ORIGINAL RESEARCH

DOES VALERIAN IMPROVE SLEEPINESS AND SYMPTOM SEVERITY IN PEOPLE WITH RESTLESS LEGS SYNDROME?

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Objective • To compare the effects of 800 mg of valerian with a placebo on sleep quality and symptom severity in people with restless legs syndrome (RLS).

Methods • A prospective, triple-blinded, randomized, placebo-controlled, parallel design was used to compare the efficacy of valerian with placebo on sleep quality and symptom severity in patients with RLS. Thirty-seven participants were randomly assigned to receive 800 mg of valerian or placebo for 8 weeks. The primary outcome of sleep was sleep quality with secondary outcomes including sleepiness and RLS symptom severity.

Results • Data were collected at baseline and 8 weeks comparing use of valerian and placebo on sleep disturbances (Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale) and severity of RLS symptoms (International RLS Symptom Severity Scale) from 37 participants aged 36 to 65 years. Both groups reported improvement in RLS symptom severity and sleep. In a nested analysis comparing sleepy vs nonsleepy participants who received 800 mg of valerian (n=17), significant differences before and after treatment were found in sleepiness (P=.01) and RLS symptoms (P=.02). A strong positive association between changes in sleepiness and RLS symptom severity was found (P=.006).

Conclusions • The results of this study suggest that the use of 800 mg of valerian for 8 weeks improves symptoms of RLS and decreases daytime sleepiness in patients that report an Epworth Sleepiness Scale (ESS) score of 10 or greater. Valerian may be an alternative treatment for the symptom management of RLS with positive health outcomes and improved quality of life. (*Altern Ther Health Med*. 2009;15(2):22-28.)

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Restless legs syndrome (RLS) is a common sleep disorder affecting up to 11% of the population.[1,2] The manifestations of RLS are quite distressing to the patient and include irritating feelings in the legs at rest or bedtime that are relieved only with movement. These symptoms affect sleep onset and quality of sleep, often resulting in depression, anxiety, and poor quality of life. Patients often report that symptoms interfere with their ability to work as well as with activities such as attending plays, concerts, and movies or any other activity that requires sitting for long periods of time. Symptom severity and frequency worsen with age,[3] sometimes causing patients to consider suicide. Studies also have shown that patients with RLS have a higher than normal incidence of anxiety and depression,[4-6] with outcomes affecting quality of life.

Although some patients can be treated successfully using pharmacological agents, other patients get little relief of their symptoms or find that pharmacological treatment (dopaminergics, benzodiazepines, opioids, and anticonvulsants) becomes less effective over time.[7] Problems with dopaminergics, the standard treatment for RLS, include augmentation and rebound of symptoms. When traditional pharmacological measures prove unsatisfactory, patients often turn to complementary and alternative medicine (CAM)—up to 67% of patients with RLS use CAM regularly to relieve symptoms.[8] Valerian is a plant-based product that is used to improve sleep because of its natural effects on relaxation.

The use of valerian, a botanical preparation with a benzodiazepine effect, can be an option for those with RLS who are willing to use an alternative to pharmaceutical drug treatment. Valerian, the common name of the herb *Valeriana officinalis*, is a plant with well-known medicinal properties[9-11] that has been used for centuries as a sleep aid, sedative, and antispasmodic. Valerian is considered a safe herb and has been used specifically for insomnia.[12] It is associated with a reduction in REM sleep during the first part of the night and an increase during the latter stages of sleep.[9] It also may improve sleep latency and decrease night awakenings.[10] Valerian has been indicated for sleep problems related to anxiety or restlessness. It has been shown to increase activity in gamma-aminobutyric acid (GABA) receptors that are involved in regulating normal sleep and has an effect similar to

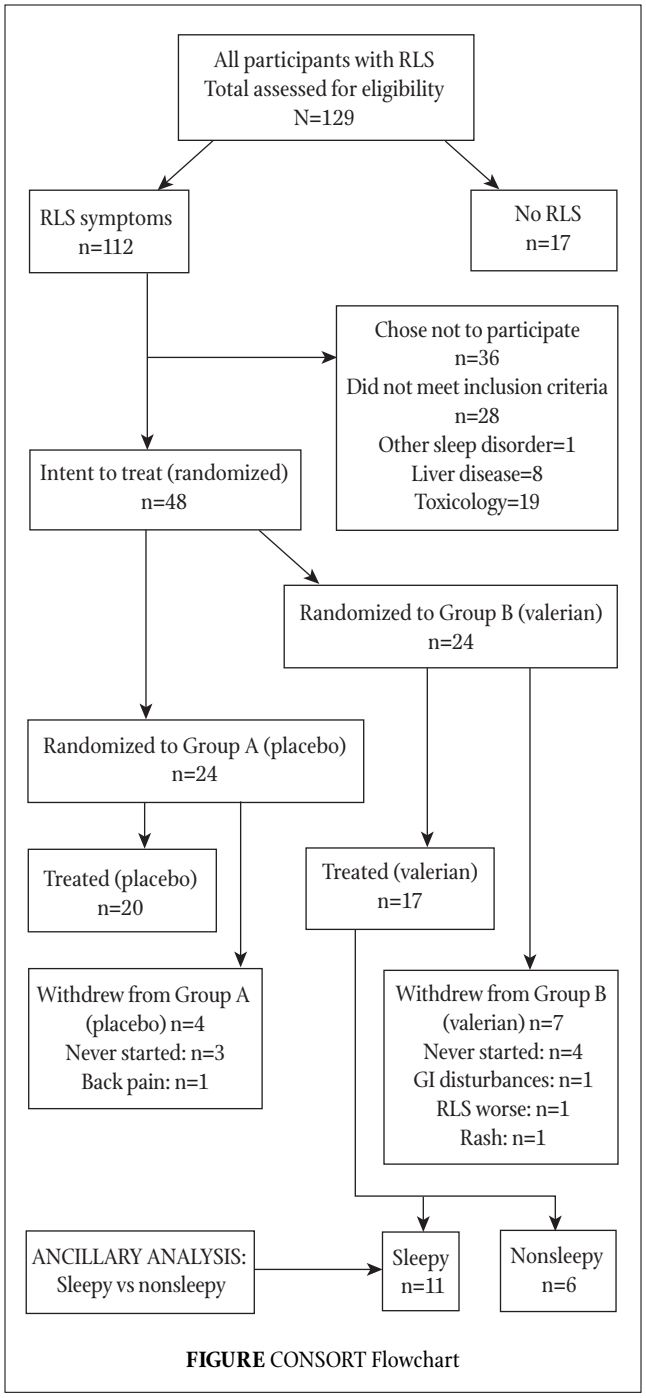

FIGURE CONSORT Flowchart

the benzodiazepines, which induce sleepiness by binding with GABA receptors.[9,11,13] Benzodiazepines are used to treat RLS but can cause daytime sleepiness and cognitive impairments, especially in the elderly. Other disadvantages of benzodiazepines include hangover effects, drug tolerance, rebound insomnia after withdrawal, and the risk of addiction.[9] The use of valerian may be preferred over benzodiazepines because it has no recognized negative side effects such as daytime sleepiness or cognitive impairments.

The purpose of this study was to compare the effects of valerian with those of placebo on sleep and RLS symptom severity. This is the first systematic trial evaluation of an herbal product as a treatment option for sleep in people with RLS. To improve the quality of reporting randomized clinical trials using herbs, the guidelines of the CONSORT Statement for Herbal Intervention were followed.[14-16]

METHODS

This exploratory pilot study is a prospective, placebo controlled, triple-blind, randomized, repeated measures study to compare the effectiveness of valerian with placebo on improving sleep and symptom severity in people with RLS. The experimental group received 800 mg of valerian 60 minutes before bedtime every night, and the control group received a placebo tablet identical in smell and sight, also 60 minutes before bedtime each night. Data were collected at baseline and 8 weeks. Forty-eight participants were randomized to each group with intent to treat (Figure). To identify people diagnosed with RLS, participants were recruited from the University of Pennsylvania Sleep Centers and RLS support groups. Inclusion and exclusion criteria appear in Table 1.

TABLE 1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Met diagnostic criteria based on the International RLS Study Group Criteria including akathisia brought on by rest, relieved with moving or walking, and worsening at night or in the evening	1. Positive toxicology report, liver function profile abnormal, and 3 *yes* answers on CAGE 2. Participation in a clinical study with an investigation drug within 3 months
2. At least 21 years old	3. Current use of vitamins or minerals beyond the recommended RDA requirements
3. Not satisfied with current treatment outcomes	4. Current use of any herbs or natural products
4. Willing to use valerian as treatment with possibility of being in control group	5. Current use of benzodiazepines or barbiturates
5. Have symptoms of RLS 3 nights a week or more	6. Another sleep disorder other than RLS
6. Commitment to treatment fidelity	7. Use of valerian within 120 days of baseline visit
	8. History of liver disease including cirrhosis, alcoholism, and hepatitis
	9. Pregnant, nursing, or intending to become pregnant in 3 months

Intervention

Herbal Medicinal Product Name

The manufacturer of the valerian was Pharmavite, LLC, distributor of Nature Made Nutritional Products, Mission Hills, California. Pharmavite provided 400-mg capsules of valerian (code A167), *Valeriana officinalis* of the botanical family *Valerianaceae*. The total valerenic acid, the active constituent, was .58 mg per capsule. The only excipient used in the product was food-grade microcrystalline cellulose. The hard shell was made of gelatin, glycerin, and water.

Characteristics of the Herbal Product

The dry root was used in the product used in the study. No extraction solvent was used. The raw material vendor (#502066) authenticated the raw material using thin layer chromatography (TLC), fourier transformer infrared spectroscopy (FTIR), and high-performance liquid chromatography (HPLC). No voucher specimen was used. Retainers are held by contract manufacturer and Pharmavite, LLC, Inc.

Dosage, Regimen, and Quantitative Description

Based on the pharmacodynamics of valerian (*Valeriana officianalis*), doses can range from 400 mg to 1200 mg to achieve sedative effects, with some doses as high as 1600 mg used in studies. After a review of the literature examining evidenced-based research, the decision was made to use 800 mg of valerian for 8 weeks.

In the few pharmacokinetics studies that exist, maximum serum concentration of valerenic acid occurs up to 2 hours after ingestion, with valerenic acid serum concentration levels at 0.9 to 2.3 ng/mL. The concentration of valerian is measurable for at least 5 hours after the valerian dose. The elimination half-life (T[1/2]) for valerenic acid was 1.1±0.6 h. The area under the concentration time curve (AUC) as a measure of valerenic acid exposure was variable (4.80±2.96 µg/mL) and not correlated with the subject's age or weight.[17] In another study, area under the plasma concentration vs time curve was 471±183 vs 539±240 hx ng x mL(-1); half-life of elimination, 13.5±4.3 vs 12.2±5.6 h.[18] These studies confirm the reason that valerian does not contribute to residual morning sedation.

Qualitative Testing

Pharmavite, LLC, provided pharmaceutical grade–quality product using current good manufacturing practices set forth by the US Food and Drug Administration (FDA) for manufacturing products[19] and has passed the product testing of valerian by ConsumerLab.com, LLC (CL), the leading provider of independent test results with the CL Seal of Approval upon acceptance by the manufacturer of the CL Seal Use License Agreement. Pharmavite, LLC, provided a certificate of analysis on the valerian root including chemical limits, microbial limits (*E coli*, *S aureus*, salmonella, total viable count, yeast and molds), and physical limits (weight, fill weight, disintegration time in water). Valerian products were tested for their total valerenic acid content (specifically acetoxyvalerenic acid, hydroxyvalerenic acid, and valerenic acid) and valernal. The valerian passed the testing requirements, including (1) meeting all FDA requirements including proper plant name, part of the plant used, form of valerian used, and amount of valerian per tablet; (2) meeting all label claims for total valernic acid content; (3) acceptable levels of lead contamination in an RDA; (4) less than .3 parts per million of cadmium based on World Health Organization Quality Control Methods for Medicinal Plant Materials; and (5) recommended USP parameters for disintegration for vitamin supplements.

For standardization, the company provided all the pills from the same lot number: PD10250. The pharmacists at the Investigational Drug Service (IDS) at the University of Pennsylvania assisted with (1) repackaging valerian in tamper-sealed prescription vials with the number of doses needed for the 8 weeks; (2) labeling that complied with the Commonwealth of Pennsylvania Board of Pharmacy, including the participants' names, date dispensed, protocol instructions for use, investigator's name, and a 24-hour contact phone number; and (3) inventory accountability, including the maintenance of logs for all study medications compliant with Good Clinical Practice (GCP), tracking date, patient, lot numbers, and expiration dating.

Placebo/control Group

The pills were shipped to the IDS at the University of Pennsylvania. The valerian was encapsulated in capsules identical in color, taste, and size to the placebo (which consisted of lactose fillers). All participants were screened for allergies, including lactose intolerance. Valerian is authorized in the United States for the treatment of sleep problems, but because it has never been used in the treatment for sleep in RLS, FDA approval of it as an Investigational New Drug (IND) was required and maintained throughout the study.

This study protocol was approved by the FDA and the Institutional Review Board (IRB) and General Clinical Research Center at the University of Pennsylvania (GCRC). Written informed consent for each study participant was obtained.

Aims and Outcomes

There were 2 aims to the study. The primary aim was to examine the efficacy of 800 mg of valerian for 8 weeks on sleep quality using the Pittsburgh Sleep Quality Index (PSQI) and sleepiness using the Epworth Sleepiness Scale (ESS) in patients with RLS. The secondary aim was to investigate whether there was a decrease in RLS symptom severity after 8 weeks of valerian treatment. The primary outcome was sleep latency measured by the PSQI. Secondary outcomes measured were sleepiness and RLS symptom severity.

Sample Size

The study was powered to include 40 participants, 20 randomized to each group. Randomization would include an equal number of men and women in each group. Twenty participants per group were needed to detect the required moderate effect size of 0.9 assuming 80% power, alpha of 0.05, and using a Student's *t*-test.

Randomization

Sequence Allocation

All participants who met eligibility requirements were randomized by statistical analysis through the IDS to 1 of 2 treatment groups: (1) active treatment group receiving 800 mg of valerian or (2) placebo.

Allocation Concealment

Labels for each randomized code were generated and randomly assigned to each participant based on patient identification

kept in a lockbox by the pharmacist. Labels were placed on the tablet containers identifying placebo or valerian with the matching label placed in a random log by patient identification.

Implementation

Assignment of participants to treatment groups took place before capsules were distributed. The pharmacists retained the master randomization codes for the entire trial. A copy of the master of the randomization code was provided to the principal investigator (PI) before the study began. The code was not broken until all trial data were collected and accepted for data analysis.

Blinding

This study was blinded with respect to treatment to all members of the project team except the pharmacist performing the randomization and management of the data. All personnel who were in contact with the participants were trained on issues of blinding. All data entered by the research coordinator contained only participant identification numbers. There was no ability for bias to be introduced by scoring data. To document the success of the blinding procedures, the participant and the research assistant completed a short form asking them to identify which intervention group they believed the participant was assigned to. Unblinded personnel (pharmacists) were not involved in outcome assessment and had minimal contact with the PI and research coordinator. The blind was only to be broken in case of emergency. Authorization to break the blind was given to the PI. The participants were to be withdrawn from the study if unblinded. One participant (taking valerian) was unblinded due to development of a rash, an expected adverse event that was not serious and reversed itself on discontinuation of the valerian.

Statistical Analysis

All study variables were initially described overall and by treatment group using standard descriptive statistics. Outliers were identified and validated. Transformations to normality were applied where necessary. Baseline demographic characteristics were compared between the placebo and valerian groups to assess the adequacy of the randomization process using bivariate techniques. These included Fisher's exact or chi-square tests, Student's *t*-tests or Mann-Whitney *U* tests, or correlation coefficients, as appropriate. Treatment group differences in the outcomes were assessed cross-sectionally (at one time period) and by overall change (difference from baseline to 8 weeks) using linear regression. All models assessed the effect of the treatment group on the outcomes, adjusting for other confounders as suggested by bivariate analyses.

RESULTS

Baseline Data

A total of 48 subjects were randomized at baseline with intent to treat; 24 in the placebo group and 24 in the valerian group. Thirty-seven participants completed the study. The average participant in the study was an unmarried, 50-year-old, white

TABLE 2 Comparison of Baseline Demographic Characteristics by Treatment Group

Characteristic n (%)*, mean±SD	Sample (N=37)	Group: Placebo (n=20)	Group: Valerian (n=17)	*P* value†
Age (years)	49.5 ± 13.1	48.7 ± 13.1	50.3 ± 13.5	.728
Female	27 (75.0)	15 (78.9)	12 (70.6)	.706
Married/partnered	13 (35.1)	8 (40.0)	59 (29.4)	.731
Race				.732
White	25 (67.6)	14 (70.02)	11 (64.7)	
Other	12 (32.4)	6 (30.0)	6 (35.3)	
Employment status‡				.591
Full-time	14 (37.8)	9 (45.0)	5 (29.4)	
Part-time	6 (16.2)	1 (5.0)	5 (29.4)	
Retired	3 (8.1)	1 (5.0)	2 (11.8)	
Unemployed	11 (29.7)	8 (40.0)	3 (17.6)	
Disability	3 (8.0)	1 (5.0)	2 (11.8)	
Education				.969
≤ High school	11 (29.7)	6 (30.0)	5 (29.4)	
Some college	26 (70.3)	14 (70.0)	12 (70.6)	
Socioeconomic status§				.303
0-10 000	3 (8.82)	2 (11.8)	1 (5.9)	
10 000-20 000	7 (20.6)	1 (5.9)	6 (35.3)	
20 000-30 000	8 (23.5)	4 (23.5)	4 (23.5)	
30 000-40 000	6 (17.6)	3 (17.6)	3 (17.6)	
40 000-50 000	3 (8.8)	2 (11.8)	1 (5.9)	
>50 000	7 (20.5)	5 (29.4)	2 (11.8)	
Cups of coffee/day				.258
0	11 (30.6)	5 (26.3)	6 (35.3)	
1	6 (16.7)	5 (26.3)	1 (5.9)	
2+	19 (52.8)	9 (47.4)	10 (58.8)	
Other caffeinated drinks/day				.774
No	9 (25.7)	5 (27.8)	4 (23.5)	
Yes	26 (74.3)	13 (72.2)	13 (76.5)	
Hours exercise/week	5.1 ± 8.9	4.4 ± 4.8	5.8 ± 12.5	.656
Smoker	14 (40.0)	7 (35.0)	7 (46.7)	.511
Family history of RLS	16 (47.1)	8 (44.4)	8 (50.0)	.746

*Percentages based on number of subjects with data for each characteristic. †Compared via Student's *t*-test, Mann-Whitney *U* test, or Fisher's exact test, as appropriate. ‡Analyzed as working full-time or part-time vs not working. §Analyzed as annual income of $0 to $30 000 vs >$30 000.

female (Table 2). Approximately half the sample was employed either full-time or part-time. The majority of the sample drank at least 2 cups of coffee per day (52.8%), as well as other caffeinated drinks (74.3%). Sixteen (47.1%) subjects had a family history of RLS. The demographic makeup of the sample was not statistically different between the 2 treatment groups (Table 2). There were no significant differences in the disease severity of patients by treatment group at baseline (Table 3). Most subjects had severe (38.9%) or very severe (19.4%) RLS symptom severity scores on admission to the study, as inclusion criteria required symptoms of 3 times or more per week.

TABLE 3 Comparison of Outcome Measures at Baseline by Treatment Group*

Outcome n (%), mean±SD	Sample (N=37)	Group Placebo (n=20)	Group Valerian (n=17)	*P* value†
ESS	11.0 ± 5.7	10.4 ± 6.1	11.7 ± 5.4	.498
PSQI Component 1 - Subjective sleep quality	2.2 ± 0.6	2.1 ± 0.6	2.3 ± 0.7	.385
PSQI Component 2 - Sleep latency	2.2 ± 1.1	2.2 ± 1.0	2.2 ± 1.2	.709
PSQI Component 3 - Sleep duration	2.0 ± 1.1	1.9 ± 1.2	2.2 ± 1.0	.510
PSQI Component 4 - Habitual sleep efficiency	1.8 ± 1.2	1.8 ± 1.4	1.8 ± 1.1	.892
PSQI Component 5 - Sleep disturbance	1.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.6	.929
PSQI Component 6 - Sleep medications	1.1 ± 1.3	0.9 ± 1.2	1.4 ± 1.3	.270
PSQI Component 7 - Daytime dysfunction	1.6 ± 1.1	1.6 ± 1.1	1.7 ± 1.2	.832
Global PSQI	13.3 ± 4.5	12.4 ± 5.0	14.4 ± 3.7	.260
RLS Symptom Severity Rating Scale score	23.6 ± 7.0	24.0 ± 8.0	23.0 ± 5.9	.752
RLS Rating scale category‡				
Mild	1 (2.8)	0 (0.0)	1 (6.3)	
Moderate	14 (38.9)	9 (45.0)	5 (31.3)	
Severe	14 (38.9)	5 (25.0)	9 (56.3)	
Very severe	7 (19.4)	6 (30.0)	7 (6.3)	

*ESS indicates Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.
†Compared via Student's *t*-test, Mann-Whitney *U* test, or Fisher's exact test, as appropriate.
‡Percentages based on number of subjects with data for each outcome.

Outcomes and Estimation

All patients experienced an improvement in sleep quality and RLS severity over the course of the study. The PSQI scores decreased across all components, as did the total scores. These decreases were statistically significant ($P<.05$) for the first 5 components. ESS also showed an improvement across all subjects ($P<.001$). RLS symptom severity showed a 4-point decrease, while RLS quality of life (QOL) increased across all component scores. Though the valerian group showed a greater improvement in the majority of sleep quality and RLS scores, we were unable to find a statistically significant difference between the placebo and valerian groups (Table 4).

TABLE 4 Amount of Improvement (Change) in Instrument Scores by Treatment Group*

Change in; mean ±SD	Sample (N=37)	Group Placebo (n=20)	Group Valerian (n=17)	*P* value†
ESS	3.0 ± 4.0	2.8 ± 3.7	3.4 ± 4.4	.637
PSQI Component 1 - Subjective sleep quality	0.7 ± 0.9	0.8 ± 0.9	0.6 ± 0.9	.481
PSQI Component 2 - Sleep latency	0.5 ± 1.0	0.6 ± 0.8	0.4 ± 1.2	.444
PSQI Component 3 - Sleep duration	0.6 ± 0.8	0.6 ± 0.7	0.6 ± 1.0	.922
PSQI Component 4 - Habitual sleep efficiency	0.5 ± 1.6	0.5 ± 1.5	0.6 ± 1.7	.598
PSQI Component 5 - Sleep disturbance	0.2 ± 0.6	0.1 ± 0.5	0.2 ± 0.8	.854
PSQI Component 6 - Sleep medications	0.5 ± 1.6	0.3 ± 1.5	0.8 ± 1.6	.276
PSQI Component 7 - Daytime dysfunction	0.7 ± 1.1	0.7 ± 1.1	0.8 ± 1.2	.721
Global PSQI	4.5 ± 4.9	4.4 ± 4.8	4.5 ± 5.3	.939
RLS Rating scale score	4.1 ± 9.8	4.7 ± 10.4	3.4 ± 9.4	.708

*ESS indicates Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.
†Compared via Student's *t*-test or Mann-Whitney *U* test as appropriate.

Ancillary Analyses

To further evaluate the effectiveness of valerian, we conducted a nested analysis to evaluate the effectiveness of valerian in the subgroup of sleepy vs nonsleepy participants based on a score of ≥10 on the ESS. The treatment group (n=17) received 800 mg of valerian for 8 weeks. Significant differences were found between sleepy and nonsleepy groups in subjective sleepiness scores ($P=.01$) before and after treatment (Table 5). In sleepy participants (scored a 10 or higher on the ESS) who were receiving valerian, significant differences ($P=.02$) were also reported using the RLS Symptom Severity Scale. A strong positive association between changes in sleepiness and RLS symptom severity was found in the valerian group ($P=.006$). These findings suggest that valerian may be beneficial for people who have severe RLS that affects unrecovered sleep and causes excessive daytime sleepiness. The most obvious changes were seen in participants who reported sleepiness measured by the Epworth using a score of ≥10.

To check blinding, patients and RNs were asked at the end of the study which treatment group they thought the patients

TABLE 5 ESS Scores Pre-valerian and Post-valerian Treatment

	Baseline	Follow-up	*P*
Score range	10-18	4-18	
Mean	14.67	10.25	
Standard deviation	3.172	5.190	.02

were in. If blinding was successful, a relationship between actual and perceived treatment would be seen. These results are seen in the cross tab between patients' believed treatment and actual treatment in Table 6. There was no significant relationship between actual and perceived treatment. In fact, patients in both groups were more likely to believe they were taking the valerian than the placebo/unsure.

TABLE 6 Blinding Results of Patients Taking Valerian vs Placebo

Patient's Believed Treatment Group n (%)	Sample (n=37)	True Treatment Group: Placebo (n=20)	True Treatment Group: Valerian (n=17)
Placebo	11 (29.7)	6 (30.0)	5 (29.4)
Valerian	17 (45.9)	8 (40.0)	9 (52.9)
Don't know	9 (24.3)	6 (30.0)	3 (17.6)

Adverse Events

Valerian is considered a natural product and has not been approved for the treatment of RLS; therefore, a moderate risk was associated with this study. Adverse events were described by seriousness, relationship to the investigational drug/supplement, and unexpected events. The PI was responsible for the overall safety monitoring of the study. The protocol was monitored by a data safety monitoring board. All adverse events were reported to the regulatory agencies. Adverse events are reported in Table 7. There were 8 withdrawals, only 3 of which were from the experimental group. Reasons for the withdrawals related to the valerian were rash, RLS symptoms worsening, and stomach irritation. The 4 who withdrew from the placebo group either changed their minds before starting treatment (n=3) or had increasing back pain (n=1).

TABLE 7 Adverse Events

GI disturbances	4
Fatigue/mental sluggishness	4
Vivid dreams	1
Agitation/restlessness	2
Headache	1
Dizziness	1
Rash	1
RLS symptoms worsening*	1
Lyme disease*	1

*Not related to valerian.

DISCUSSION

The results of this pilot suggest that valerian may improve RLS symptom severity and sleepiness. The most obvious changes were found in participants who reported sleepiness who were in the placebo vs valerian group. There are little data with which to compare our findings, as this study reports the first documented findings of valerian in people with RLS.

Valerian is associated with a reduction in REM sleep during the first part of the night but an increase during the latter stages of sleep, minimizing natural sleep stage composition. It also has effects on sleep latency, night awakenings, and quality of sleep. Clinical trials suggest that with repeated administration, valerian produces sleep-inducing effects without altering sleep architecture at modest doses; at higher doses (900-1200 mg), valerian extracts increase delta power on EEG.[20-24] The frequency of REM-phases declined during the first half of the night, whereas a surplus appeared during the second part of the night.[25] In another study, valerian reduced the number of waking episodes and increased REM sleep with a clinical tendency to increase sleep efficiency. A reduction in stages 1 and 2 with an increase in delta sleep was also observed.[26] These studies may support our findings in participants who had higher scores of daytime sleepiness, possibly indicating altered sleep architecture, which valerian may have improved. In participants who were not sleepy, differences were not seen because sleep architecture may not have been causing sleep deprivation resulting in excessive daytime sleepiness.

Other studies comparing valerian and benzodiazepines in a general population reported significant differences between benzodiazepines and valerian, indicating that valerian has no residual effects when taken in the morning and tested for in the afternoon and at 24 hours. In controlled studies comparing withdrawals from benzodiazepines and valerian, only the benzodiazepine group had withdrawal symptoms at the end of treatment. In fact, valerian has been used to alleviate benzodiazepine withdrawal.[22] In our study, we did not find any reports of residual effects of the valerian. The evidence indicates that valerian is a relatively safe substitute for benzodiazepines to aid in sleep, particularly because valerian does not cause the cognitive impairment or negative psychomotor effects often seen with benzodiazepines or other sleep aids.[27] It also can be noted that side effects of valerian are easily reversed with discontinuation.

There were several important methodological lessons from this clinical trial. First, while this preparation of valerian showed a statistically significant improvement in RLS and sleepiness, the amount of improvement compared to placebo was less than the pilot study was powered to find. A post-hoc analysis revealed a total sample size of 60 would identify significant differences between groups.

Research reports have identified concerns of the placebo effect in people with RLS that relate to the measurement of primary endpoints and the progression of the condition, which include exacerbation of symptoms for unknown reasons (possibly related to stressful life events). This unique responsiveness of RLS to both dopaminergic agents and opioids places it at the

crossroad of the 2 systems implicated in the placebo response. A meta-analysis of RLS studies provided insight into the issue of the placebo effect in RLS studies. In 24 clinical trials, the pooled placebo response rate was 40.09% and was larger in studies that used the International Restless Legs Syndrome Survey, a subjective measure, as a primary endpoint. The placebo effect was very small when using periodic limb movements in sleep (PLMS) and was absent when measuring sleep efficiency. Using PLMS as an objective measure and primary endpoint for future studies will control for the placebo response recently reported in RLS studies.[28,29] Because we did not use any objective measures in this study, the placebo effect may explain why we did not find differences between the treatment and placebo groups. Thus, an important result of the pilot study was appreciation of the magnitude of the placebo effect. The placebo effect has been reported to be considerably less significant when measuring PLMS,[28,29] which we will use as a primary endpoint in future studies using actometry, a precise in-home measure of PLMS.

Another concern was the use of the 4 diagnostic criteria used to include participants in the study. Since the study originated, it has been documented that using these 4 criteria have resulted in an overdiagnosis of RLS and a more heterogeneous study sample. Since then, a more precise instrument has been developed, the Telephone Diagnostic Interview (TDI), based on the 4 diagnostic criteria, to determine RLS diagnosis with 99% accuracy.[30] Overall, this pilot study demonstrated a benefit from valerian treatment and helped to establish treatment effect sizes that consider the placebo effect.

CONCLUSION

RLS is a devastating sleep disorder that affects millions of individuals. Current medications for RLS are limited by withdrawal effects, rebound, augmentation, and other significant adverse side effects. Additionally, these medications stop working over time, leaving patients with no options for treatment. Valerian has been shown to have sleep-inducing effects in several studies; however, other studies have had equivocal findings. Consistently, we find that valerian is a safe herb with minimal adverse events and suggest higher doses could be used in research studies. It is unknown if valerian efficacy is improved over time, by dosage, or by dosing. It is also unknown if valerian works better in some sleep disorders than others. Valerian may work better in subgroups of people who report sleepiness, as in this study it may have improved other sleep outcomes that were not objectively measured (by actigraphy or polysomnography) that show an improvement in sleep quality (eg, sleep efficiency, sleep latency). Further research needs to be done on the efficacy of valerian, specifically in patients who have a higher score on sleepiness and RLS symptom severity.

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