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. 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. 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. 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). Brazil has an estimated prevalence rate of 2.5%-4.4%, 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.

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. 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.

Women are more susceptible to sleep disturbance than men, and this disturbance intensifies after the 5th decade. 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 flushes. These symptoms can initiate, promote, or worsen sleep disturbance in this stage of life. Certain drugs used for menopause can be an option for the treatment of these sleep disturbances.

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. 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. Despite these findings, the studies where 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 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 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 ≤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.

Unlike Roizemblat, 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>
<thead>
<tr>
<th>Author</th>
<th>Dx FM</th>
<th>Objectives</th>
<th>Participants</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roizenblatt et al 15/2001 - <em>Arthritis and Rheumatism</em></td>
<td>ACR-1990</td>
<td>Characterize the patterns of alpha EEG sleep and their associations with pain and sleep in FM patients</td>
<td>40 FM and 43 HC post menopausal</td>
<td>Pain and Q5 QT BDI PSG: TST, SL, SE, %SS (TST); SWS; AI.</td>
<td>FM &gt; % 1 N-REM S • FM &gt; αAt S 2 N-REM S and SWS; FM &lt; SQS and &gt; pain FM &gt; α phasic/tonic pattern than HC 72% FM painful symptoms worse after sleep and &gt; number of tender points</td>
<td>Evaluations of sleep by EEG can help to identify the sleep α intrusions in FM with severe symptoms. These findings may be useful in selecting appropriate therapeutic modalities.</td>
</tr>
<tr>
<td>Klerman et al 14-2001 - <em>Journal of Clinical Endocrinology and Metabolism</em></td>
<td>ACR-1990</td>
<td>Assess the cortisol level, melatonin level and CBT in FM compared with HC</td>
<td>10 FM and 12 HC -pre-menopausal</td>
<td>Self-rated pain scores Interview from DSM-IV FIQ AT 3 weeks/ PSG 3 nights. Cortisol, melatonin level and CBT</td>
<td>FIQ &gt; FM Cortisol/melatonin level and CBT were similar in both FM &gt; pain and stiffness</td>
<td>Results suggest that abnormalities in circadian phase do not contribute to the pathophysiology of fibromyalgia</td>
</tr>
<tr>
<td>Landis et al 18-2003 - <em>Brain, Behavior and Immunity</em></td>
<td>ACR-1990</td>
<td>Compare pain, psychic variables, SQ, and indicators of immune system functioning in midlife women with FM</td>
<td>33 FM and 37 HC</td>
<td>BDI R SCL-90 POMS &amp; SS PSG 2 nights T lymphocytes and natural killer cell activity Urine cortisol</td>
<td>FM: &lt; pain threshold, &gt; number of tender points; &gt; psychic stress &gt; Depression Index, &lt; SQS FM &lt; SE; &gt; SL and &lt; %NREM 2 S % Lymphocytes T and natural killer similar</td>
<td>Showed minimal alterations of immune system and absence of relation with FM symptoms and natural killer lymphocytes function. * more studies are needed</td>
</tr>
<tr>
<td>Chervin et al 17-2009</td>
<td>ACR-1990</td>
<td>Explore physiologic differences, between FM associated with disturbed sleep, daytime sleepiness, fatigue, or pain</td>
<td>15 FM and 15 HC</td>
<td>SD McGill PQ and GBS CES-D SSE PSG 3 nights Urine cortisol HRV</td>
<td>FM &gt; pain, fatigue and depression FM &gt; McGill and GBS Index FM &gt; CES-D scores PSG unspecific alterations: &gt; n. SS αSP in SWS does not differ from HC FM &gt; HRV</td>
<td>New approaches are needed, with junction analysis of HRV. These could bring consistent physiologic measures that would distinguish sleep from FM and HC</td>
</tr>
<tr>
<td>Diaz-Piedra 20-2015 - <em>Sleep Medicine</em></td>
<td>ACR-2010</td>
<td>Assess SQ predictors in FM, with emphasis in PSG, pain, depression and anxiety</td>
<td>60 FM, 39 HC</td>
<td>PSQI, ESS, HADS, McGill PQ, PSG: 2 nights</td>
<td>FM &gt; PSQI, ESS &gt; 10; FM &gt; anxiety and depression indexes FM &gt; SE, and &gt; %NREM 1 S &gt; W%</td>
<td>Multidisciplinary treatments would be more effective in improving SQ I-CBT would be more effective than AD in FM patients.</td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th>Author</th>
<th>Dx FM</th>
<th>Objectives</th>
<th>Participants</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenfeld – 2015</td>
<td>ACR-1990</td>
<td>Characterize the PSG and qEEG features of FM and compared with a control sleep disorder population</td>
<td>133 FM and 252 without FM</td>
<td>ESS PSG - 1 night</td>
<td>FM - 45% OSA and 17% AHI ≥15 FM &gt; TST</td>
<td>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</td>
</tr>
<tr>
<td>Bugra, Çetin – 2018</td>
<td>ACR-2010</td>
<td>Investigate sleep structure in FM in order to shed light on the etiology of disordered sleep in FM patients.</td>
<td>17 FM patients</td>
<td>PSG 1 night</td>
<td>&gt; IL6 levels related to &gt; % N1S, &gt; Level of IL6 related to &gt; AI Ttm: &gt; SQS and improve psychiatric and clinical variables &gt; IL6 levels: &gt; VAS latency REM</td>
<td>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</td>
</tr>
</tbody>
</table>

**TABLE 1** (Continued)

Abbreviations: ACR, American College of Rheumatology; AD, antidepressants; AHI, apnea/hypopnea index; AT, actigraphy; AAT, auditory arousal threshold; α; At S 2 NREM, alpha activity stage 2 non-REM sleep; AI, Arousal Index; αSP, 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; FM, fibromyalgia; GBS, Gracely Box Scale; HADS, Hospital Anxiety and Depression Scale; 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-REM5, percentage of stage 1 non-REM sleep; %SS, percentage shifts of sleep; >: bigger; <: smaller.
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. 17

Others studied attempted to associate poor sleep in FM with immune system changes (percentage of T lymphocytes and natural killer [NK] cells) 18 or inflammatory markers (interleukin [IL]-6, IL-1, and tumor necrosis factor-alpha). 19 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, 17,19,20 anxiety 19,20 and poor quality of life. 14,19

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. 10

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. 21 The etiology of these disturbances is still fairly speculative, 10 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. 22 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. 23 Although the literature does not allow conclusions, sleep-related complaints should be taken into consideration. In 2003, Kravitz et al 21 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). 21,24 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. 25,27,28 Tansupswatdikul et al 29 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 28 or decreased number of sleep awakenings 27; 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 25,27 (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 30...
<table>
<thead>
<tr>
<th>Author</th>
<th>Objectives</th>
<th>Intervention</th>
<th>Participants</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polo-Kantola, Päivi</td>
<td>Assess the effect of HT on sleep of post-menopausal women</td>
<td>HT with estrogen - gel and patch</td>
<td>63 menopausal ♂ with sleep related complains</td>
<td>• RPC, with crossing over, comparing HT and PB</td>
<td>• HT &gt; SQ &lt;Tiredness &lt; night awakenings</td>
<td>HT- Subjective benefit, related to the symptom’s relief. The effect on asymptomatic women remains unanswered</td>
</tr>
<tr>
<td>Kalleinen, N</td>
<td>Evaluated the effect of HT with EPT on sleep of PM and LPM women</td>
<td>PM: 2 mg VE 16 days and 2 mg VE + NT 12 days or PB</td>
<td>17 PM and 18 LPM</td>
<td>• RPC, PSQ: 2 consecutive nights</td>
<td>• EPT: improve VMS</td>
<td>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</td>
</tr>
<tr>
<td>Hachul, Helena</td>
<td>Assess objective and subjective SQ of menopausal women, in HT with E or E + P</td>
<td>CEE 0,625 + MPA 5 mg, ▪ Group 1: phase 1 CEE Phase 2 CEE + AMP ▪ Group 2: Phase 1 PB Phase 2, PB + MPA</td>
<td>• Group 1:14, Group 2:19 1 year of menopause or FSH &gt; 30</td>
<td>• RPC, Phase 1: T 1: Q, PSG FSH, intervention. Phase 2: T 2: Q - P SG - FSH, after 12 weeks begin P, in both groups Phase 3: T3: Q - FSH, Q: SQS, ESS, KI E, P, L, FSH level</td>
<td>• Group 1: &lt; KI, &lt; HF, &lt; apnea in T2 and &lt; apnea, sleepiness and tired legs in T3. Group 2: &lt; HF, bruxism in T3 Grupo 1 &lt; PLM score AH1 Improvement Group 1 after E, and in both groups, after P</td>
<td>Improvement SQS happens independently of the effects on objective quality of sleep. 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.</td>
</tr>
<tr>
<td>Silva, Betania</td>
<td>Evaluate the impact of HT in menopausal women with insomnia</td>
<td>EV 1 mg + Trimegestone 0,125 mg or PB.</td>
<td>12 ♂ peri or 5YM + VMS + SE &lt; 80% 1* PSG</td>
<td>• RPC, First evaluation: IK, MRS, PSQ, P SG G1: HT = 5 G2: HB = 7</td>
<td>• G 1 Improve IK and MRS PSQ: SE &gt; group 1. PSQI - Improvement in group 1.</td>
<td>Besides the small sample, HT improve SQS and SE evaluated by PSG</td>
</tr>
</tbody>
</table>
| Toffol, Elena            | 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               | 17 PM - FSH < 23 IU/ml 18 post M -amenorrhea > 1 year                      | • RPC, Initial evaluation and 6 months after intervention BDI; STAI; BNSQ; SSS; EQ5D | No differences in melatonin levels was found between the 2 groups, HT and PB. Post M women in HT showed a delay in melatonin peak of 2.4 h | More research is needed to better understand the HT effects on melatonin secretion and its probable interaction with mood and quality of sleep. | (Continues)
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.

Lampio\textsuperscript{22} / 2016 - Maturitas

Evaluate risk factors for sleep disturbance, before the onset of menopause

Did not describe

81.9, 5 years follow-up; 27 PM, 40 Post M and 14 Post M + HT

Prospective; 5 years follow-up

Group Post M without HT, and Post M with HT

BDI Severity of VS (1-4) & QoL - 1 to 6

Predictors for bad sleep: higher BDI, frequent night sweats, CNS medication use, personal crises, unsatisfactory perceived health & HT benefited sleep quality

Part of CNS-M was prescribed for chronic pain; important for help to identify predisposing factors for sleep disturbance in earlier midlife

DIAS et al.\textsuperscript{37} evaluated the influence of the age at menopause on painful and non-painful hypersensitivity in chronic musculoskeletal pain. The results and methods adopted by each study are summarized in Table 2.

Although menopausal FM and sleep appear to be closely associated, few studies have investigated the nature of this association. Frange et al.\textsuperscript{37} 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. This was consistent with previous findings that women with insomnia were more likely to report higher levels of pain intensity and climacteric symptoms. However, it is important to note that the relationship between insomnia and pain in postmenopausal women may not be straightforward and may be influenced by various factors, including hormonal changes, sleep quality, and psychological factors.

Additionally, studies have shown that women who experience more severe VMS are more likely to have poor sleep quality and that sleep disturbance is a significant predictor of VMS. For example, a study by Martínez-Jauand et al.\textsuperscript{35} evaluated the influence of the age at menopause on painful and non-painful hypersensitivity in chronic musculoskeletal pain. The main findings of this study are highlighted in Figure 3. The results and methods adopted by each study are summarized in Table 2.

**Table 2 (Continued)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Objectives</th>
<th>Intervention</th>
<th>Participants</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tansupwattdikul\textsuperscript{29} / 2015 - Climacteric</td>
<td>Evaluate the effects of E on SQ of post M women without severe VMS</td>
<td>Transdermal estradiol patch 50 μg (Climara®)</td>
<td>• 40 Post M W • Insomnia Dx by ICSD-2 • Patients with severe VMS were excluded</td>
<td>RPC • 2 month - patch E or PB • Insomnia - ISI, ESS • ATG - 7 days + sleep diary</td>
<td>No statistically significant differences between groups PB and E for ISI and EESS</td>
<td>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.</td>
</tr>
<tr>
<td>Lampio\textsuperscript{22} / 2016 - Maturitas</td>
<td>Evaluate risk factors for sleep disturbance, before the onset of menopause</td>
<td>Did not describe</td>
<td>81.9, 5 years follow-up; 27 PM, 40 Post M and 14 Post M + HT</td>
<td>Prospective; 5 years follow-up</td>
<td>Group Post M without HT, and Post M with HT</td>
<td>Predictors for bad sleep: higher BDI, frequent night sweats, CNS medication use, personal crises, unsatisfactory perceived health &amp; HT benefited sleep quality</td>
</tr>
</tbody>
</table>

**Abbreviations:** AHIL, 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 Sleepless Scale; EQSD, EuroQol Quality of Life Questionnaire; EV, estradiol valerate; FSH, follicular stimulating 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, questionnaires; QoL, 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; Tt, treatment; SYM, 5 years of menopause;VAS, visual analog scale; VE, valerate estradiol; VMS, vasomotor symptoms; W, women.
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.\textsuperscript{38} 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.\textsuperscript{39,40} 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-allo-dynic 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.\textsuperscript{41}

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.\textsuperscript{41} 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 progesterone could improve chronic insomnia and even improve genitourinary symptoms, sexual dysfunction and a significant improvement in the quality of life of menopausal women.\textsuperscript{41}
<table>
<thead>
<tr>
<th>Author</th>
<th>FM</th>
<th>Objectives</th>
<th>Participants</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waxmann²⁰/ 1986 - Postgraduate Medicine</td>
<td>4 &quot;tender points&quot; + fatigue and sleep disturbance</td>
<td>Evaluate the relation: menopause (natural or surgical) with FM</td>
<td>100 FM ♀</td>
<td>Do not describe in detail, but evaluated the association with depression, anxiety and hysterectomy</td>
<td>Average age: 48 years, 68 menopausal</td>
<td>Menopause is seen as a central factor on promoted sleep disturbance, depression and consequently stress and FM</td>
</tr>
<tr>
<td>Pamuk³¹/ 2005 - Clinical and Experimental Rheumatology</td>
<td>ACR-2010</td>
<td>Evaluate the effects of menopause and menstrual cycle in ♀ with FM</td>
<td>152 ♀ FM 80 ♀ PM 72 ♀ post-M</td>
<td>FIQ: somatization symptoms Duke AD VAS - CWP and fatigue (0-100) VAS- paresthesia and sleep dist. (0-10) Pain duration (years) and morning stiffness (minutes)</td>
<td>25% post-M- CWP and FM begin after menopause 26,4% ♀ worsening of symptoms after menopause severity and &gt; pain duration in Post-M ♀ 48% ♀ reported pain and fatigue worsening on menstrual period</td>
<td>Physicians should take into account the effects of menopause and the menstrual cycle on the perception of pain in female subjects with FM</td>
</tr>
<tr>
<td>Wilbur²² / 2006 - Health Care for Women International</td>
<td>ACR-1990</td>
<td>Evaluate whether/how the climacteric symptoms affect ♀ FM/ CFS</td>
<td>216 ♀ with FM or CFS or both 61% FM 8% CFS 31% both</td>
<td>Symptom list - Washington Women's Health Group Presence of symptoms last 2 weeks Symptoms severity: 1 to 3 (mild - severe)</td>
<td>♀ in perimenopause or post-M, greater severity of GI, MS and VM symptoms</td>
<td>Symptoms are similar in health and FM/CWP ♀ ♀ with FMS/CFS experienced these symptoms with greater intensity</td>
</tr>
<tr>
<td>Pamuk³²/ 2009 - Clinical Rheumatology</td>
<td>ACR -1990 FM ACR - 1987 RA</td>
<td>Assess and compare the effects of natural or surgical menopause in ♀ with FM/RA</td>
<td>182 ♀ post-M 115 ♀ FM 67 ♀ RA</td>
<td>FIQ Duke-AD</td>
<td>Early menopause 38.3% ♀ FM/13.4% ♀ AR HT 16.5% ♀ FM/ 6% ♀ RA 58% ♀ FM, symptoms developed after menopause and 26% of them developed in the first year of menopause</td>
<td>Findings suggest that estrogen deficiency related to early or surgical menopause may be associated with the development of FM</td>
</tr>
<tr>
<td>Vincent³⁴/ 2011 - Journal of Pain Research</td>
<td>ACR -1990</td>
<td>Assess whether HT can be a worsening factor of FM</td>
<td>813 ♀ - total 328 HT 60 HT 24 HT + UOP 244 HT + BOP</td>
<td>FIQ SF36</td>
<td>Pain (FIQ) worse in HT. SF 36: physical function/pain - worse HT FIQ score &gt; HT x non-HT FIQ work ability, pain, fatigue, stiffness, depression worse in HT</td>
<td>Results suggest further investigations of the mechanisms that involve FM and HT</td>
</tr>
</tbody>
</table>

(Continues)
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.

ORCID

Rejane Camila Alvarenga Dias https://orcid.org/0000-0002-2223-302X
Jaime Kulak Junior https://orcid.org/0000-0002-8588-8074
Eloise Haydéê Ferreira da Costa https://orcid.org/0000-0002-3085-0079
Renato Mitsunori Nishihara https://orcid.org/0000-0002-1234-8093

REFERENCES


