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Original Article

A randomized clinical trial of valerian fails to improve self-reported, polysomnographic, and actigraphic sleep in older women with insomnia ☆

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Abstract

Objective: To test the effects of nightly valerian (*Valeriana officinalis*) extract to improve sleep of older women with insomnia.
Methods: Participants in this phase 2 randomized, double-blind, crossover controlled trial were 16 older women (mean age = 69.4 ± 8.1 years) with insomnia. Participants took 300 mg of concentrated valerian extract or placebo 30 min before bedtime for 2 weeks. Sleep was assessed in the laboratory by self-report and polysomnography (PSG) at baseline and again at the beginning and end of each treatment phase (total of nine nights in the laboratory) and at home by daily sleep logs and actigraphy.
Results: There were no statistically significant differences between valerian and placebo after a single dose or after 2 weeks of nightly dosing on any measure of sleep latency, wake after sleep onset (WASO), sleep efficiency, and self-rated sleep quality. In comparing each treatment to baseline in separate comparisons, WASO significantly increased (+17.7 ± 25.6 min, $p = .02$) after 2 weeks of nightly valerian, but not after placebo (+6.8 ± 26.4 min, NS). Side effects were minor and did not differ significantly between valerian and placebo.
Conclusion: Valerian did not improve sleep in this sample of older women with insomnia. Findings from this study add to the scientific evidence that does not support use of valerian in the clinical management of insomnia.

Keywords: Valerian; Women; Aging; Phytotherapy; Sleep; Insomnia; Complementary therapies; Alternative medicine

1. Introduction

Older adults commonly experience disturbed sleep with nearly 50% reporting insomnia symptoms of prolonged sleep latency, frequent nocturnal or early morning awakenings with an inability to return to sleep [1,2]. Polysomnographic (PSG) recordings of sleep in older adults also show frequent awakenings, increased nighttime wakefulness, and reduced slow-wave sleep [3,4]. Women are more likely than men to report insomnia and this gender difference increases with age [5]. Insomnia is associated with negative health consequences including impaired daytime function, fatigue, reduced quality of life, and increased healthcare utilization [6,7]. Additionally, insomnia is a risk for major depression [8], and prolonged sleep latency and reduced sleep efficiency are

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associated with an excess risk of dying after controlling for age, gender, and medical burden [9]. Older adults frequently use prescription hypnotics, sedating anti-depressants, or over-the-counter sedating antihistamines to treat insomnia [10,11] despite observations that many of these drugs further disrupt sleep and have untoward side effects, e.g., daytime sleepiness, drug tolerance, memory impairments, dry mouth, constipation, and rebound insomnia on withdrawal of the medication [12,13].

Complementary and alternative medical (CAM) therapies may be useful for management of insomnia in older adults. The 2003 National Sleep Disorders Research Plan recognized as a priority the importance of studies evaluating CAM therapies for sleep disturbances [14]. National surveys indicate that over 50% of middle-aged to older adults use daily dietary supplements, particularly herbal products, and such use is estimated to increase among older adults in the United States over the next few decades [15–17]. Recent analyses of the 2002 National Health Interview Survey Data revealed that a large number of adults use herbal preparations (including valerian) and behavioral strategies to self-manage their insomnia and believe these strategies are very effective [18,19]. Despite evidence of widespread interest, research evidence is lacking on the efficacy of many CAM therapies, especially in older adults.

Valerian, derived from the root of the plant *Valeriana officinalis*, is an herbal supplement that is commonly used as a sleep aid and has been recommended as potentially useful for older adults [20]. Valerian contains a variety of chemical compounds including valerenic acid and derivatives (hydroxyvalerenic acid, acetoxcyvalerenic acid, and valerenal) [21] that may act synergistically to exert sedative effects. Similar to conventional sedative-hypnotic medications, constituents of valerian are believed to activate gamma-aminobutyric acid (GABA) receptors that are involved in sleep promotion and regulation. Constituents of valerian have also been shown through *in vitro* and animal studies to affect other receptors – adenosine and glutamine (an amino acid that is metabolized into GABA) – involved in regulation of sleep and waking [22–26].

Few studies have tested the effects of valerian in older adults. In an early double-blind, placebo-controlled randomized clinical trial (RCT) of 150 German elder home residents, a greater proportion of those given valerian for 30 days (compared to placebo) had reduced self-reported sleep disturbance (significance not reported) [27]. In another double-blind, placebo-controlled RCT of 78 elder home residents with sleep disturbance, a significantly greater proportion of individuals given valerian for 14 days compared to placebo self-reported reduced sleep latency and improved sleep maintenance [28]. In an 8-day double-blind, placebo-controlled RCT of 14 older women with insomnia, no significant differences were found between the valerian ($n = 8$) and placebo ($n = 6$) groups on self-report or PSG sleep onset or maintenance outcomes [29]. These studies tested preparations of *V. officinalis* that were extracted and concentrated using either water alone [28,29] or a preparation with a high concentration of valepotriate constituents [27]. Only one double-blind crossover RCT tested an ethanolic valerian extract (similar to the product used in the current study) in 16 older adults [30]. This study reported no significant differences among a single dose of placebo, 300 mg valerian, or 600 mg valerian on self-report, PSG sleep onset or maintenance outcomes. Overall, this mixed evidence is far from conclusive in supporting efficacy for valerian to improve sleep.

The aim of this double-blind, placebo-controlled crossover RCT was to determine whether a single dose or 2 weeks of nightly valerian treatment would improve sleep outcomes in older women reporting insomnia. We hypothesized that valerian administration (compared to placebo) would improve both self-report and PSG measures of sleep. In addition, we used continuous daily actigraphy throughout the trial to ascertain the effect of valerian on sleep/wake patterns when participants were at home. The primary study outcome measures were wake after sleep onset (WASO) and sleep efficiency (SE) from self-report, PSG, and actigraphy; sleep latency (SL) from self-report and PSG; and overall sleep quality (SQ) from self-report only.

2. Methods

2.1. Sample and screening

The study was approved by the University of Washington Human Subjects Institutional Review Board. Subject recruitment and data collection occurred between November 2004 and February 2006. A sample of older women with self-reported symptoms of insomnia was recruited from the greater Seattle community. Inclusion criteria were (a) generally healthy women 55–80 years of age, at least 5 years past menopause, and not taking hormone replacement therapy; (b) no medical or psychiatric condition that would cause sleep disturbance; (c) a score of $\geqslant 5$ on the Pittsburgh Sleep Quality Index (PSQI), indicating overall disturbed sleep [31,32]; (d) a score of <22 on the Insomnia Severity Index (ISI), indicating no severe insomnia [33]; (e) evidence from a 2 week diary of $\geqslant 30$ min sleep onset latency or wake after sleep onset for at least 3 nights/week; and (f) a complaint of daytime sleepiness or fatigue. These eligibility criteria for insomnia are generally consistent with DSM-IV and research criteria for insomnia (e.g., sleep log based prolonged sleep latency and/or WASO for at least 3 nights/week and a daytime consequence) [34,35]; although no specific duration of symptoms was required. Exclusion criteria were (a) sleep

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disorders (e.g., sleep apnea, restless legs syndrome, periodic limb movements (PLMs) in sleep) or severe self-reported insomnia; (b) shift work or unstable sleep schedule; (c) trans-meridian travel ($\geqslant$3 time zones) within the past 4 weeks; (d) body mass index $\geqslant$32 kg/m^2 or $<$18 kg/m^2; (e) significant current major illness (e.g., cancer); (f) abnormal TSH; (g) cognitive impairment (a score of $<$26 on the Mini Mental Status Exam, MMSE) [36]; (h) current major psychiatric disease (Patient Health Questionnaire, PHQ) [37]; (i) significant perceived current life stress (Life Events Stress Scale, LES) [38]; (j) current use of sleep medications; (k) use of tobacco within 6 months; (l) excessive use of alcohol ($\geqslant$3 drinks/day or $\geqslant$6 drinks/week); and (m) caffeine use ($\geqslant$3 caffeinated drinks/day). Potential participants ($n = 71$) were screened using a three-phase procedure used in previous studies from our group [39].

2.1.1. Screening phase 1, phone interview

After providing oral consent, participants were screened by telephone for major inclusion criteria, e.g., age, menopause status, insomnia symptoms, previous sleep disorder diagnosis, except insomnia, and other major study criteria. If potential participants met this level of screening, a 2-week sleep log and screening questionnaires (MMSE, PHQ, LES) were mailed to them with instructions to complete and return them in an envelope provided.

2.1.2. Screening phase 2, clinical assessment

Participants who met study criteria from phase 1 screening and for insomnia based on the sleep logs were scheduled for a clinical interview with the research nurse coordinator. Participants provided written informed consent and completed a clinical interview that included review of the sleep logs and questionnaires, a physical examination, standard laboratory tests (e.g., TSH, general metabolic panel, lipids), and review of medications, alcohol and caffeine consumption.

2.1.3. Screening phase 3: sleep laboratory

Once participants ($n = 18$) passed the first two phases of screening, they were scheduled for a screening sleep study at the School of Nursing Sleep Research Laboratory. In addition to the standard head and face electrodes used for scoring sleep stages [40], pretibial electrodes were placed for recording leg movements, nasal pressure cannula were placed to measure airflow (Pro-Tech Services, Inc., Mukilteo, WA), inductance plethysmography bands were placed around the chest and abdomen to record respiratory effort (XactTrace, EMBLA, Broomfield, CO), a pulse oximeter was placed on an index finger (Nonin XPod, Nonin Med, Plymouth, MN), and a small microphone was placed on the throat lateral to the trachea to measure snoring (Pro-Tech Services, Inc., Mukilteo, WA). Two women were excluded from further participation for an apnea–hypopnea index of $\geqslant$15 events/h, but none showed evidence of periodic limb movement disorder ($>$10 PLM-associated arousals/h). For participants meeting full inclusion criteria, the screening night served as a time of adaptation to the sleep laboratory setting (Night 1 of the study).

2.2. Sleep recording procedures

Participants were scheduled to arrive in the Sleep Research Laboratory approximately 2 h before their scheduled bedtime and slept in temperature-controlled, sound-attenuated rooms. Bedtimes and risetimes for each participant were determined from their individual 2-week sleep log and remained the same throughout all laboratory nights. Participants carried out their usual daytime activities and were asked to maintain their assigned bedtimes and risetimes at home and to avoid napping if they routinely did not nap. No instructions were given to participants to not nap if they routinely napped. Participants were permitted to have caffeine in usual amounts in the morning but were asked to abstain from consuming caffeine or alcohol in the afternoon and evening prior to the sleep recording nights. In addition to scalp electrodes placed for PSG recording, actigraphs were placed on the non-dominant wrist. Participants were instructed in how to use the event marker on the actigraph and given a small battery operated clock to use for recording bedtimes and risetimes in their sleep logs.

The laboratory protocol for this study was similar to that of a typical drug trial for the evaluation of a sedative or hypnotic medication on sleep using a within-subject crossover design. The study flow is shown in Fig. 1. After the baseline assessment (Night 2), participants were randomly assigned to a treatment group (valerian or placebo) and began treatment phase 1. On Night 3 in the laboratory, participants took their assigned capsules 30 min before bedtime and recordings from this night were used to evaluate effects of a single dose of valerian or placebo on sleep. The next morning, before participants went home, they were instructed to take the capsules 30 min before bedtime, to keep a daily sleep log, and to wear the actigraph over each 24-h period for the next 2 weeks (Nights 4–14). Participants returned to the laboratory for two consecutive nights to evaluate effects of 2 weeks of nightly valerian or placebo dosing on sleep (Nights 15 and 16). After a 13-day washout period (Nights 17–29), participants returned to the laboratory for two consecutive nights (Nights 30 and 31) and began treatment phase 2. After a re-adaptation night (Night 30), participants were crossed over to receive either valerian or placebo (Night 31). Participants were sent home and continued to take valerian or placebo nightly, to complete a daily sleep log, and to wear an actigraph for 2 weeks (Nights 32–42). They returned to the laboratory for two consecutive nights (Nights 43 and 44). Laboratory data

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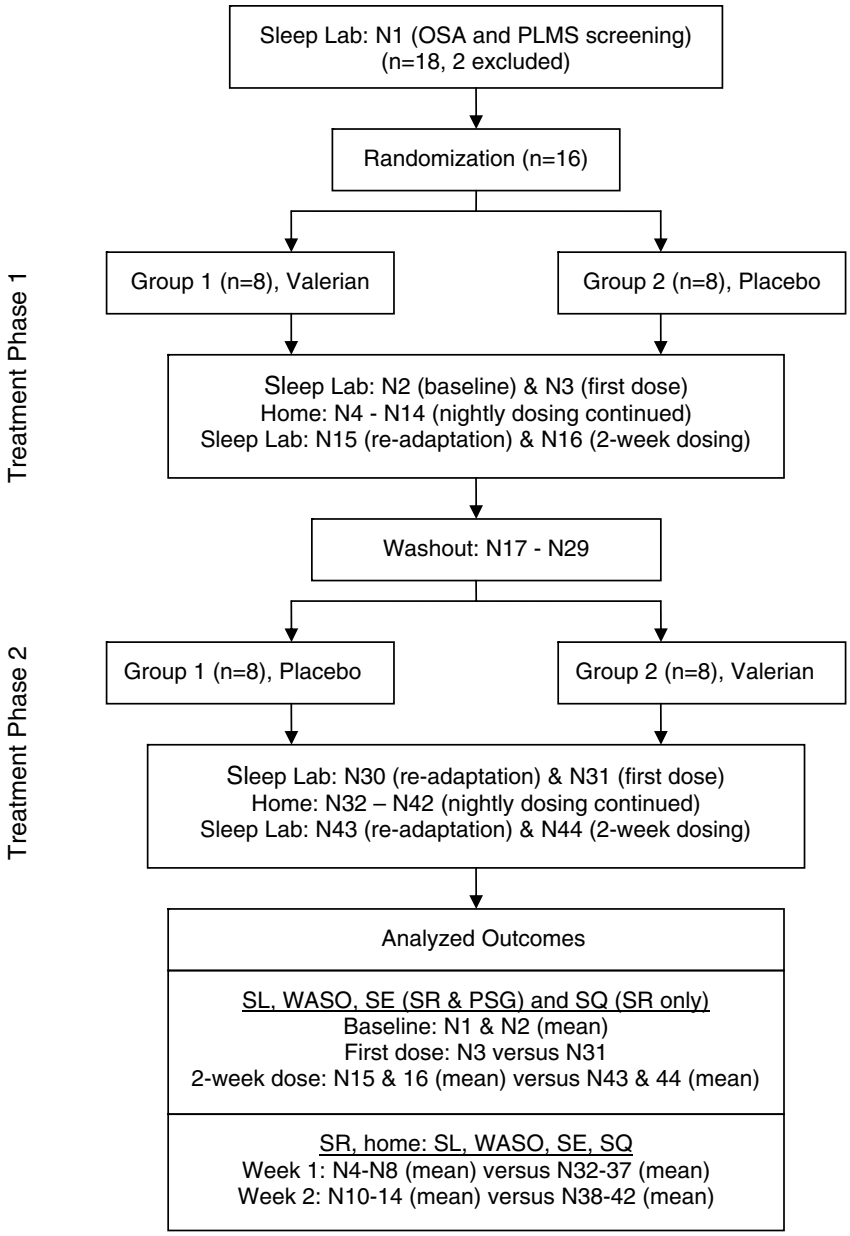

Fig. 1. Study flow diagram. Night 1 for screening also served as the pre-baseline adaptation night in the sleep lab. Night 30 (re-adaptation at the beginning of phase 2) was not included in statistical analyses. Abbreviations: N, night; OSA, obstructive sleep apnea; PLMS, periodic limb movements in sleep; SR, self-report; PSG, polysomnography; SL, sleep latency; WASO, wake after sleep onset; SE, sleep efficiency; SQ, sleep quality.

from Nights 3 and 31 were used to evaluate effects of a single dose of valerian or placebo and Nights 15, 16, 43 and 44 were used to evaluate effects of 2 weeks of nightly valerian/placebo dosing.

2.3. Randomization

The University of Washington Investigational Drug Service (IDS) randomly assigned participants to either valerian or placebo. The IDS assigned the valerian and placebo bottles code numbers and kept record of group assignments. The research nurse and participants remained blind to group assignment until each individual participant completed the trial. At a follow-up visit, participants were asked which treatment they believed they received in that study phase and were informed of the actual treatment order. All laboratory staff and investigators were blinded to treatment order until the statistical analyses were completed.

2.4. Intervention

The herbal supplement used in this study was *V. officinalis L.* root (Valerianaceae, valerian root). The prod-

uct used was Nature's Resource® valerian root extract 100 mg softgels (Pharmavite, LLC., San Fernando, CA), which were standardized by HPLC to contain 0.8% valerenic acid per 100 mg extract. Pharmavite provided a certificate of analysis confirming product standardization and the absence of microbial contaminants. Both the valerian softgels and the placebo were enclosed in opaque capsules (size 00, blue 4; Gallipot, Inc., St. Paul, MN) for identical appearance. The placebo was formulated by UW Investigational Drug Services and filled with 600 mg lactose (Spectrum Chemicals and Laboratory Products, San Pedro, CA). Only one lot of both valerian and placebo was used in the study. To "odorize" the placebo for masking purposes, the placebo capsules were stored in proximity to (but not touching) a particularly odiferous capsule formulation of valerian (Nature's Way Products, Inc., Springville, UT) for a few days. The distinctive odor of valerian was subsequently retained by the placebo capsules. Subjects took 300 mg (3 softgels, 100 mg each) of valerian 30 min before their scheduled bedtime.

2.5. Sleep laboratory assessments

2.5.1. Self-reported sleep: Morning Sleep Questionnaire (MSQ)

To assess self-reported sleep in the laboratory, the Morning Sleep Questionnaire (MSQ) was administered upon the participant's awakening. Participants reported their bedtime, rise time, and estimates of SL and WASO. Participants rated their sleep quality (SQ, 1 = terrible to 9 = great). Time in bed (TIB, time between bedtime and awakening), total sleep time (TST = time in bed minus WASO and SL) and SE (TST/TIB * 100) were calculated.

2.5.2. Polysomnographic recordings and sleep stage scoring

Electrodes for recording the electroencephalography (EEG), electrooculogram (EOG), and electromyogram (EMG) were placed according to standard criteria [40]. Central (C3 and C4) and occipital (O1 and O2) leads were referenced to a linked A1–A2 lead connected to a 10 kΩ resistor. Signals from these leads were sampled at 200 Hz and amplified, recorded, and digitized by the EMBLA Somnologica 3.1.2 data acquisition recording system (EMBLA). Prior to each recording session, the EEG, EOG, and EMG signals were calibrated. The EMBLA Somnologica 3.1.2 software was used to score sleep and wake stages in 30 s epochs by an experienced sleep technologist according to standard criteria [40]. Sleep variables were computed with a locally developed software program and included non-rapid eye movement (NREM) Stages 1–4 and REM as percentages of sleep period time, as well as the primary study outcomes of SL (time from lights out to first epoch of stage 2 sleep), WASO, and SE (TST/TIB * 100).

2.6. Home-based sleep assessment

2.6.1. Self-reported sleep: sleep logs

Participants completed a 2-week sleep log during screening and throughout each study phase. The logs included bedtime, rise time, SL, WASO, and SQ ratings (1 = terrible to 9 = great). TIB, TST (TIB-WASO-SL), and SE (TST/TIB * 100) were calculated.

2.6.2. Wrist actigraphy

Actiwatch®-64 actigraphs (Mini Mitter Company, Inc.) were used to obtain an objective sleep assessment when participants were at home. These devices are piezo-electric accelerometers about the size of a watch and are worn on the wrist. The Actiwatch was set to record activity counts in 30-s epochs. Actiwatch activity counts represent both the occurrence and magnitude of arm movements. Movement data were sampled at a rate of 32 Hz. Data were analyzed using Actiware-Sleep version 3.4 (Mini Mitter Company, Inc.). Bedtime and rise-time were entered in the software based on a participant's sleep log entries. Each epoch was scored as sleep or wake using the automatic algorithm in the software (set to a medium sensitivity threshold). Sleep onset and offset were scored as the first/last 10 min (20 epochs) of the sleep record scored as sleep with $\leqslant 1$ epoch scored as wake. Outcomes included SE (TST/TIB * 100) and WASO (time scored as wake between sleep onset and sleep offset).

2.7. Data analysis

Data were analyzed using SPSS 14.0. Descriptive statistics, including measures of central tendency and variance, were calculated for each of the study's main outcomes. Non-parametric tests were used due to the small sample size. Paired tests (Wilcoxon signed-ranks tests) were used for all analyses because of the crossover design. Because no significant differences were found between the first and second nights in the laboratory (adaptation and baseline) or between the two consecutive nights of 2-week nightly dosing, data from these nights were averaged. No treatment-order effects or carry-over effects were found by pairwise tests, such that the valerian and placebo data were analyzed without specific attention to treatment order. The primary analyses compared self-report and PSG sleep outcomes between valerian and placebo for single dose and after 2 weeks of nightly dosing. Additional analyses compared each treatment to the baseline self-report and PSG sleep outcomes. For analyzing actigraphy recordings at home, the average of the first five home nights was compared to the average of the last five home nights in each study treatment phase. An α of 0.05 was set for all tests.

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3. Results

3.1. Sample characteristics

Demographics and clinical characteristics derived from screening questionnaires for the sample are presented in Table 1. The participants were mostly well-educated and married. All but one of the participants was White. Several participants had minor comorbidities (e.g., arthritis), but none had major illnesses, and five reported that they had hot flashes in their daily sleep logs. Baseline PSG sleep characteristics are listed in Table 2.

3.2. Self-report sleep outcomes

None of the mean self-report sleep outcomes (SL, WASO, SE, and overall SQ) in the laboratory differed significantly between valerian and placebo or were significantly improved compared to baseline after a single dose or after 2 weeks of nightly dosing (Table 3). To explore whether effects of valerian were evident in the home setting that were not observed in the laboratory, mean self-report sleep outcomes were analyzed from daily sleep logs. There were no significant differences between valerian and placebo on mean self-reported SL, WASO, SE or overall SQ during the first (mean of the first five home days) or second (mean of the last five home days before returning to the sleep laboratory) week. However, compared to baseline (mean of the last five days of screening sleep logs), mean self-reported SL was significantly shorter during the second treatment week, but decreased SL occurred both with valerian (-9.8 min, $Z = -1.97$, $p = .05$) and placebo (-12.0 min, $Z = -.2.30$, $p = .02$). Mean self-reported WASO, SE, and SQ from the home sleep logs did not differ significantly from baseline with either treatment.

Table 1
Demographic and clinical characteristics

Demographics	
Age (years, mean ± SD)	69.4 ± 8.1
Ethnicity (*n*)	
Asian or Pacific Islander	1
White	15
Marital status (*n*)	
Married/partnered	11
Divorced/separated	5
Income, mean range	25,000–29,999
Education (*n*)	
High school	3
College	10
Graduate school	3
Employment (*n*)	
Retired	11
Employed	4
Unemployed	1
Clinical characteristics (mean ± SD)	
Mini Mental Status	29.1 ± 1.0
Geriatric Depression Scale	6.2 ± 4.8
Pittsburgh Sleep Quality Index	8.8 ± 2.3
Insomnia Severity Index	11.1 ± 3.9
Life Events Stress	
Number of events	3.4 ± 2.6
Severity	7.9 ± 7.7

Table 2
Baseline polysomnography

Sleep variables[a]	Mean (SD)
Time in bed (min)	467.7 (51.6)
Sleep period time (min)	442.3 (61.6)
Total sleep time (min)	318.3 (65.8)
Sleep latency (min)	19.7 (21.5)
WASO (min)	121.8 (54.2)
Sleep efficiency (%TIB)	68.1 (12.2)
Stages (% of sleep period time)	
Wake	27.4 (11.5)
NREM 1	9.1 (4.3)
NREM 2	36.5 (10.3)
NREM 3 and 4 (SWS)	9.6 (7.6)
REM	17.1 (5.0)

[a] Baseline PSG-defined sleep variables outcomes represent the average of Nights 1 and 2 (screening and baseline) in the sleep laboratory.

3.3. Polysomnographic sleep outcomes

Mean PSG SL, WASO, and SE did not differ significantly between valerian and placebo after a single dose or after 2 weeks (see Table 4). In comparing each treatment to baseline in separate comparisons, WASO significantly increased ($+17.7 \pm 25.6$ min, $Z = -2.33$, $p = .02$) after 2 weeks of nightly valerian, but not after placebo ($+6.8 \pm 26.4$ min, NS). Although sleep architecture was not an outcome of the study, we found no differences in the percentage of time spent in any sleep stage (non-REM 1–4, REM) between valerian and placebo after a single dose or after 2 weeks (Wilcoxon signed-ranks, $p > .05$).

3.4. Actigraphic sleep outcomes

Actigraphic measures were obtained as an objective assessment of sleep at home during both phases of the trial. Actigraphy-based WASO and SE did not show significant differences between valerian and placebo during the first (average of the first five home days) or second (average of the last five home days) week at home (see Table 4). No baseline actigraphic sleep measures were obtained, and sleep latency was not specifically analyzed because it is generally underestimated by actigraphy in persons with insomnia [41,42].

3.5. Adverse events and side effects

No severe adverse events occurred, and no participants withdrew from the trial. Participants were given

Table 3
Self-reported sleep outcomes from laboratory and home nights[a]

	Sleep latency (min)	WASO (min)	Sleep efficiency (%)	Sleep quality (1–9)
Sleep laboratory nights[b]				
Baseline	14.3 (8.5)	17.5 (16.4)	93.4 (5.2)	6.1 (1.6)
Single night				
Valerian	14.8 (11.5)	28.3 (37.5)	93.6 (7.5)	6.0 (1.6)
Placebo	14.8 (9.9)	28.3 (30.5)	90.6 (9.5)	6.2 (1.3)
Two-weeks				
Valerian	24.7 (23.3)	32.0 (32.0)	88.9 (8.7)	5.9 (1.8)
Placebo	22.7 (22.0)	36.0 (45.6)	87.9 (12.7)	6.4 (1.4)
Home nights[b]				
Baseline	30.7 (24.3)	52.0 (41.3)	83.8 (10.3)	5.9 (1.3)
First week				
Valerian	23.3 (16.2)	47.2 (28.5)	85.9 (8.1)	5.9 (1.0)
Placebo	21.3 (12.6)	48.3 (32.3)	86.4 (7.2)	6.2 (0.9)
Second week				
Valerian	20.8 (21.8)	43.4 (30.1)	87.8 (8.6)	6.5(0.9)
Placebo	18.6 (11.8)	55.9 (48.6)	85.3 (11.0)	6.4 (0.9)

Data are presented as mean (standard deviation). Wake after sleep onset = WASO.

[a] Wilcoxon signed-ranks, two-sided, were used to evaluate the primary outcome valerian versus placebo, all $p > .05$.

[b] Sleep laboratory nights: baseline = mean of Night 1 and Night 2, single night = Night 3/31 only, 2-week dose = mean of the last two dosing nights (Nights 15 and 16/Nights 43 and 44). Home nights: baseline = mean of last five screening nights, first week = mean of the first five home nights (Nights 4–8/Nights 32–36), and second week = mean of the last five home nights (Nights 10–14/Nights 38–42).

Table 4
Polysomnographic and actigraphic sleep outcomes[a]

	Sleep latency (min)	WASO (min)	Sleep efficiency (%)
Polysomnography[b]			
Baseline	19.7 (21.5)	121.8 (54.2)	68.1 (12.2)
Single night			
Valerian	12.6 (6.1)	122.6 (66.4)	67.4 (15.2)
Placebo	14.4 (10.9)	139.9 (65.2)	66.5 (15.8)
Two-weeks			
Valerian	20.3 (15.8)	139.5 (60.4)	65.7 (13.8)
Placebo	15.6 (9.8)	128.6 (61.0)	68.1 (11.1)
Actigraphy[b]			
First week			
Valerian	NA	47.1 (16.8)	83.9 (6.7)
Placebo		47.9 (15.7)	84.0 (5.7)
Second week			
Valerian	NA	53.8 (24.3)	83.4 (5.6)
Placebo		48.6 (22.4)	84.4 (4.6)

[a] Wilcoxon signed-ranks, two-sided, were used to evaluate the primary outcome valerian versus placebo, all $p > .05$.

[b] Polysomnography: baseline = mean of Night 1 and Night 2, single night = Night 3/31 only, 2-week dose = mean of the last two dosing nights (Nights 15 and 16/Nights 43 and 44). Actigraphy: baseline = mean of last five screening nights, first week = mean of the first five home = nights (Nights 4–8/Nights 32–36), and second week = mean of the last five home nights (Nights 10–14/Nights 38–42).

a list of 25 potential symptoms (with spaces to write in additional symptoms) in their daily sleep logs, such that the occurrence of any symptom was reported daily throughout each treatment phase. No participants filled in symptoms other than those listed. Participants reported a mean of 6.8 ± 4.0 symptoms while taking valerian and 6.4 ± 5.2 while taking placebo. The number of days during which symptoms were recorded did not significantly differ between valerian and placebo treatment phases (Wilcoxon signed-ranks, $p > .05$).

3.6. Treatment allocation concealment

To assess allocation concealment, participants were asked to state which intervention they believed they received. Half of the participants correctly guessed the treatment given during phase 1 (seven participants) and phase 2 (eight participants). None of the participants reported noticing a difference between the odor of the masked valerian and placebo capsules.

4. Discussion

This study tested the effects of valerian on sleep in older women with insomnia in a manner consistent with typical self-administration of valerian in the U.S. Both after a single dose and 2-week nightly dosing of valerian, none of the self-report, PSG, or actigraphic sleep outcomes showed improvement of sleep compared to placebo. Self-reported sleep latency in the home sleep logs improved equally with both treatments indicating a placebo effect, but this could also reflect a regression to the mean. Compared to baseline PSG, greater nocturnal wakefulness was observed after 2 weeks of valerian than was observed after 2 weeks of placebo. One case in the literature has reported stimulation, not sedation, with valerian [43], and this is recognized by herbalists as a potential paradoxical effect of valerian [44].

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Previous studies of valerian have been generally inconclusive. Although participants reported improved sleep with valerian in two studies of older persons, one study did not use statistical tests to compare the valerian and placebo groups [27], and the other study tested the proportion reporting improvement rather than actual ratings of sleep quantity and quality [28]. Two studies of older persons reported no significant differences in self-report or PSG sleep outcomes [29,30]. A recent RCT in persons with arthritis using a higher dose (600 mg) of the same valerian preparation used in this trial also reported no significant improvements in either self-report or actigraphic sleep outcomes, but PSG outcomes were not assessed [45].

The current study was initiated before recent evidence has emerged that shows valerian is a less promising therapy than suggested by earlier research. The most recent studies with rigorous designs reported no significant benefits on sleep outcomes from valerian treatment [46–50] and a similar conclusion was made by an expert panel at the recent National Institutes of Health State of the Science Conference on insomnia [51]. In addition, a recent systematic review of both the English and German literature conducted by several authors of the current study concluded that the body of evidence on valerian and valerian combination preparations does not support the efficacy of the herb as a sleep aid [52]. However, a recent meta-analysis found improved self-reported sleep quality to be a dichotomous (improved versus not improved) variable when comparing valerian to placebo [53]. This review also reported inconsistent effects of valerian on self-reported sleep latency and PSG sleep outcomes, consistent with the other studies. Although some of the reviewed studies reported improvement with valerian administration over time [27,29,54], few studies found significant improvement in any of the sleep outcomes when valerian was compared to placebo. Despite evidence from *in vitro* studies of valerian effects on neuropeptide systems involved in sleep mechanisms [22,24], dried valerian extract has not shown clinical efficacy as a sleep aid.

In the current sample, some inconsistencies between the self-report, PSG and actigraphy sleep outcomes were noted. Compared to self-report outcomes in the laboratory, self-reports in the daily logs showed longer sleep latencies, greater amounts of nocturnal wakefulness, and lower sleep efficiencies, but curiously similar overall sleep quality. Sleep logs and actigraphic measures at home showed similar amounts of nocturnal wakefulness (~40–60 min) and sleep efficiency (~85%). However, an opposite pattern was observed in the laboratory. PSG-derived WASO was increased and SE was reduced, compared to self-report outcomes (both in the laboratory and at home) and to actigraphy at home. The discrepancy between actigraphy and PSG may be related to an underestimation of wakefulness by actigraphy [41,42]. The discrepancy between self-report and PSG may represent some degree of acclimation to disrupted sleep among the older women. Previous studies have reported similar findings indicating that some older women underestimate the severity of their sleep disturbances as recorded by PSG [3,55]. In a previous study, Vitiello and colleagues reported moderately disrupted sleep on PSG recordings in older healthy women who did not complain of sleep problems, but this pattern was not observed in healthy older men [3]. More research is needed to explore moderators between objective measures and perceptions of sleep, especially in older women and men.

On all three types of sleep measures (self-report, PSG, and actigraphy), women showed more problems with sleep maintenance than sleep onset. These observations are consistent with findings from a recent meta-analysis that showed greater problems with sleep maintenance with aging [4]. Valerian may not be a good choice for treating sleep maintenance insomnia given the following findings from a recent pharmacokinetic study: valerenic acid (a pharmacologically active marker compound for valerian) was increased in serum within an hour, but no detectable levels were observed 4 h after administration [56]. This pharmacokinetic pattern avoids residual sedation in the morning and suggests that, if valerian was beneficial as a sleep aid, effects would most likely facilitate sleep onset. However, the results from our recent extensive review of the literature did not find evidence to support the efficacy of valerian to treat sleep onset insomnia. Our observation of increased nocturnal wakefulness on PSG after two weeks of valerian provides evidence that valerian has the potential to increase problems with sleep maintenance in older women.

We had hoped that the results of this phase 2 clinical trial would provide preliminary data from a well-defined sample of older women with insomnia for a larger study of valerian effects on sleep. Had valerian shown similar improvement in sleep as had been reported in a previous clinical trial comparing a hypnotic to placebo in older adults with insomnia [57], a sample size of 15 would have provided 81% power to detect a 10% increase in self-reported sleep efficiency (95% confidence interval 3.68–16.32) and a 7% increase in PSG sleep efficiency (95% confidence interval 2.17–11.83). Although the findings from this study are limited by the stringent eligibility criteria and small sample size, the *lack* of a valerian effect to improve sleep outcomes was clear; a finding consistent with evidence from several other recently published rigorous trials of valerian. Any future research on valerian could be focused on the potential efficacy of different valerian preparation types, such as tinctures, rather than the typical testing of over-the-counter products. Future research on herbal therapies for insomnia could also report, and possibly limit, the

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sample to specific types of insomnia symptoms (e.g., sleep onset problems versus sleep maintenance problems). Such specificity would clarify whether or not a product is differentially efficacious depending on the symptom pattern.

In summary, a phase 2 randomized crossover trial both of one day and 2-week nightly valerian treatment did not improve self-reports, PSG, or actigraphic sleep outcomes in older women with insomnia. No improvement occurred in PSG sleep outcomes with either valerian or placebo; conversely, nocturnal wakefulness increased with valerian. Thus, we do not recommend use of valerian for sleep disturbance in older women with insomnia.

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