NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.1776

SCIENTIFIC INVESTIGATIONS

Nighttime Awakenings Responding to Gabapentin Therapy in Late Premenopausal Women: A Case Series

Thomas Guttuso Jr., M.D.

Department of Neurology, University at Buffalo, Buffalo, NY

Insomnia related to nighttime awakenings is known to be more prevalent in women than men. Three cases are presented here of late premenopausal women experiencing frequent nighttime awakenings that responded well to bedtime treatment with gabapentin. In one case, what started as isolated nighttime awakenings slowly progressed to awakenings accompanied by typical menopausal night sweats. This led to the theory that the initial isolated nighttime awakenings in this patient may have been secondary to a menopausal etiology related to low serum estradiol levels. In the subsequent 2 cases, early follicular phase serum estradiol was confirmed to be low. It is theorized that isolated nighttime awakenings in some premenopausal women may be caused by low serum estradiol, triggering events physiologically related to menopausal night sweats. Further research is needed to determine if low early follicular phase serum estradiol is associated with nighttime awakenings in premenopausal women not experiencing night sweats.

Keywords: Insomnia, estradiol, menopause, awakenings, night sweat, hot flash

Citation: Guttuso T. Nighttime awakenings responding to gabapentin therapy in late premenopausal women: a case series. *J Clin Sleep Med* 2012;8(2):187-189.

Menopausal night sweats, which are hot flashes that occur at night, are common in postmenopausal women and are significantly more bothersome to women than daytime hot flashes,[1] most likely because of the associated interference with sleep.[2] Many women with night sweats will report that they first awaken and then, about 10-30 seconds later, experience the feeling of internal heat and observable sweating (personal observations). Daytime hot flashes are frequently preceded by an aura of a "sense of anxiety" and sometimes by a "change in heart rate" just prior to the feeling of internal heat and observable sweating.[3]

It is known that with each clinical hot flash, there is a predictable increase in several serum hormones, the largest of which is in serum adrenocorticotropic hormone (ACTH), which rises to about 120% above baseline levels.[4] This sympathetic surge could account for the aura-associated symptoms preceding a daytime hot flash and for the nighttime awakening preceding a night sweat. Although the auras and awakenings are typically linked to hot flashes and night sweats, respectively, the following 3 cases suggest that nighttime awakenings may occur in isolation and years before the night sweats classically associated with menopause.

BRIEF SUMMARY

Current Knowledge/Study Rationale: It is known that women experience insomnia at significantly higher rates than men and that this disparity may be related to cycling hormones, however, the sleep-related physiology of this association is unknown. Three cases are presented here suggesting that insomnia due to nighttime awakenings in some cycling premenopausal women may be physiologically related to menopausal night sweats and may also improve with bedtime gabapentin, a treatment known to be effective for hot flashes and night sweats.

Study Impact: These cases may represent the first description of a novel sleep disorder unique to women found to have low serum estradiol and nighttime awakenings. This proposed sleep disorder has been coined LUNAs and may help to explain the higher prevalence of insomnia in women.

CASE 1

In 9/2006, a 48-year-old white female having regular monthly menses presented with a chief complaint of frequent nighttime awakenings for the previous 3 years. The patient reported having sudden awakenings from deep sleep, "as if I have been shocked awake," followed by great difficulty returning to sleep. These unexplained awakenings occurred 2-3 times a night ≥ 3 nights a week. The sleep disruption was causing excessive daytime sleepiness, difficulty concentrating at work, and irritability. She had been taking oral contraception daily for about 12 years. A 6-month trial of trazodone at bedtime and a 4-month trial of amitriptyline at bedtime were both ineffective.

Two years after the awakenings started, in 2005, the patient underwent a nocturnal polysomnogram that was normal (respiratory distress index: 3.6/h and occasional periodic limb movements).

In 7/2006, the patient began noticing that after some of her typical unexplained nighttime awakenings, she would feel hot and occasionally sweaty. Her serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were found to be normal, at 3.0 and 1.1 mIU/mL, respectively, while she was still taking oral contraception. Under the presumption that the patient was now experiencing menopausal night sweats, her primary physician increased her dose of oral contraception. There was no improvement in her symptoms after 2 months. The patient was not interested in taking hormone replacement therapy. The patient denied symptoms of restless legs syndrome

(RLS), periodic leg movements of sleep (PLMS), or snoring during sleep.

Gabapentin 300 mg at bedtime (qhs) was initiated in 9/2006, based on evidence of efficacy in the treatment of hot flashes and night sweats[5-7] and improved sleep in such patients.[8] The patient experienced benefit after the first dose of gabapentin, reporting a full night's sleep without any awakenings or night sweats. This degree of efficacy persisted for about 2 weeks, at which time the isolated nighttime awakenings began to recur, sometimes accompanied by feeling hot and sweaty. The dose of gabapentin was increased to 600 mg qhs, which again resolved the symptoms. The patient also reported normalized daytime alertness, concentration, and mood. The side effect of early morning dizziness occurred infrequently and did not affect any activities of daily living. Attempts at discontinuing gabapentin resulted in recurring night sweats and awakenings.

Three months later, in 12/2006, oral contraception was discontinued. Regular monthly menses continued until 9/2007, when menses began occurring every other month until 4/2008 when menses stopped. In 10/2008, serum FSH and LH were clearly in the postmenopausal ranges, at 114.0 and 51.7 mIU/mL, respectively.

This case led to the hypothesis that nighttime awakenings in late premenopausal women may be caused by declining systemic estradiol triggering isolated nighttime sympathetic surges without any subsequent night sweats. This hypothesized novel sleep disorder associated with low serum estradiol causing nighttime awakenings was coined LUNAs.

CASE 2

A 42-year-old white female having regular monthly menses presented in 1/2010, complaining of 2 years of worsening nighttime awakenings, excessive daytime sleepiness, and irritability. The patient had experienced hot flashes and night sweats with her 2 pregnancies at 33 years and 38 years, which fully resolved postpartum. The patient denied any hot flashes or night sweats at the time of presentation. The patient reported that almost every night over the previous 2 years, she would have 2-5 nighttime awakenings occurring at predictable times and causing great difficulty returning to sleep. The patient also noticed that the awakenings were more frequent and severe for 1-2 days before her menses and the first 4-5 days of her menses every month. The patient denied symptoms of RLS or PLMS or snoring during sleep.

The nighttime awakenings were postulated to be LUNAs due to the patient's age and the exacerbation of symptoms just before and during menses, the time of the menstrual cycle when serum estradiol is at its lowest.

Due to the favorable response of the patient in Case 1 to gabapentin treatment, gabapentin 300 mg qhs was initiated. The patient reported near full resolution of the nighttime awakenings within 2 days. A side effect of early morning sedation was mild and resolved within 4 days. About 2 weeks later, the nighttime awakenings began to return and gabapentin was increased to 600 mg qhs with good effect for about 6 weeks, when the dose again needed to be increased (to 900 mg qhs). The nighttime awakenings would recur when the patient forgot to take gabapentin. The daytime sleepiness and irritability reported before starting gabapentin resolved after about 3 weeks of gabapentin treatment.

On 6/29/11—while still having regular monthly menses and still taking 900 mg of gabapentin qhs—serum FSH, LH, and estradiol on day 3 of her menstrual cycle were 13.7 mIU/mL, 7.0 mIU/mL, and 32.2 pg/mL, respectively, and on day 14 were 13.7 mIU/mL, 39.1 mIU/mL, and 665.3 pg/mL, respectively. Ovulation was likely occurring on day 14 in this patient, evidenced by the high LH and estradiol levels.

CASE 3

A 46-year-old white female presented in 3/2011 with a chief complaint of nighttime awakenings, concentration problems, and daytime sleepiness and fatigue for the previous 6 years. The problem had progressed to the point that over the previous year she began needing to drink coffee throughout the day in order to stay awake at work. Almost every night she reported awakening around 02:30 for no apparent reason with great difficulty returning to sleep. These nighttime awakenings were not accompanied by feeling hot or sweaty. During daylight savings time, the awakenings would change by 1 hour for a few months and then return to 02:30. For 3 months prior to presentation, the patient noticed occasional spells of feeling very warm during the day without any flushing or sweating. The patient denied symptoms of RLS, PLMS, or snoring during sleep.

At 36 years of age, about 4 years prior to the nighttime awakenings, she experienced 2 weeks of severe hot flashes and night sweats after having an ovary removed for cysts causing abdominal pain.

The patient had regular monthly menses until 44 years of age, about 4 years after the nighttime awakenings started, when she developed heavy menstrual bleeding and had a 52 mg levonorgestrel intrauterine device (IUD) placed. The IUD did improve her heavy menses but did not affect her nighttime awakenings.

Since the nighttime awakenings had been slowly worsening since the age of 40 and the patient was starting to experience daytime spells consistent with mild hot flashes, the nighttime awakenings were suspected to be LUNAs. For this reason, gabapentin 300 mg qhs was initiated for 3 nights and then increased to 600 mg qhs for better effect. The nighttime awakenings fully resolved within 4 days except for occasional awakenings at 02:30, after which the patient was quickly able to return to sleep. After 2 weeks of gabapentin treatment the patient reported greatly improved daytime alertness, concentration, and energy and was able to stop drinking coffee at work. The patient denied any side effects from gabapentin.

After 8 weeks of gabapentin therapy, while still having regular monthly menses, serum FSH, LH, and estradiol on day 2 of her menstrual cycle were 6.3 mIU/mL, 5.1 mIU/mL, and 50 pg/mL, respectively, and on day 14 were 4.7 mIU/mL, 4.8 mIU/mL, and 150 pg/mL, respectively.

DISCUSSION

Although it is proposed that the insomnia occurring in these 3 cases was caused by low serum estradiol levels triggering nighttime awakenings physiologically related to menopausal night sweats, in only 2 of these cases was estradiol assessed and shown to be low during the early follicular phase. It certainly is possible that the low serum estradiol in these 2 cases

Table 1—Summary of 3 cases

Patient age at onset of nighttime awakenings	History of hot flashes or night sweats?	Low early follicular phase serum estradiol?	Subjective improvement of nighttime awakenings with gabapentin qhs?	Final qhs gabapentin dose	Transient gabapentin side effects
45yo (Case 1)	yes	?	yes	600 mg	Dizziness
40yo (Case 2)	yes	yes (32.2pg/mL)	yes	900 mg	Sedation
40yo (Case 3)	yes	yes (50pg/mL)	yes	600 mg	None

was simply coincidental and not causally related to the occurrence of the nighttime awakenings. In addition, gabapentin's positive effects on nighttime awakenings reported in these 3 cases may have been due to its known general sleep-enhancing actions[9] and not to a specific effect on the nighttime awakenings theorized here to have been caused by low serum estradiol and coined LUNAs.

On the other hand, these cases, summarized in **Table 1**, may be the first report of a novel sleep disorder unique to women. A large meta-analysis showed insomnia to be more common in females than males, and for the disparity to increase with increasing age.[10] Also, premenopausal women with irregular menstrual cycles, which often signal declining estradiol levels, are twice as likely to report insomnia symptoms such as nighttime awakenings as those with regular menstrual cycles.[11] These findings support an association between declining serum estradiol and insomnia in women.

The 3 cases reported here also support this association. None of the women noted nighttime awakenings until after 40 years of age, a time when estradiol levels in some women may be declining. The patient in Case 2 noticed clear worsening of her nighttime awakenings during the days of her menstrual cycle when serum estradiol was at its nadir. Indeed, Cases 2 and 3 were both found to have low serum estradiol on day 3 (32.2 pg/mL) and day 2 (50 pg/mL), respectively, of their menstrual cycles. In contrast, a normal day 2-7 serum estradiol in premenopausal women over 40 years of age is 73-78 pg/mL,[12,13] while postmenopausal levels are < 20 pg/mL.

Although serum estradiol was not assessed in Case 1, what began as isolated nighttime awakenings at 45 years of age slowly morphed into awakenings occasionally followed by night sweats at 48 years, implicating a similar physiological process underlying these conditions. Finally, all 3 patients' nighttime awakenings resolved with a single bedtime dose of gabapentin, a therapy known to be an effective treatment for hot flashes and night sweats.[5-7] The fact that the nighttime awakenings in Case 1 failed to respond to oral contraception drugs (OCDs) may have been due to the much lower estrogen dose found in OCDs (about 0.05 mg) than in hormone replacement therapy (about 0.60 mg), which is the only FDA-approved therapy for menopausal hot flashes and night sweats.

In summary, the proposed LUNAs are hypothesized to be physiologically related to night sweats and to occur in women several years before menopausal symptoms would typically be expected to occur. Further research is needed in premenopausal women with isolated nighttime awakenings to determine if early follicular phase serum estradiol levels are significantly decreased compared to age-matched control women without nighttime awakenings and to exclude other contributing conditions such as sleep apnea or PLMS.

REFERENCES

1. Guttuso T Jr., McDermott MP, Ng P, Kieburtz K. Effect of L-methionine on hot flashes in postmenopausal women: a randomized controlled trial. *Menopause* 2009;16:1004-8.
2. Erlik Y, Tataryn IV, Meldrum DR, Lomax P, Bajorek JG, Judd HL. Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-4.
3. Kronenberg F. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci* 1990;592:52-86.
4. Genazzani AR, Petraglia F, Facchinetti F, Facchini V, Volpe A, Alessandrini G. Increase of proopiomelanocortin-related peptides during subjective menopausal flushes. *Am J Obstet Gynecol* 1984;149:775-9.
5. Guttuso T Jr., Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337-45.
6. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366:818-24.
7. Reddy SY, Warner H, Guttuso T, Jr., et al. Gabapentin, Estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol* 2006;108:41-8.
8. Yurcheshen ME, Guttuso T, McDermott M, Holloway RG, Perlis M. Effects of gabapentin on sleep in menopausal women with hot flashes as measured by a Pittsburgh Sleep Quality Index factor scoring model. *J Womens Health (Larchmt)* 2009;18:1355-60.
9. Lo HS, Yang CM, Lo HG, Lee CY, Ting H, Tzang BS. Treatment effects of gabapentin for primary insomnia. *Clin Neuropharmacol* 2010;33:84-90.
10. Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep* 2006;29:85-93.
11. Hachul H, Andersen ML, Bittencourt LR, Santos-Silva R, Conway SG, Tufik S. Does the reproductive cycle influence sleep patterns in women with sleep complaints? *Climacteric* 2010;13:594-603.
12. Burger HG, Dudley EC, Hopper JL, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. *J Clin Endocrinol Metab* 1999;84:4025-30.
13. Randolph JF Jr., Sowers M, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. *J Clin Endocrinol Metab* 2004;89:1555-61.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2011
Submitted in final revised form October, 2011
Accepted for publication November, 2011

Address correspondence to: Thomas Guttuso Jr., M.D., Assistant Professor of Neurology, University at Buffalo, 3435 Main Street, 97 Farber Hall, Buffalo, NY 14214; Tel: (716) 829-5454; E-mail: tguttuso@buffalo.edu

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Guttuso is the inventor on US Patent 6,310,098, which is owned by the University of Rochester, covering the use of gabapentin for treating hot flashes and night sweats. Dr. Guttuso does not receive financial compensation on the sales of generic gabapentin or brand name Neurontin for any use. Dr. Guttuso may receive royalties on the sales of a gabapentin-related drug only if such a drug is FDA-approved for treating hot flashes.