

## PRIMARY MENOPAUSAL INSOMNIA: DEFINITION, REVIEW, AND PRACTICAL APPROACH

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### ABSTRACT

**Objective:** To present a case of primary menopausal insomnia with hot flashes to introduce recent changes in technology and nomenclature of sleep medicine and to review presentation, diagnosis, and therapies for menopausal insomnia.

**Methods:** Clinical findings and results of sleep evaluation in the menopausal study patient are presented with details about polysomnography performed before and after therapy with pregabalin.

**Results:** A 56.5-year-old female athlete with severe hot flashes and insomnia of 12 years' duration was treated with pregabalin, which ameliorated the hot flashes and sweats and improved sleep quality and architecture. Menopause is associated with hormonal and metabolic changes that disrupt sleep. Disruption of sleep can in turn lead to morbidity and metabolic sequelae. Hormonal treatment, although effective, carries risks unacceptable to many patients and physicians. To date, nonhormonal therapies of symptomatic menopause have not been objectively studied for effects on sleep efficiency and architecture. Primary menopausal insomnia is insomnia associated with menopause and not attributable to secondary causes. Polysomnographically, it seems characterized by a high

percentage of slow-wave (N3) sleep, decreased rapid eye movement sleep, cyclic alternating pattern, and arousals.

**Conclusions:** Primary menopausal insomnia is probably mediated through a mechanism separate from hot flashes, and one can occur without the other. Thermal dysregulation and sleep abnormalities of menopause are probably related to more general changes mediated through loss of estrogenic effects on neuronal modulation of energy metabolism, and more clinical direction is expected as this research field develops. Identification of sleep disorders in menopausal women is important, and polysomnographic evaluation is underused in both clinical and research evaluations of metabolic disturbances. (**Endocr Pract.** 2011; 17:122-131)

### Abbreviations:

**CAP** = cyclic alternating pattern of arousal; **EEG** = electroencephalogram; **GABA** =  $\gamma$ -aminobutyric acid; **N1** = stage 1 sleep; **N2** = stage 2 sleep; **N3** = slow-wave sleep; **OSA** = obstructive sleep apnea; **PLMD** = periodic limb movement disorder; **R** = rapid eye movement sleep; **RLS** = restless legs syndrome

### INTRODUCTION

"In spite of the great advances of modern physiology and, especially, of the assistance given our understanding of the physiological disturbances connected with cessation of ovarian and testicular secretion by recent laboratory studies, there is much as yet unexplained in the symptomatology of the menopause. This is a matter of importance to every medical practitioner as the disorders and discomforts of this period have a striking nervous as well as physical effect. Particularly are the vasomotor symptoms hard to control and vexatious to the patient" (1).

So begins a contribution to the *California State Medical Journal* in 1918, to demonstrate little change through the last century in our view of the vexatious symptoms of menopause.

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For many women, menopause presents a major turning point in sleep quality (2). Menopause often brings pathologic changes that seem to disrupt sleep. These changes include sleep-related breathing disorders, arthritis, reflux, and symptoms of thermal dysregulation referred to descriptively as hot flashes. With 40% reduction in use of oral sex steroid hormone by postmenopausal women in the year following publication of the Women's Health Initiative (3), prevalence of chronic insomnia in perimenopausal and menopausal women is now greater than 50% (4). Often considered a mere nuisance by patients and physicians, research has confirmed that disruption or curtailment of sleep can lead to significant morbidity, including depression, accidental trauma, poor memory, and metabolic syndrome.

Despite its prevalence and associated morbidity, menopausal insomnia has received inadequate physiological study, underlying mechanisms are unknown, and definitive diagnosis and treatment remain elusive. The American Association of Clinical Endocrinologists guidelines for management of menopause mention insomnia as 1 of 4 symptoms of the climacteric (5), but due to insufficient research, these guidelines could not specifically address treatment.

Hot flashes (or in England, hot flushes) remain the most common symptom associated with loss of estrogens and progesterone. Hot flashes occur in 60% to 80% of all women with natural or iatrogenic menopause. This symptom causes considerable distress and impairment of quality of life, and many women associate hot flashes with poor sleep.

The relationship between sleep disruption and hot flashes, however, is no longer clear. While complaints of severe hot flashes seem to correlate with complaints of insomnia (4) and sleep fragmentation (6), a recent physiological study that importantly controlled for sleep-related breathing disorders suggests that a cause-effect relationship between hot flashes and sleep disruption does not exist (7). Also, suppression of sex hormones with leuprolide for 5 weeks produces hot flashes, but no change in objective sleep quality (8). Menopausal hot flashes and insomnia are, therefore, separate problems that often coexist and become subjectively, if not physiologically, linked.

Insomnia is "repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate time and opportunity for sleep, and results in some form of daytime impairment" (9). Daytime impairments include decreased mood, fatigue, malaise, or cognitive problems—all common concerns of perimenopausal women.

*Primary menopausal insomnia* can be defined as insomnia associated with menopause in which sleep disturbances are not due to other disorders such as sleep apnea, periodic limb movements, or pain. Recent work suggests primary menopausal insomnia is characterized by increase

in awakenings and, perhaps, a paradoxical increase in slow-wave sleep (N3) that reverts to normal with hormone therapy (10-12).

A case of menopausal insomnia will introduce recent changes in technology and nomenclature of sleep medicine and serve as a departure point for review of presentation, diagnosis, and therapies for menopausal insomnia. I will review what is known about underlying mechanisms, but also what is not known, and plead for more objective, physiological studies of effects of menopause and its treatment on sleep.

## CASE

A 56.5-year-old female athlete (body mass index = 20.3 kg/m<sup>2</sup>) with family history of thrombotic disorder was referred for severe hot flashes (more than 6 daily) and insomnia of 12 years' duration. Sweats were first associated with menstrual irregularity, which her gynecologist associated with perimenopausal state. She had no significant comorbidity and took no medication. Last menstrual period was at age 50 years. She came to clinical attention after her restless sleep disrupted sleep of her husband. In view of concomitant complaints compatible with sleep apnea, including nocturnal restlessness, nonrefreshing sleep, awakenings, snoring, and vivid dreams, she was referred for polysomnography.

### Diagnostic Methods

Sleep evaluation included history, examination, Epworth Sleepiness Scale (13), and polysomnography. One technician, blinded to treatment, scored both polysomnographic studies by standard clinical protocols (14). Montage for polysomnography included 6-lead electroencephalogram (EEG), electro-oculogram, mentalis surface electromyography, anterior tibialis surface electromyography, electrocardiography, nasal/buccal airflow by thermocouple, thoracic and abdominal effort by piezo-belt transduction, intercostal surface electromyography, and oxyhemoglobin saturation by pulse oximetry.

Fast Fourier transform analysis of EEG was performed on overlapping (50%) time windows of 4 s (Welch method, Hamming window) (15). For presentation, results were averaged to obtain 1 spectrum per 30-second epoch.

### Results of Diagnostic Procedures

Initial polysomnography demonstrated sleep disruption associated with a cyclic alternating pattern of arousal (CAP) (16), increased wake during sleep, and increased stage 1 sleep (N1), which is best thought of as a transitional stage of sleep between wake and sleep. There was smaller percentage of time in deeper stage 2 sleep (N2) and rapid eye movement sleep (R). Overall, these findings indicate sleep of low quality. Normally, poor sleep is also associated with smaller percentage of time in slow-wave sleep

(N3), but this patient paradoxically had increased time in this stage. Results of initial diagnostic polysomnography are summarized in Table 1.

### Review of Treatment Options

Hormonal therapy provides effective treatment for both insomnia and hot flashes (see Discussion), but has fallen from favor with many patients and physicians following publicity of risks associated with oral use of conjugated estrogens and medroxyprogesterone (3,17,18). Although this patient did not have a known coagulopathy, risk of thrombotic events in the context of family history convinced her hematologist to recommend avoidance of hormonal therapy.

Behavioral therapies have found limited use in treatment of menopausal insomnia and/or hot flashes. None have been studied polysomnographically to quantitate effects on sleep. In general, behavioral therapy has aimed at eliminating risk factors for hot flashes, including high body mass index and smoking, and avoidance of high ambient temperatures and dehydration. In a study designed to decrease sympathetic nervous system activation, women treated with paced-breathing showed significant declines in hot flash frequency (19), but treatment was not associated with decrease in markers of sympathetic nervous system activity (20). None of these therapies has a known effect on sleep. Exercise has been advocated as treatment for menopausal insomnia. Although low-intensity walking or yoga

proved ineffective in a randomized controlled trial (21), a study of more intense exercise demonstrated improvement in subjective sleep quality (22).

Selection of nonhormonal medications for treatment of menopausal insomnia remains difficult, as none have been studied for efficacy on objective measurements of sleep. Selective serotonin-norepinephrine reuptake inhibitors may control hot flashes (23-26), but are associated with insomnia and arousals during sleep. Use of these drugs in older women, including those without depression, carries greater likelihood of sleep disturbances (27). Efficacy of selective serotonin-norepinephrine reuptake inhibitors in treatment of menopausal sleep disturbances remains unknown but unlikely.

Effects of clonidine on menopausal insomnia also remain unstudied. Clinicians still use clonidine therapy for hot flashes, but with varied results. Of 10 trials comparing clonidine with placebo, only 4 trials reported reduced frequency of hot flashes. Meta-analysis of these 4 trials demonstrated average reduction in hot flashes of only 1.6 per day (28).

Symptoms of menopausal insomnia seem to improve with zolpidem (29) and eszopiclone (30), but objective changes in menopausal sleep quality have not been reported. Although these medications have US Food and Drug Administration approval for short-term treatment of insomnia, they have not been shown to specifically improve physiological measures of sleep quality in

**Table 1**  
**Sleep Latency and Architecture Before and 8 Months After Initiation of Pregabalin Treatment in Study Patient**

Characteristics	Pretreatment	Posttreatment
Epworth sleepiness scale	6/24	3/24
Weight, kg	56.1	57.1
Blood pressure, mm Hg	124/82	105/75
Sleep efficiency <sup>a</sup> , %	74	91
Sleep latency, min	32.0	20.5
Wake during sleep <sup>a</sup> , %	21	5
Stage 1 (N1) <sup>a</sup> , %	15	9
Stage 2 (N2) <sup>a</sup> , %	34	54
Slow wave sleep (N3) <sup>a</sup> , %	18	13
Rapid eye movement sleep (R) <sup>a</sup> , %	12	18
Spontaneous arousals, No. per hour	13.7	5.8
Mean $\delta$ -power, $\mu V^2$	556(10 <sup>6</sup> )	0.33(10 <sup>6</sup> )
Mean $\alpha$ -power, $\mu V^2$	2019(10 <sup>3</sup> )	22.3(10 <sup>3</sup> )
Mean $\beta$ -power, $\mu V^2$	2346(10 <sup>3</sup> )	12.3(10 <sup>3</sup> )

<sup>a</sup> Expressed as a percentage of sleep period time.  $\delta$  Activity <4 Hz;  $\alpha$  Activity is 8-12 Hz;  $\beta$  activity is 12-30 Hz.

symptomatic, menopausal women. Physiological confirmation of improved sleep quality is important, as these  $\gamma$ -aminobutyric acid<sub>A</sub> (GABA<sub>A</sub>)-receptor modulators potentially cause or worsen sleep-related breathing disorders, a frequent problem in this age group. Furthermore, amnesic effects of GABA<sub>A</sub>-receptor agonists can mask sleep disruption and make questionnaires unreliable.

Gabapentin can provide relief of hot flashes (31-33) and has compared favorably with estrogens for this condition (34). Like gabapentin, pregabalin binds the  $\alpha_2$ - $\delta$  subunit of the voltage-dependent calcium channel (35), and has similar effects on hot flashes (36). Risks include orthostasis, edema, and fatigue. Although there are no physiological studies of effects of this class of medication on menopausal insomnia, pregabalin was selected for trial in this patient and, after informed consent, self-titrated over 4 weeks to 100 mg every evening.

### Results of Treatment

After 6 months treatment, the patient was symptomatically and physiologically improved. If the patient accidentally omitted a dose, she experienced immediate return of both hot flashes and insomnia. Blood pressure was lower with no change in weight (Table 1). On treatment, hot flashes and symptomatic sleepiness improved (Table 1). After 8 months of therapy, polysomnography demonstrated normal sleep efficiency and architecture (Table 1 and Fig. 1). Simplistically, the sum of  $\alpha$  (8-13 Hz) and  $\beta$

(>14 Hz) power appears to vary continuously and inversely with depth or quality of sleep (37). Treatment reduced by greater than 99% mean power of EEG in  $\alpha$  and  $\beta$  ranges (Table 1, Fig. 1). Hypnogram and spectral analysis (Fig. 1) graphically demonstrate decrease in arousals, improved sleep architecture, reduction in N3 and low frequency power, and increase in R.

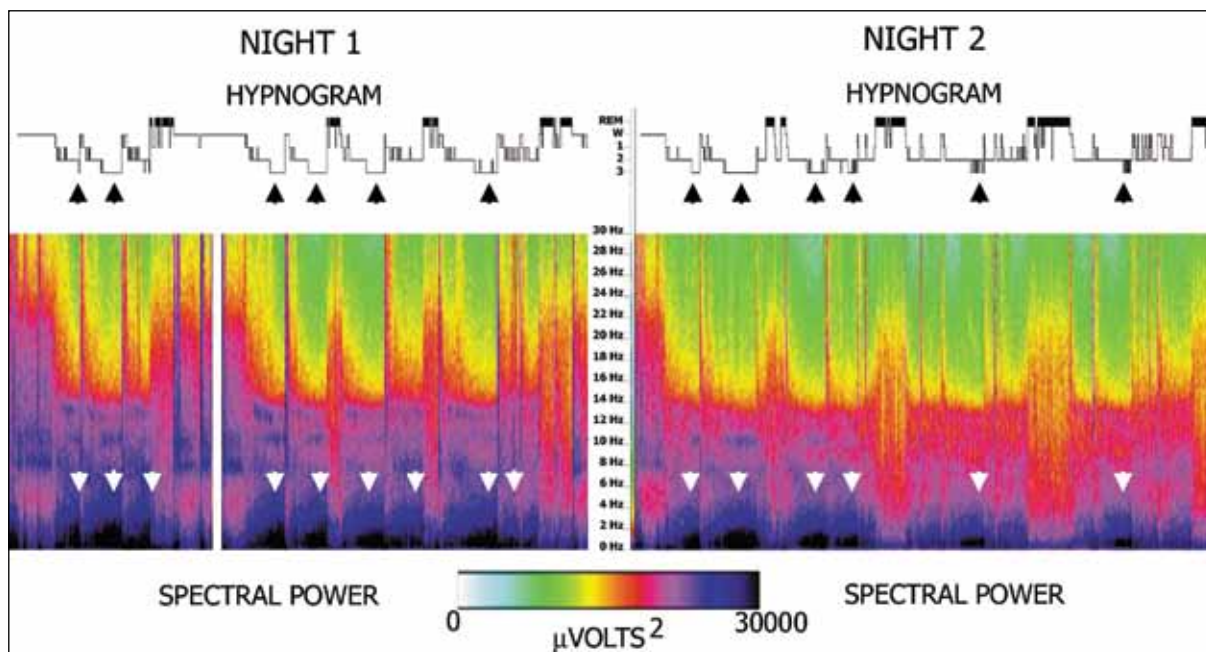
### DISCUSSION

#### Presentation of Primary Menopausal Insomnia

Clinical presentation of this patient seems typical for primary menopausal insomnia. Although pretreatment symptoms of sleepiness were significant, the patient remained unaware of daytime sleepiness until it resolved. Like many patients with sleep disorders, she sought help only after her bed-partner expressed concern. Although women might not express concern directly to their physician, when given the opportunity through phone questionnaire, most menopausal women report poor sleep (4). Insomnia can precede menopause by years, and menopause can exacerbate symptoms. For these women, the etiology of insomnia is often multifactorial, and early referral to a subspecialist in sleep medicine might be necessary.

#### Diagnosis of Primary Menopausal Insomnia

As defined in the preceding text, diagnosis of menopausal insomnia requires consideration of other disorders



**Fig. 1.** Power spectrum generated through fast Fourier transform analysis of electroencephalogram in 1 study at baseline (NIGHT 1) and after treatment for 8 months with pregabalin (NIGHT 2). Broad bands in hypnogram at top indicate rapid eye movement (REM) sleep. Arrowheads indicate periods of slow wave sleep or N3 in the hypnogram and associated areas of the power spectrum. Increase in REM and decrease in N3 and  $\delta$ -power are noted on treatment. Abbreviations: 1, stage 1 sleep or N1; 2, stage 2 sleep or N2; W, wake.

(Table 2). An early diagnostic decision is whether to proceed with polysomnography or therapeutic trial. In general, polysomnography should be performed whenever a sleep-related breathing disorder or periodic limb movement disorder (PLMD) is suspected, initial diagnosis is uncertain, treatment fails, or precipitous arousals occur with violent

or injurious behavior (38). Although a simplified list of problems that might indicate need for study or consultation by a sleep medicine specialist is found in Box 1, more precise tools for determining need for polysomnography in evaluation of insomnia can be found in recent guidelines (39). Brief discussion of common disorders that must

**Table 2**  
**Common Causes of Insomnia in Perimenopausal and Menopausal Women**

Disorder	Features
Primary menopausal insomnia (working definition)	Menopause or perimenopause Arousals from sleep Decrease in stage 2 and rapid eye movement sleep Possible increase in slow wave sleep Absence of other disorders to explain findings. Polysomnographic improvement with hormone therapy
Inadequate sleep hygiene	Irregular sleep-wake times Inadequate exercise Sleeping with lights Insufficient time in bed Noisy sleep environment (eg, radio, music)
Sleep related breathing disorder (obstructive sleep apnea, upper airway resistance syndrome)	>5 episodes of apnea or hypopnea per hour Snoring (usual) Restless sleep Diaphoresis Morning headache Hypertension Fasting hyperglycemia Dysmenorrhea Amenorrhea Nocturia
Restless legs syndrome	Irresistible urge to move limbs at rest Improvement with movement Association with periodic limb movement (80%-90%) May be associated with low ferritin
Periodic limb movements	Trains of limb muscle twitching during sleep (>15 movements/h) Like restless legs syndrome, caused or aggravated by selective serotonin-norepinephrine reuptake inhibitors or low ferritin
Mood disorders	Depression Anxiety Early awakening
Pain syndromes	Arthritis Fibromyalgia
Insomnia due to medication or substance	Selective serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants Lipid-soluble $\beta$ -adrenergic blocker Corticosteroids Alcohol Caffeine Pseudoephedrine

**Box 1****Indications for Polysomnography—  
Signs or Symptoms That Suggest Sleep Apnea or  
Periodic Limb Movement Disorder<sup>a</sup>**

Loud snoring  
 Nonrefreshing sleep  
 Daytime sleepiness  
 Medication-resistant hypertension  
 Neck size >40 cm (women)  
 Observed episodes of apnea  
 Fasting hyperglycemia  
 Morning headache  
 Congestive heart failure  
 Asymptomatic atrial fibrillation  
 Cerebrovascular accident  
 Arousals with dangerous behavior

<sup>a</sup> More precise tools for determining need for polysomnography in evaluation of insomnia can be found in recent guidelines (39).

be considered before diagnosis of primary menopausal insomnia follows.

**Primary Sleep Disorders Common in Menopause*****Inadequate Sleep Hygiene***

To meet the definition of insomnia (*v.s.*), a patient must have adequate time and opportunity for sleep. For many patients, the task of providing an appropriate environment and time for sleep is daunting. General instructions for sleep hygiene are widely available. Behavioral therapy can help. For some patients, impairment resolves with adequate sleep.

***Obstructive Sleep Apnea***

Due to associated morbidity and close relationship to menopause, obstructive sleep apnea (OSA) deserves special attention in evaluation of menopausal insomnia. OSA mimics other sleep disorders, including narcolepsy, PLMD, and parasomnias, and can also mimic primary menopausal insomnia. OSA can cause both insomnia and night sweats. Also, close to half of premenopausal women with OSA report dysmenorrhea or amenorrhea that resolves with positive airway pressure treatment (40). In patients with risks for or features of sleep-related breathing disorders, clinicians might consider OSA before attributing complaints of sweats and irregular menses to perimenopause.

Menopause is a risk factor for OSA, even after adjustment for body mass index and neck circumference (41). In a polysomnographic study of 1000 women, prevalence of OSA was low in premenopausal women (0.6%) and postmenopausal women taking hormone therapy (0.5%), but

5-fold higher (2.7%) in postmenopausal women (42). In the Wisconsin Sleep Cohort Study, odds ratios for severe OSA were 3.5 in menopausal women and 1.1 in perimenopausal women (43). Increase in prevalence of OSA in menopausal women has been attributed not only to weight gain and change in body habitus, but also to changes in sex hormones (44), leptin (45), and other undefined mechanisms.

Decrease in progesterone might contribute directly to development of postmenopausal OSA. Progesterone increases respiratory drive and has been used to treat mild OSA (46). Other progestins might have similar effects, eg, treatment with estradiol and dienogest improved OSA compared with baseline and placebo, but estradiol alone had no effect (47).

Despite known association between menopause and OSA, OSA remains underdiagnosed in middle-aged women. In the Wisconsin Sleep Cohort Study, 93% of women with moderate to severe OSA were not diagnosed before entry (48), a finding that seems egregious when one considers OSA is a risk factor for hypertension, insulin resistance, diabetes, nonalcoholic fatty liver disease, accelerated atherosclerosis, atrial fibrillation, and sudden death. The high prevalence of undiagnosed OSA also suggests that metabolic and endocrinologic research in menopausal women should control for this disorder.

***Restless Legs Syndrome and PLMD***

Restless legs syndrome (RLS) and PLMD are common in menopausal women, but they do not appear directly related to menopause. RLS is characterized by an urge to move the legs that is worse at night and with rest, and which improves immediately with movement (9). PLMD is diagnosed in adults when polysomnography demonstrates stereotyped, transient (0.5 to 5 s) movements that occur in trains of 4 or more at a rate of more than 15 per hour (9). Neither RLS nor PLMD responds to estrogen therapy (49). PLMD occurs in 80% to 90% of patients with RLS, but mechanism of the link is unknown.

Secondary RLS and/or PLMD occurs commonly with selective serotonin-norepinephrine reuptake inhibitor treatment. A low-normal ferritin concentration (<50 ng/mL) has also been associated with RLS and PLMD, and mechanisms related to abnormal iron metabolism in substantia nigra have been proposed (50). Menopausal women with a history of menorrhagia might therefore carry high risk for PLMD.

***Other Disorders***

Other disorders associated with poor sleep such as fibromyalgia and depression are not considered primary sleep disorders, but they occur commonly with menopause and can be associated with complaints of insomnia. Cause and effect are unclear; symptoms of these disorders can be caused or aggravated by poor sleep quality for any reason (51-54). Prevalence of these disorders and their potential

relationship to menopausal sleep disorders warrant brief discussion.

#### Depression

Although depression might cause insomnia, insomnia can trigger depression. Increase in sleep disturbances might be one reason for increase in depression in menopause. Treating insomnia to prevent depression has been suggested by a study in which the odds ratio for developing depression after 1 year was 39.8 for patients with unremitting insomnia and 1.6 in those in whom insomnia resolved with treatment (55).

#### Fibromyalgia

Association of pain with menopause has been so strong that menopausal arthritis was a recognized condition from at least 1925 through 1944 (56). To date, a cause for fibromyalgia has not been defined. Sleep disturbances might cause or at least exacerbate fibromyalgia. Disruption of sleep produces nociceptive hyperalgesia and can increase pain syndromes, *c.f.* (57). Interestingly, pregabalin has been approved for use in fibromyalgia. In a placebo-controlled trial of pregabalin, modest improvements were noted in pain and subjective sleep quality (58). We await polysomnographic studies of sleep in these patients, with special attention to menopausal women.

### Proposal of a Working Definition of Primary Menopausal Insomnia

In the case presented, polysomnography demonstrated numerous arousals, CAP, increased wake (W), increased N1, decreased R, and increased N3 (Table 1). Although high N3 in the context of sleep disruption might seem paradoxical, as this stage is considered a “deep” stage of sleep, it might be pathologic in menopausal insomnia and might represent a variant of CAP. Woodward and Freedman previously noted high N3 in association with hot flashes and suggested this represents a compensatory thermoregulatory response to increased body temperature (10). In 11 lean, asymptomatic, postmenopausal women, Antonijevic et al (11) found high N3 with unusual carryover of N3 into the last half of the night at the expense of stage R and in the presence of increased awakenings. These findings resolved with low-dosage (0.05 mg) topical estradiol. Similar normalization of sleep was seen in our patient after treatment with pregabalin (Table 1, Fig. 1). Although one explanation for increase in N3 might be low frequency activity due to intermittent sweat artifact, we found little difference in general appearance and amplitude of slow wave activity after treatment. Nonetheless, explanation for paradoxical increase in N3 and  $\delta$  power remains open, and formal polysomnographic definition of primary menopausal insomnia awaits more research. In this context, a working definition of primary menopausal insomnia is summarized in Table 2 and the summary section below.

### Mechanism of Primary Menopausal Insomnia

The presence of sleep abnormalities without symptomatic hot flashes in the study of Antonijevic et al (11) further supports the premise developed in the Introduction that sleep disturbances associated with primary menopausal insomnia occur independently of hot flashes. The observation that estrogens and pregabalin seem to exert similar effects on primary menopausal insomnia suggests that a common neuronal pathway or mechanism might be involved.

A mechanism for primary menopausal insomnia remains unknown. Hormonal therapy improves subjective and objective sleep quality in menopausal women, and speculation that primary menopausal insomnia is related to changes in effects of estrogen and progesterone on central nervous system control of metabolism seems reasonable. As with hot flashes, proposed mechanisms must explain relatively normal sleep of men and young girls and include a mechanism by which reduction in normal adult female sex steroid hormone action induces poor sleep.

Sedative effects of progesterone should be considered as we investigate mechanism and design and study therapies for menopausal insomnia. Sedative effects of progesterone on rats and adaptation to daily injections were first reported more than 50 years ago by Hans Selye (59). Progesterone appears to exert effects on GABA<sub>A</sub> receptors directly, *c.f.*, (60) and through more potent action of progesterone metabolites (particularly 5 $\alpha$ -pregnanolone and 5 $\beta$ -pregnanolone) (61,62). Importantly, medroxyprogesterone and other progestins might not function as GABA-receptor agonists. Although both progesterone and progestins such as low-dosage megestrol acetate improve hot flashes, only progesterone improves sleep (63). When given with conjugated estrogen, both medroxyprogesterone and progesterone are effective for treatment of hot flashes, but only progesterone is associated with improved sleep efficiency and decreased wake after sleep onset (64). Improvement in sleep efficiency was also seen after brief treatment with progesterone in 10 postmenopausal women screened for sleep disorders (12).

### Role of the Central Nervous System in Primary Menopausal Insomnia and Hot Flashes

If we view sleep and thermoregulation as activities associated with energy homeostasis, the complex world of estrogen-mediated effects on central nervous system control of metabolism suddenly opens. Estrogenic effects on central nervous system neurons, neuropeptides, and hormones that control sleep, appetite, mood, metabolic rate, body temperature, and locomotion are now under intense study in animal models. These interactions will be critical to our understanding of mechanisms underlying primary menopausal insomnia and hot flashes, but are beyond the scope of this review. The reader is referred to one of many recent reviews of this area (65).

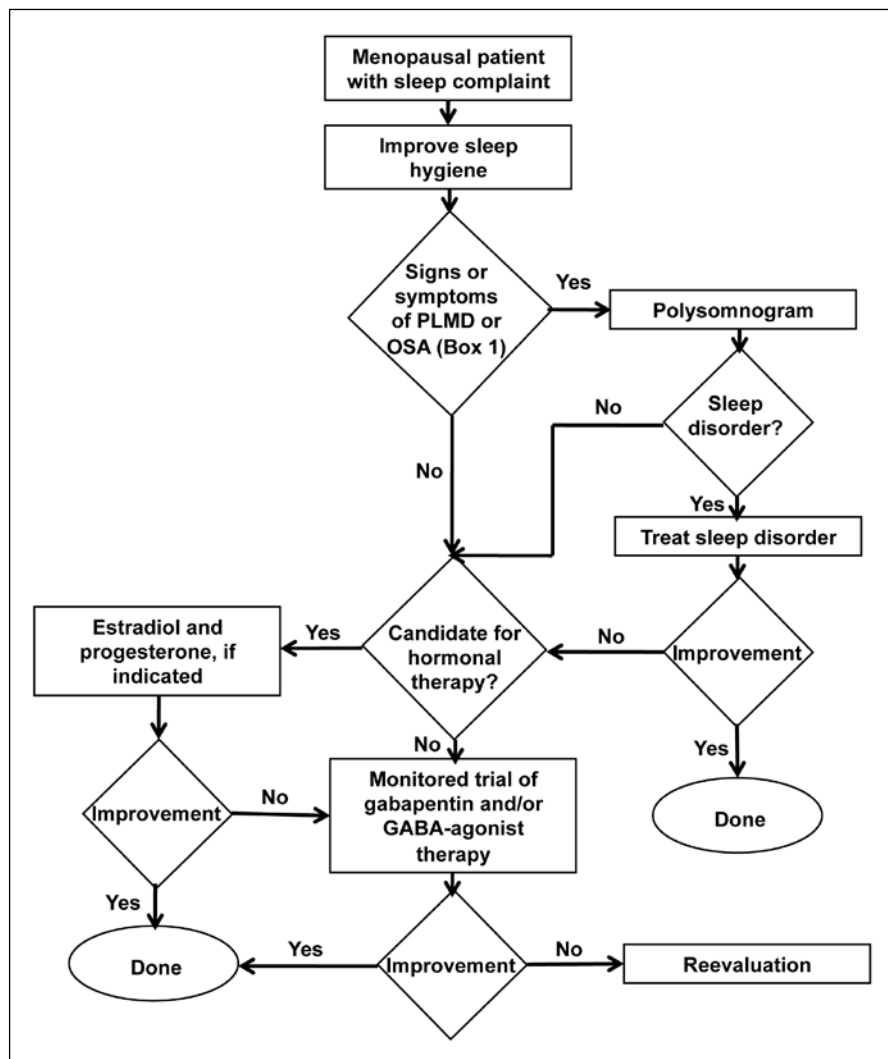
**CONCLUSION**

Primary menopausal insomnia is insomnia associated with menopause that is not attributable to other causes. Polysomnographically, it seems characterized by increase in arousals, CAP, high percentage of N3 sleep, and decreased percentage of stage R sleep. These findings can occur with or without hot flashes and are reversible with hormone therapy.

Primary menopausal insomnia is probably mediated through a mechanism separate from hot flashes, as one can occur without the other. Progesterone, but not necessarily other progestins, might prove to be an especially important medication in treatment of menopausal insomnia, as it not only improves sleep, but also hot flashes and mild sleep-related breathing disorders. Sleep abnormalities and thermal dysregulation of menopause are likely related to more general changes associated with loss of effects of sex

steroids on neuronal modulation of energy metabolism, and more clinical direction awaits further development of this research field.

Decisions on appropriate treatment for menopausal sleep complaints have been hampered by insufficient knowledge of the mechanisms linking change in ovarian function with insomnia, and general absence of information on physiological effects on sleep of nonhormonal treatment. Discussion above underscores the importance of evaluation for sleep disorders in older women and suggests that polysomnography has been underused in both clinical evaluation and research of metabolic disturbances in this group of patients. In the context of this review, I present a simple algorithm for a clinical approach to menopausal patients with sleep concerns in Figure 2. Hopefully this algorithm will be shortlived and modified extensively in the near future on the basis of new research.



**Fig. 2.** Proposed algorithm for management of menopausal insomnia. GABA,  $\gamma$ -aminobutyric acid; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder.



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## DISCLOSURE

The author has no multiplicity of interest to disclose.

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