >: bigger; <: smaller.



Abbreviations: **OSA**: Obstructive Sleep Apnea; **PLM**: Periodic Limbic Movement; **I-CBT**: Insomnia – Cognitive Behavior Therapy; **PSG**: Polysomnography; **D/A**: Delta/Alpha ratio.

**FIGURE 1** Studies' main results - FM and sleep disturbance

of sleep stages. Alpha intrusions in NREM sleep were not statistically significant, but their studies only involved a small number of patients. Chervin also assessed other parameters, such as auditory arousal threshold and heart rate variability (HRV), and compared these parameters between patients with FM and healthy controls. He found a decreased short-term HRV and especially ratio-based HRV among FM subjects suggested diminished parasympathetic and decreased complexity of autonomic nervous system function in FM.<sup>17</sup>

Others studies attempted to associate poor sleep in FM with immune system changes (percentage of T lymphocytes and natural killer [NK] cells)<sup>18</sup> or inflammatory markers (interleukin [IL]-6, IL-1, and tumor necrosis factor-alpha).<sup>19</sup> Landis found minimal alterations of the immune system and absence of alterations of NK lymphocytes function and FM symptoms. Çetin Bugra found higher IL-6 levels related to pain, assessed by a visual analog scale, and higher latency REM. The main findings can be seen in Figure 1.

Poor quality of sleep in patients with FM was found to be associated with high rates of depression,<sup>17,19,20</sup> anxiety<sup>19,20</sup> and poor quality of life.<sup>14,19</sup>

Given the divergences found in the methodology and results, the exact nature of the sleep disorders of the FM patients cannot be determined, and need to be better elucidated in further investigations.

### 3.3 | Menopause and sleep disturbance

Poor sleep is a common condition between FM and menopause, and it can lead to short- and long-term dysfunction. In a short time period, poor sleep can induce memory and attention deficits and decrease quality of life. In the long term, repercussions can be serious, including higher prevalence of diabetes, obesity, depression and raised mortality due to cardiovascular problems.<sup>10</sup>

During the transition to menopause, around 43%-47% of women will experience some kind of sleep disturbance, while they are also experienced by 15% of the general population.<sup>21</sup> The etiology of these disturbances is still fairly speculative,<sup>10</sup> but a 5 years follow-up study found frequent night sweats, depressive symptoms, use of central nervous system medication, personal crises and unsatisfactory perceived health as predictors for poor sleep after menopause.<sup>22</sup> The studies that objectively compared sleep patterns, via PSG or similar methods, during menopausal transition, are few and limited in number of patients and nights evaluated. The majority of studies in the literature are observational and do not control for confounding factors, such as presence of comorbidities, use of medication, and presence of previous sleep disturbances. The results are also inconsistent and discordant.<sup>23</sup> Although the literature does not allow conclusions, sleep-related complaints should be taken into consideration. In 2003, Kravitz et al<sup>21</sup> observed that 38% of women in their study presented difficulties with sleep. Their complaints were more frequent in late perimenopause and surgical post-menopause, compared with other stages of menopause (45.4% and 47.6%, respectively).<sup>21,24</sup> Therefore, regardless of the causes, sleep disturbances should be investigated, and treatment should be considered. Moreover, the effect of HT in these patients is an interesting topic to be investigate.

The studies that evaluated the effects of HT on climacteric women's sleep are listed in Table 2.

### 3.4 | Discussion

Among the seven studies that analyzed the effects of HT on sleep, five of them found that HT improves the subjective parameters of sleep. There was an improvement of clinical symptoms, such as the vasomotor symptoms, with HT in several studies.<sup>25,27,28</sup> Tansupswatdikul et al<sup>29</sup> evaluated objective and subjective parameters of sleep before and after HT transdermal estrogen in menopausal women. Once the hormone clearly improves the hot flushes, the authors excluded women with severe vasomotor symptoms in order to preserve the blindness of the study. No statistically significant difference was observed between the pattern of sleep of women in the estradiol and placebo groups.

Other authors observed an improvement in objective sleep parameters, such as enhanced sleep efficiency<sup>28</sup> or decreased number of sleep awakenings<sup>27</sup>; however, their work involved samples of reduced size.

Roughly, taken together these studies suggested that, independent of the effects in the objective sleep parameters observed by PSG or AG, HT seems to improve subjective sleep parameters, especially in patients who are experiencing more climacteric symptoms<sup>25,27</sup> (Figure 2).

### 3.5 | Fibromyalgia and menopause

Before the establishment of the diagnostic criteria of FM in 1990, some authors already suggested a role of estrogen deficiency in the development or aggravation of FM symptoms. Waxman et al<sup>30</sup>

**TABLE 2** Summary of the studies that assessed the effect of HT on sleep

Author	Objectives	Intervention	Participants	Methodology	Results	Comments
Polo-Kantola, Päivi <sup>25</sup> / 1998 - <i>American Journal of Obstetrics and Gynecology</i>	Assess the effect of HT on sleep of post-menopausal women	HT with estrogen - gel and patch	63 menopausal ♀ with sleep related complains	<ul style="list-style-type: none"> <li>RPC, with crossing over, comparing HT and PB</li> <li>VAS for 8 sleep parameters</li> <li>BDI, BNSQ, Climacteric Symptoms Score</li> <li>Estradiol and FSH levels</li> </ul>	<ul style="list-style-type: none"> <li>HT &gt; SQ &lt; Tiredness &lt; night awakenings</li> <li>Improvement related to climacteric and somatic/mood symptoms, but 15 ♀ asymptomatic showed improved sleep</li> </ul>	HT- Subjective benefit, related to the symptom's relief. The effect on asymptomatic women remains unanswered
Kalleinen, N <sup>26</sup> / 2008 - <i>Climacteric</i>	Evaluated the effect of HT with EPT on sleep of PM and LPM women	PM: 2 mg VE 16 days and 2 mg VE + NT 12 days or PB LPM: 2 mg VE + 0,7 mg NT or PB	17 PM and 18 LPM	<ul style="list-style-type: none"> <li>RPC</li> <li>PSG: 2 consecutive nights</li> <li>BNSQ, BDI, EQ5D.</li> <li>Vasomotor symptoms.</li> <li>3 months, before and after</li> </ul>	<ul style="list-style-type: none"> <li>EPT: improve VMS</li> <li>PM objective sleep variables similar in both groups - EPT e PB</li> <li>LPM sleepiness/insomnia scores were similar in both EPT and PB.</li> <li>&gt;arousals number and S1 arousals in EPT group X PB.</li> </ul>	Women LPM and PM there was no benefit of HT in the quality of sleep, but this therapeutic modality should be considered if the patient has other symptoms, no concerns about sleep disturbance
Hachul, Helena <sup>27</sup> / 2008 - <i>International Journal of Gynecology and Obstetrics</i>	Assess objective and subjective SQ of menopausal women, in HT with E or E + P	CEE 0,625 + MPA 5 mg, Group 1: phase 1 CEE Phase 2 CEE + AMP Group 2: Phase 1 PB Phase 2, PB + MPA	<ul style="list-style-type: none"> <li>Group 1:14</li> <li>Group 2:19</li> <li>1 year of menopause or FSH &gt; 30</li> </ul>	<ul style="list-style-type: none"> <li>RPC</li> <li>Phase 1: T 1: Q, PSG FSH, intervention.</li> <li>Phase 2: T 2: Q - PSG -FSH, after 12 weeks begin P, in both groups</li> <li>Phase 3: T3: Q - PSG FSH</li> <li>Q: SQS, ESS, KI</li> <li>E, P, LH and FSH level</li> </ul>	<ul style="list-style-type: none"> <li>Group 1: &lt; KI, &lt; HF, &lt; apnea in T2 and &lt; apnea, sleepiness and tired legs in T3.</li> <li>Group 2: &lt; HF, bruxism in T3</li> <li>Grupo 1 &lt; PLM score</li> <li>AHI improvement Group 1 after E, and in both groups, after P</li> </ul>	<ul style="list-style-type: none"> <li>Improvement SQS happens independently of the effects on objective quality of sleep</li> <li>P Tam: &lt; objective awakening of sleep, &lt; memory and anxiety complains &lt; snoring and apnea complains. * Important: respiratory effects of P in short term.</li> </ul>
Silva, Betania <sup>28</sup> / 2011 - <i>Archives of Women's Mental Health</i>	Evaluate the impact of HT in menopausal women with insomnia	EV 1 mg + Trimegestone 0,125 mg or PB.	<ul style="list-style-type: none"> <li>12 ♀ peri or 5YM + VMS</li> <li>+SE &lt; 80% 1<sup>a</sup> PSG</li> </ul>	<ul style="list-style-type: none"> <li>RPC</li> <li>First evaluation: IK, MRS, PSQI, PSG</li> <li>G1: HT = 5</li> <li>G2: PB = 7</li> </ul>	<ul style="list-style-type: none"> <li>G 1 Improve IK and MRS</li> <li>PSG: SE &gt; group 1.</li> <li>PSQI - Improvement in group 1.</li> </ul>	Besides the small sample, HT improve SQS and SE evaluated by PSG
Toffol, Elena / 2014 - <i>Maturitas</i>	Evaluate the effect of HT in melatonin secretion and level of pre- and menopausal women	PM -EV, 16 days and EV + NT 12 days; or PB PostM: EV + NT or PB	<ul style="list-style-type: none"> <li>17 PM - FSH &lt; 23 IU/ mL</li> <li>18 post M -amenorrhea &gt; 1 year</li> </ul>	<ul style="list-style-type: none"> <li>RPC</li> <li>Initial evaluation and 6 months after intervention</li> <li>BDI; STAI; BNSQ; SSS; EQ5D</li> </ul>	<ul style="list-style-type: none"> <li>No differences in melatonin levels was found between the 2 groups, HT and PB;</li> <li>Post M women in HT showed a delay in melatonin peak of 2.4 h</li> </ul>	More research is needed to better understand the HT effects on melatonin secretion and its probable interaction with mood and quality of sleep.

(Continues)



TABLE 2 (Continued)

Author	Objectives	Intervention	Participants	Methodology	Results	Comments
Tansupwatdikul. <sup>29</sup> / 2015 - <i>Climacteric</i>	Evaluate the effects of E on SQ of post M women without severe VMS	Transdermal estradiol patch 50 µg (Climara®)	<ul style="list-style-type: none"> <li>40 Post M W*</li> <li>Insomnia Dx by ICSD-2</li> <li>Patients with severe VMS were excluded</li> </ul>	<ul style="list-style-type: none"> <li>RPC</li> <li>2 month - patch E or PB</li> <li>Insomnia - ISI, ESS</li> <li>ATG - 7 days + sleep diary</li> </ul>	<ul style="list-style-type: none"> <li>No statistically significant differences between groups PB and E for ISI and EES</li> <li>No statistically significant differences between groups for AT parameters</li> </ul>	<ul style="list-style-type: none"> <li>Patients without severe VMS do not have benefits with HT for subjective or objective sleep parameters; however the results can't be extrapolated to other periods of menopause.</li> </ul>
Lampio <sup>22</sup> / 2016 - <i>Maturitas</i>	Evaluate risk factors for sleep disturbance, before the onset of menopause	Did not describe	<ul style="list-style-type: none"> <li>81 ♀, 5 years follow-up; 27 PM,</li> <li>40 Post M and 14 Post M + HT</li> </ul>	<ul style="list-style-type: none"> <li>Prospective; 5 years follow-up</li> <li>Group Post M without HT, and Post M with TH</li> <li>BDI Severity of VS (1-4)</li> <li>QoL - 1 to 6</li> </ul>	<ul style="list-style-type: none"> <li>Predictors for bad sleep: higher BDI, frequent night sweats, CNS medication use, personal crises, unsatisfactory perceived health</li> <li>HT benefited sleep quality</li> </ul>	<ul style="list-style-type: none"> <li>Part of CNS-M was prescribed for chronic pain; Important for help to identify predisposing factors for sleep disturbance in earlier midlife</li> </ul>

Abbreviations: AHI, apnea/hypopnea Index; AT, actigraphy; BNSQ, Basic Nordic Sleep Questionnaire; BDI, Beck Depression Inventory; CNS-M, central nervous system medication; CEE, conjugated equine estrogen; Dx, diagnostic; E, estrogen; EPT, estrogen progestogen therapy; ESS, Epworth Sleepiness Scale; EQ5D, Euroqol Quality of Life Questionnaire; EV, estradiol valerate; FSH, follicular stimulant hormone; G1, group 1; G2, group 2; HF, hot flushes; HT, hormone therapy; ICSD-2, International Classification of Sleep Disorders 2; ISI, Insomnia Severity Index; KI, Kupperman Index; LPM, late post-menopausal; LH, luteinizing hormone; MRS, menopause rating scale; MPA, medroxyprogesterone acetate; NT, norethisterone; P, progesterone; PB, placebo; PLM, periodic limbic movements; PSG, polysomnography; PM, pre-menopausal; PostM, postmenopausal; PSQI, Pittsburg Sleep Quality Index; Q, quality of life; RPC, randomized placebo controlled; SE, sleep efficiency; SQ, sleep quality; SQS, subjective quality of sleep; STAI, state/trait anxiety index; T, timing; TH, treatment; 5YM, 5 years of menopause; VAS, visual analog scale; VE, valerate estradiol; VMS, vasomotor symptoms; W, women

observed that menopause precedes FM diagnosis in 65% of patients and suggested that sleep deprivation and depression in menopause could be the main factors promoting FM.

Other studies attempted to associate FM symptoms with surgical menopause by hysterectomy or oophorectomy.<sup>30,34</sup> They found a positive correlation between FM and the abrupt decline in hormones in surgical menopause. Moreover, menopause resulted in a decline in quality of life and poor sleep quality.

The results and methods adopted by each study are summarized in Table 3.

### 3.6 | Discussion

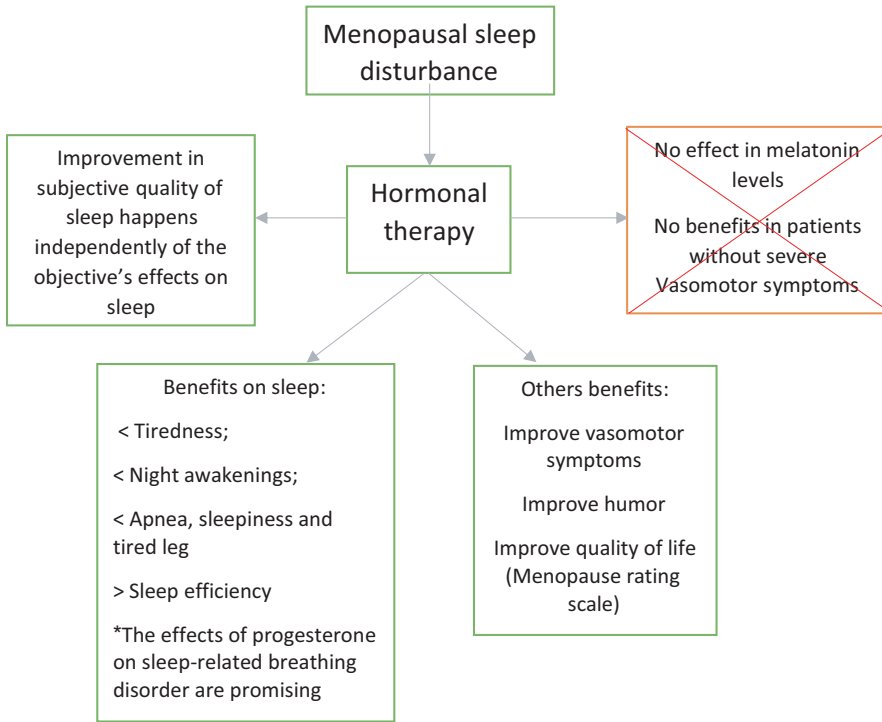
Martínez-Jauand<sup>35</sup> evaluated the influence of the age at menopause onset in patients with FM and the pain/no-pain sensory threshold. Different questionnaires were used to evaluate depression, anxiety, and pain. The FM patients had high incidence of menopause onset before the age of 49, as well as elevated depression and anxiety scores. FM patients whose menopause started before the age of 49 exhibited more intense pain and lower thresholds of pain/no-pain sensitivity than those whose menopause started after the age of 49. Therefore, the authors concluded that the abrupt decline in ovarian hormones possibly contributed to the development of painful and non-painful hypersensitivity in chronic musculoskeletal pain. The main findings are highlighted in Figure 3.

Blummel et al<sup>36</sup> studied a large sample of women (more than 8000) in Latin America and evaluated the menopausal status and presence of climacteric symptoms through a menopausal rating scale. This scale evaluates somatic, psychological, and urogenital aspects of menopause, such as vasomotor symptoms, depression, and vaginal dryness. Even though more than 90% of women declared themselves healthy, 63% showed some degree of muscle or joint ache (MJA), and this was considered severe in 15%. Women with severe-very severe MJA were older and less educated. Surgical menopause is associated with more pain intensity, and the presence of severe pain is associated with vasomotor symptoms in 60% of the patients, compared with only 8% in asymptomatic patients.<sup>36</sup>

## 4 | DISCUSSING THE INTERPLAY BETWEEN MENOPAUSE, FM, AND SLEEP

Although menopause, FM, and sleep appear to be closely associated, few studies have investigated the nature of this association. Frange et al<sup>37</sup> evaluated the effect of insomnia on pain in postmenopausal women and found that those with insomnia suffered from more intense pain and climacteric symptoms than those without insomnia. No statistically significant differences regarding pain intensity and objective sleep parameters were found between groups.

In 2008, Sadreddini et al<sup>11</sup> evaluated the effect of raloxifene in patients with FM. Even though it is not a form of HT, it is a selective estrogen receptor modulator, and this study also found significantly higher response rates than placebo in treating FM by improving pain and



**FIGURE 2** Studies' main results - hormonal therapy and sleep

fatigue, reducing tender point counts, sleep disturbance and recovery of usual activities as measured by the Stanford Health Assessment Questionnaire. This study took 16 weeks and evaluated 100 patients.

In contrast, Stenning et al<sup>38</sup> in 2011, found that hormonal replacement therapy with transdermal estradiol does not affect self-estimated pain or experimental pain responses in postmenopausal women suffering from FM, when compared to placebo. It is relevant to consider that the study took 8 weeks, and 29 women were randomly chosen.

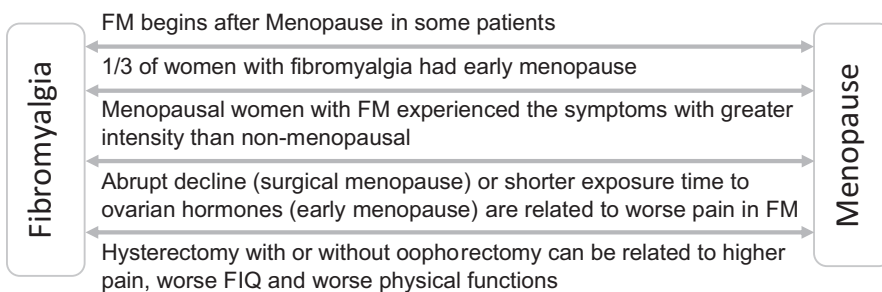
Finally, Hernandez-Leon et al<sup>39,40</sup> analyzed reserpine-induced FM models and found that in the absence of ovarian hormones (ovariectomized rats) there was an increase in muscle nociceptors and exacerbating pain and also altered sleep architecture by the increase of total wake time (38%), diminution of the NREM stage (slow wave sleep [SWS]-I 33% and SWS-II 76%), and abolition of REM. This study also found that 17-beta-estradiol had analgesic and anti-allodynic effects when administered to the animals, suggesting that it could be useful in this model of induced FM.

These findings suggested that the menopausal status of patients with FM is a factor that must be considered, particularly for those

women with surgical menopause or premature ovarian failure and those presenting moderate to severe vasomotor symptoms. In such cases, HT should be considered and individualized.<sup>41</sup>

The position statement of the North American Menopausal Society (NAMS) is that women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications to HT, the benefit-risk ratio is most favorable for treatment of bothersome vasomotor symptoms and for those at elevated risk for bone loss or fracture. The contraindications for HT include unexplained vaginal bleeding, severe active liver disease, prior estrogen-sensitive breast or endometrial cancer, coronary heart disease (CHD), stroke, dementia, personal history or inherited high risk of thromboembolic disease, porphyria cutanea tarda, or hypertriglyceridemia.<sup>41</sup> More common adverse effects include nausea, bloating, weight gain, fluid retention, mood swings (progestogen-related), breakthrough bleeding, headaches, and breast tenderness.

A literature review found that HT in the form of low-dose estrogen or progestogen could improve chronic insomnia and even improve genitourinary symptoms, sexual dysfunction and a significant improvement in the quality of life of menopausal women.<sup>41</sup>



**FIGURE 3** Studies' main findings relating FM and menopause

Abbreviations: FM: Fibromyalgia; FIQ: Fibromyalgia Impact Questionnaire

**TABLE 3** Summary of the studies that analyzed FM and menopause

Author	FM	Objectives	Participants	Methodology	Results	Comments
Waxmann <sup>30</sup> / 1986 - Postgraduate Medicine	4 "tender points" + fatigue and sleep disturbance	Evaluate the relation: meno- pause (natural or surgical) with FM	100 FM ♀	<ul style="list-style-type: none"> <li>Do not describe in detail, but evaluated the association with depression, anxiety and hysterectomy</li> </ul>	<ul style="list-style-type: none"> <li>Average age: 48 years, 68 menopausal</li> <li>65 menopause before FM.</li> <li>65 - ♀ 21 bilateral oophorectomy, 30 unilateral oophorectomy, 14 natural menopause</li> </ul>	Menopause is seen as a central factor on promoted sleep disturbance, depression and consequently stress and FM
Pamuk <sup>31</sup> / 2005 - Clinical and Experimental Rheumatology	ACR-2010	Evaluate the effects of menopause and menstrual cycle in ♀ with FM	<ul style="list-style-type: none"> <li>152 ♀ FM</li> <li>80 ♀ PM</li> <li>72 ♀ post-M</li> </ul>	<ul style="list-style-type: none"> <li>FIQ: somatization symptoms Duke AD</li> <li>VAS - CWP and fatigue (0-100)</li> <li>VAS- paresthesia and sleep dist. (0-10)</li> <li>Pain duration (years) and morning stiffness (minutes)</li> </ul>	<ul style="list-style-type: none"> <li>25% post-M- CWP and FM begin after menopause</li> <li>26,4% ♀ worsening of symptoms after menopause</li> <li>severity and &gt; pain duration in Post-M ♀</li> <li>48% PM ♀ reported pain and fatigue worsening on menstrual period</li> </ul>	Physicians should take into account the effects of menopause and the menstrual cycle on the perception of pain in female subjects with FM
Wilbur <sup>32</sup> / 2006 - Health Care for Women International	ACR-1990	Evaluate whether/how the climacteric symptoms affect ♀ FM/ CFS	<ul style="list-style-type: none"> <li>216 ♀ with FM or CFS or both</li> <li>61% FM</li> <li>8% CFS</li> <li>31% both</li> </ul>	<ul style="list-style-type: none"> <li>Symptom list - Washington Women's Health Group</li> <li>Presence of symptoms last 2 weeks</li> <li>Symptoms severity: 1 to 3 (mild - severe)</li> </ul>	<ul style="list-style-type: none"> <li>♀ in perimenopause or post-M, greater severity of GI, MS and VM symptoms</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms are similar in health and FM/CWP ♀</li> <li>♀ with FMS/CFS experienced these symptoms with greater intensity</li> </ul>
Pamuk <sup>33</sup> / 2009 - Clinical Rheumatology	<ul style="list-style-type: none"> <li>ACR -1990 FM</li> <li>ACR - 1987 RA</li> </ul>	Assess and compare the effects of natural or surgical menopause in ♀ with FM/RA	<ul style="list-style-type: none"> <li>182 ♀ post-M</li> <li>115 ♀ FM/67 ♀ RA</li> </ul>	<ul style="list-style-type: none"> <li>FIQ</li> <li>Duke-AD</li> </ul>	<ul style="list-style-type: none"> <li>Early menopause 38,3% ♀ FM/13,4% ♀ AR</li> <li>HT 16,5% ♀ FM/ 6% ♀ RA</li> <li>58% ♀ FM, symptoms developed after menopause and 26% of them developed in the first year of menopause</li> </ul>	<ul style="list-style-type: none"> <li>Findings suggest that estrogen deficiency related to early or surgical menopause may be associated with the development of FM</li> </ul>
Vincent <sup>34</sup> / 2011 - Journal of Pain Research	ACR-1990	Assess whether HT can be a worsening factor of FM	<ul style="list-style-type: none"> <li>813 ♀ - total</li> <li>328 HT</li> <li>60 HT</li> <li>24 HT + UOP</li> <li>244 HT + BOP</li> </ul>	<ul style="list-style-type: none"> <li>FIQ</li> <li>SF36</li> </ul>	<ul style="list-style-type: none"> <li>Pain (FIQ) worse in HT.</li> <li>SF 36: physical function/pain - worse HT</li> <li>FIQ score &gt; HT x non-HT</li> <li>FIQ work ability, pain, fatigue, stiffness, depression worse in HT</li> </ul>	<ul style="list-style-type: none"> <li>Results suggest further investigations of the mechanisms that involve FM and HT</li> </ul>

(Continues)



TABLE 3 (Continued)

Author	FM	Objectives	Participants	Methodology	Results	Comments
Martinez <sup>35</sup> / 2013 - <i>Clinical Rheumatology</i>	ACR-1990	Investigate the influence of age at onset of menopause and painful/ non-painful sensibility in FM	72 FM - 32 HC separated about the onset of menopause: before (early) or after age 49.	<ul style="list-style-type: none"> <li>BDI</li> <li>STAI</li> <li>WHYMPI</li> <li>EHI</li> </ul>	<ul style="list-style-type: none"> <li>FM &gt; scores depression, anxiety</li> <li>FM &gt; incidence early menopause &gt; dysmenorrhea</li> <li>FM &gt; score WHYMPI-pain and &lt; scores WHYMPI-activity</li> <li>FM and early menopause &lt; painful and non-painful sensory threshold</li> </ul>	<ul style="list-style-type: none"> <li>Abrupt decline or shorter exposure time to ovarian hormones can contribute to pain hypersensitivity in FM/ CWP</li> </ul>

Abbreviations: BDI, Beck Depression Inventory; BOP, bilateral oophorectomy; CWP, chronic widespread pain; CFS, chronic fatigue syndrome; Duke AD, Duke Anxiety-Depression Scale; Diagnostic; EHI, Edinburgh Handedness Inventory; FM, fibromyalgia; FIQ, Fibromyalgia Impact Questionnaire; GI, gastrointestinal; HC, Healthy control; HT, hysterectomy; MS, musculoskeletal; PM, premenopausal; Post-M, postmenopausal; RA, rheumatoid arthritis; SF36, Short Form-36 Health Survey; STAI, State Trait Anxiety Inventory; UOP, unilateral oophorectomy; VAS, visual analog scale; VM, vasomotor; WHYMPI, West Haven-Yale Multidimensional Pain Inventory.

## 5 | CONCLUSION

In light of the present review it is clear that further studies are needed to elucidate the nature of the association between menopause, sleep and persistent pain syndromes, such as FM. It seems plausible that the symptoms caused by the menopausal hormone deficits, as well as the psychic stress and mood swings could contribute to disrupt sleep and may be responsible for the development or worsening of FM-related symptoms. If this is real, then medical specialists who deal with persistent pain should be aware that hormonal deficits can influence the physical and/or psychological health of their patients, and therefore should investigate their menopausal status. Moreover, a multidisciplinary therapeutic model that involves rheumatologists, gynecologists, psychotherapists, and other nonpharmacological approaches should be considered for some of these patients.

## CONFLICT OF INTEREST

All the authors declare they do not have any conflicts of interest.

## ETHICAL APPROVAL

This manuscript complies with the ethical rules applicable for this journal. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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