Valerian-Hops Combination and Diphenhydramine for Treating Insomnia: A Randomized Placebo-Controlled Clinical Trial

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Context: Insomnia is a prevalent health complaint associated with daytime impairments, reduced quality of life, and increased health-care costs. Although it is often self-treated with herbal and dietary supplements or with over-the-counter sleep aids, there is still little evidence on the efficacy and safety of those products.

Objective: To evaluate the efficacy and safety of a valerian-hops combination and diphenhydramine for the treatment of mild insomnia.

Design and Setting: Multicenter, randomized, placebo-controlled, parallel-group study conducted in 9 sleep disorders centers throughout the United States.

Patients: A total of 184 adults (110 women, 74 men; mean age of 44.3 years) with mild insomnia.

Interventions: (1) Two nightly tablets of standardized extracts of a valerian (187-mg native extracts; 5-8:1, methanol 45% m/m) and hops (41.9-mg native extracts; 7-10:1, methanol 45% m/m) combination for 28 days (n = 59), (2) placebo for 28 days (n = 65), or (3) 2 tablets of diphenhydramine (25 mg) for 14 days followed by placebo for 14 days (n = 60).

Outcome Measures: Sleep parameters measured by daily diaries and polysomnography, clinical outcome ratings from patients and physicians, and quality of life measures.

Results: Modest improvements of subjective sleep parameters were obtained with both the valerian-hops combination and diphenhydramine, but few group comparisons with placebo reached statistical significance. Valerian produced slightly greater, though nonsignificant, reductions of sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and greater reductions than placebo at the end of 28 days of treatment. Diphenhydramine produced significantly greater increases in sleep efficiency and a trend for increased total sleep time relative to placebo during the first 14 days of treatment. There was no significant group difference on any of the sleep continuity variables measured by polysomnography. In addition, there was no alteration of sleep stages 3-4 and rapid eye movement sleep with any of the treatments. Patients in the valerian and diphenhydramine groups rated their insomnia severity lower relative to placebo at the end of 14 days of treatment. Quality of life (Physical component) was significantly more improved in the valerian-hops group relative to the placebo group at the end of 28 days. There were no significant residual effects and no serious adverse events with either valerian or diphenhydramine and no rebound insomnia following their discontinuation.

Conclusions: The findings show a modest hypnotic effect for a valerian-hops combination and diphenhydramine relative to placebo. Sleep improvements with a valerian-hops combination are associated with improved quality of life. Both treatments appear safe and did not produce rebound insomnia upon discontinuation during this study. Overall, these findings indicate that a valerian-hops combination and diphenhydramine might be useful adjuncts in the treatment of mild insomnia.

Keywords: Insomnia, valerian, hops, herbal therapies, diphenhydramine, antihistamines, sleep disorder, treatment

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INTRODUCTION

INSOMNIA IS A WIDESPREAD HEALTH COMPLAINT IN THE GENERAL POPULATION AND IN MEDICAL practices. An estimated one third of the adult population presents insomnia symptoms at least occasionally, about 15% are dissatisfied with their sleep, and between 6% and 10% meet criteria for an insomnia syndrome.[1-2] Insomnia is not a trivial complaint, as it can produce impairments of daytime functioning, reduce quality of life, and increase health-care costs.[3-4]

Despite significant progress made in the pharmacologic and behavioral treatment of insomnia in the last few years,[5-7] only a small proportion of those who suffer from insomnia actually seek professional treatment. Many people with insomnia do not wish to use conventional hypnotic drugs because of concerns about side effects and the risks of tolerance and dependence, and others do not want to spend the time and efforts required with behavioral therapies. In turn, there is an increasing interest in the use of complementary and alternative medicines, such as herbal and dietary supplements,[8-10] partly because of their natural properties and perceived relative absence of residual effects.

Herbal products such as valerian, hops, chamomile, and passionflower are widely marketed as natural sleep aids. Of those herbal products, valerian (Valeriana officinalis L.) has received the most research attention for sleep.[9-13] Most of the evidence from randomized clinical trials suggests that, with repeated administration, valerian produces a mild sleep-inducing effect,

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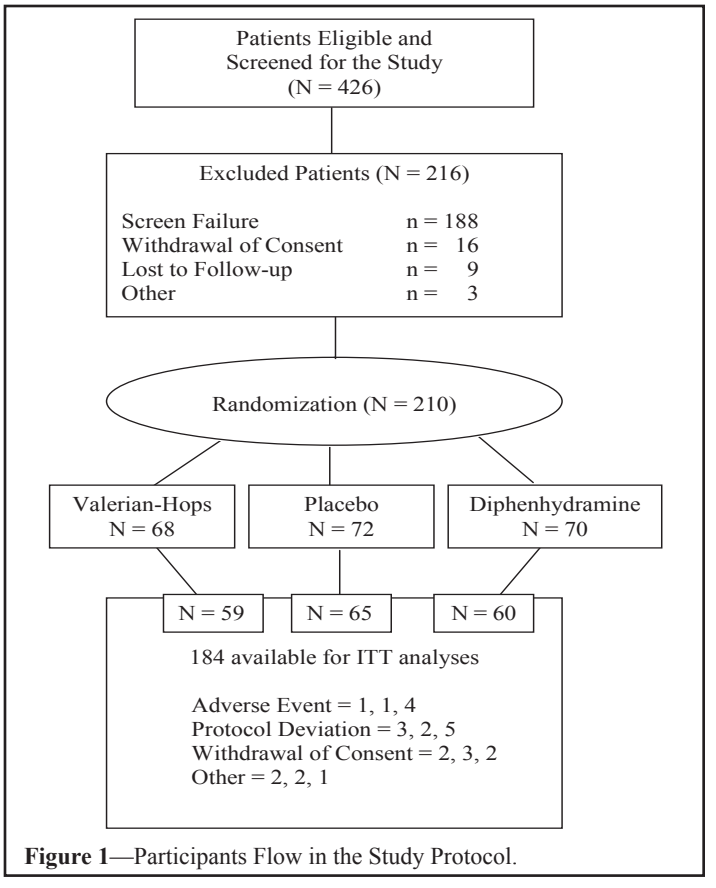

Figure 1—Participants Flow in the Study Protocol.

without causing alteration of the sleep architecture or significant residual effects.[9,10,12,14] Studies have examined doses ranging from 400 to 1200 mg of valerian extract alone[15-21] or combined with other herbal extracts, such as hops, balm, or passionflower.[22-24] There is no clear evidence of an acute effect with a single dose of valerian and no evidence of a dose-response relationship either.[25] However, higher doses (900-1200 mg) of extract increase delta power on quantitative electroencephalography[26] and produce more subjective sleepiness the following morning relative to placebo.[18] The most plausible mechanism of action involves a role for the $GABA_A$ receptors, most likely because of the relatively high content of GABA itself in valerian extracts.[13] Recent research also points to adenosine-receptor activity as the main contributor of its relaxing and sleep-inducing effects.[27]

Despite some promising results, the available evidence on valerian is difficult to interpret because of the variety of preparations tested for related indications. In addition, most studies have been conducted with small sample sizes, often composed of healthy volunteers without evidence of sleep disturbances, and few studies have used polysomnography (PSG) to document outcomes. Additional placebo-controlled randomized clinical trials with subjects presenting evidence of sleep disturbances are needed to evaluate more adequately the efficacy and safety of valerian. The objective of the present study was to evaluate the efficacy and safety of a valerian-hops combination for mild insomnia, against another commonly used sleep aid, diphenhydramine, and a placebo-control condition.

METHODS

Subjects

Prospective subjects with occasional insomnia were recruited through media advertisements and a recruiting firm. Inclusion criteria were (1) aged between 25 and 65 years old; (2) subjective complaint of difficulties initiating (sleep latency > 30 min) and/or maintaining sleep (time awake after sleep onset > 30 min) for a minimum of 2 nights and a maximum of 4 nights per week and for at least a 1-month duration[28,29]; and (3) general good health without evidence of clinically significant disease as determined by medical history, physical examination, and urine drug screens. Exclusion criteria were (1) disease that could affect the action of the study medication; (2) current or past history of serious, severe, or unstable physical (eg, congestive heart failure, chronic obstructive pulmonary disease, diabetes, thyroid disease) or psychiatric illness (eg, major depression, generalized anxiety disorder); (3) evidence of another sleep disorder (eg, sleep apnea, restless legs syndrome, periodic limb movements), irregular sleep patterns, or occupations involving evening or night shift work; (4) allergies or suspected intolerance to the study medications or any antihistamines; (5) current use of substances or medications known to affect sleep, including prescription psychotropics, sedatives, hypnotics, nicotine-replacement therapies, over-the-counter sleep aids, or herbal products; (6) current or recent (within 1 year) alcohol or drug abuse; and (7) pregnancy or lactation.

Prospective subjects completed a 2-phase screening evaluation. Of those who inquired about the study, 426 were considered eligible after the initial telephone screening (see Figure 1). Of those, 216 were excluded after the screening visit, which involved a medical history, brief physical examination, urine screen for drugs of abuse, urine pregnancy test for women of childbearing potential, and completion of demographics, medical, and sleep questionnaires. The remaining 210 subjects were randomly assigned to 1 of 3 groups: valerian-hops combination (n = 68), placebo (n =72), and diphenhydramine (n = 70). Figure 1 presents a summary of participants' flow in the study protocol. The institutional review board of each participating center approved the study, and all patients provided written informed consent at the screening visit.

MEASURES

Sleep Diaries

Following the screening visit, participants kept daily sleep diaries for at least a 14-day baseline period, a 28-day treatment period, and an additional 14-day follow-up after treatment discontinuation. They completed their diary cards every morning and brought them in at each clinic visit. Telephone calls to the subjects were made periodically throughout the study to ensure compliance with properly recording their sleep data on diary cards. Several parameters were monitored on the diaries (eg, bed time, arising time, medication intake, sleep latency, number and duration of awakenings, morning alertness/sluggishness). The main outcome variables were sleep latency, total sleep time, and sleep efficiency (ratio of total sleep time to the actual time spent in bed and multiplied by 100).

Polysomnography

A subset of subjects (n = 75) were randomly selected to complete 3 nights of PSG evaluation in the sleep laboratory, including 1 night at baseline, 1 night at the end of Week 1 of treatment, and 1 night at the end of Week 2 of treatment. The first night of

PSG evaluation served both as a screening and baseline evaluation. Bedtime and arising time in the sleep laboratory were kept within 30 minutes of the subject's habitual sleep schedule at home (as determined by sleep diaries kept during the 2 weeks preceding baseline PSG recording). Total recording time was approximately 7.5 hours (± 30 minutes). Subjects were prohibited from drinking caffeine or alcohol after 3:00 PM on the day of their sleep evaluation. Standard PSG montage, including electroencephalograms, electromyograms, and electrooculograms, were used according to standardized procedures and derivations.[30] In addition, respiratory effort, airflow, oxygen saturation, and anterior tibialis electromyograms were monitored during the first night to screen for sleep apnea and periodic limb movements during sleep. Experienced technicians at a central scoring center (lead investigator's site) blindly scored all PSG records according to standardized criteria using 30-second epochs.[30] The primary dependent variables were sleep latency (time from lights out to persistent sleep), total sleep time, and sleep efficiency. Secondary variables included time awake after sleep onset (from initial sleep onset until last awakening), number of awakenings or arousals, and the percentages of time spent in Stages 1 to 4 and rapid eye movement (REM) sleep.

Clinical Outcome Ratings

All study participants completed the Insomnia Severity Index at each visit. The Insomnia Severity Index is a validated 7-item scale that yields a quantitative index of insomnia severity.[31] Ratings on a 0- to 4-point scale were obtained on the perceived severity of sleep onset, sleep maintenance, and early morning awakening problems; interference with daytime functioning; noticeability of impairment caused by the sleep problem; concern caused by the sleep problem; and satisfaction with current sleep pattern. A composite score is obtained by summing up the 7 ratings, and higher scores indicated more severe insomnia (total score ranges from 0-28, with scores from 0-7 = no insomnia, 8-14 = mild, 15-21 = moderate, and 22-28 = severe insomnia). The Insomnia Severity Index has adequate psychometric properties and has been shown to be sensitive to changes in clinical trials of insomnia.[31-33] The Clinical Global Impression scale was completed by treating clinicians or investigators at the end of the first (Week 1), second (Week 2), and fourth weeks of treatment (Week 4). The Clinical Global Impression is a widely used measure in clinical trials reporting on a patient's status on a scale of 0 (worsening) to 4 (very much improved) since initiating treatment. The Beck Depression Inventory-II[34] is a 21-item self-report measure that was administered at the initial screening visit to exclude prospective patients with significant depressive symptomatology (Beck Depression Inventory score > 23).

The SF-36 Health Survey

The SF-36[35] is a self-rated measure of functioning, health status, and well-being, which has been extensively used for estimating quality of life in the general population and with various medical patients. There are 8 component scores (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health), as well as Physical and Mental Health summary scores. Reliability estimates of the different scales vary between .76 and .90. It has been validated with numerous other health questionnaires.[36,37] This instrument was administered at the screening/baseline visit and at the end of the second (Week 2) and fourth weeks (Week 4) of treatment.

Compliance and Adverse Events

Participants were asked to monitor their compliance with the study medication on their sleep-diary cards. In addition, the study sites maintained a log to record the number of study medications dispensed to each subject and the number of unused tablets returned by the subject. Subjects were instructed to return all unused study medication to the site at each visit. Compliance was defined as the consumption of complete daily doses for at least 5 out of 7 nights and 10 out of 14 nights at Day 7, Day 14, and Day 28, respectively. Adverse events were systematically evaluated at each visit with the following standard question "Have you felt unwell or experienced any unusual symptoms since your last visit?"

Study Design and Procedures

The study was conducted at 9 sites located throughout the United States. After the initial telephone screening, prospective subjects attended 6 visits at the participating sites. Visit 1 was a screening/evaluation visit, including a medical and sleep history and a brief physical examination, urine drug screen and pregnancy test (where applicable), and administration of the Beck Depression Inventory, the Insomnia Severity Index, and the SF-36. Informed consent was obtained at that visit prior to performing any study specific procedures. All subjects who were still considered eligible for enrollment were provided with daily sleep diaries to be completed over the subsequent 14 days. At Visit 2, subjects who fulfilled inclusion criteria (based on their baseline sleep diaries) were randomly assigned to 1 of 3 groups and were dispensed the study medication. Subsequent clinical visits were conducted at Day 7 (Visit 3), Day 14 (Visit 4), Day 28 (Visit 5), and day 42 (Visit 6). PSG assessments were conducted at Visits 2, 3, and 4.

The 3 groups included (1) valerian-hops combination (2 tablets each night for 28 days; each tablet contained 187 mg of valerian native extracts) and 41.9 of hops native extracts (n = 68); (2) placebo (2 tablets each night for 28 days; these tablets of inactive ingredients matched the size, shape, and color of the valerian-hops tablets) (n = 72); (3) diphenhydramine (2 tablets each night for 14 days; these were 25-mg tablets of marketed Sominex® followed by 2 placebo tablets for the remaining 14 nights) (n = 70).

RESULTS

Data Analysis

The primary efficacy parameters were subjective sleep latency, sleep efficiency, and total sleep time, as measured by daily diaries (Table 2). Secondary efficacy parameters included the same sleep variables based on PSG, clinical outcome ratings from patients (Insomnia Severity Index) and clinicians (Clinical Global Impression), and quality of life (SF-36 scale). The primary endpoint was Week 2, with baseline to Week 2 comparisons involving all 3 groups. The secondary endpoint was Week 4, with baseline to Week-4 comparisons involving only valerian-hops and placebo groups (because subjects who received diphenhydramine during the first 2 weeks were switched to placebo and were no longer suitable at Week 4 as controls). χ^2 statistics were used to analyze categorical data (eg, sex, race, Clinical Global Impression ratings) and analyses of variances (ANOVAs) and covariances (ANCOVAs) were used with continuous variables (eg, sleep parameters, Insomnia Severity Index, SF-36 scores). All analyses were

Table 1—Demographic and Clinical Characteristics

Variable	Group			
	Valerian-Hops (n= 59)	Placebo (n = 65)	Diphenhydramine (n = 60)	Total (N = 184)
Age, y	43.9 (10.5)	45.2 (10.2)	43.8 (9.7)	44.3 (10.1)
Sex, No. (%)				
Men	24 (40.7)	26 (40.0)	24 (40.0)	74 (40.2)
Women	35 (59.3)	39 (60.0)	36 (60.0)	110 (59.8)
Race, No. (%)				
Caucasian	49 (83.1)	48 (73.8)	48 (80.0)	145 (78.8)
Black	2 (3.4)	12 (18.5)	11 (18.3)	25 (13.6)
Asian	2 (3.4)	2 (3.1)	0	4 (2.2)
Hispanic	4 (6.8)	3 (4.6)	1 (1.7)	8 (4.3)
Other	2 (3.4)	0	0	2 (1.1)
Mean height, in. (SD)	66.3 (4.7)	66.3 (4.0)	66.6 (3.46)	66.4 (4.1)
Mean weight, lb (SD)	166.9 (38.4)	168.2 (41.0)	169.9 (28.9)	168.3 (36.4)

conducted with α level set at .05, but analyses of primary end points that approached significance (P < .1) are still reported.

Preliminary analyses were computed to examine homogeneity of sites and groups. Because of low enrollment at 3 of the 9 participating sites, data from those 3 centers were pooled together for the preliminary analyses. For the test of homogeneity at baseline, the 3 groups were compared using an ANOVA with treatment and center as factors and sleep latency as the dependent variable. Those analyzes revealed significant differences across groups (P = .02) and sites (P = .05), suggesting that groups and sites were not homogeneous at baseline on the primary efficacy parameter of sleep latency. Therefore, ANCOVAs, using baseline scores as covariate, were computed for all subsequent analyses. Also, due to the skewed distribution of sleep latency differences at Week 2 and Week 4, nonparametric statistics were used (Cochran-Mantel-Haenszel test), in addition to the parametric tests.

Patient Subsets and Demographics

Of the 210 subjects who were randomly assigned to groups, 6 took no medication and 20 had either no baseline or no Week 2 assessments for the primary efficacy parameter. The intent-to-treat subset included 184 subjects (valerian-hops = 59, placebo = 65, diphenhydramine = 60). This subset was composed of 110 women and 74 men; 79% were Caucasians, and the average age was 44.3 years (SD = 10.1 years) (See Table 1). The demographic and efficacy analyses are based on the intent-to-treat subset of 184 subjects. Demographic parameters (age, sex, race) were homogeneous across the 3 groups.

Sleep Parameters

Table 2 shows the means and SD of the sleep parameters for each assessment phase. Sleep diary data are based on 7 consecutive days of self-monitoring at each assessment phase. PSG data are based on 1 night at each assessment phase. For subject diary data, the 7 days prior to the baseline visit were used to calculate baseline scores. The Week 2 averages were calculated from Day 8 through Day 14, and the Week 4 averages from Day 22 to Day 28. If subjects' diary-card data were missing for 4 or more days in a week, the data of the efficacy parameters for that subject at that visit were not used.

Table 2—Sleep Variables

Variable	Group		
	Valerian-Hops	Placebo	Diphenhydramine
		Sleep Latency, min	
Sleep diary			
Baseline	35.07 (25.79) 59	27.88 (20.96) 65	25.69 (13.73) 60
Week 2	27.54 (25.02)	23.77 (21.49)	21.62 (12.87)
Week 4	25.89 (28.10)	23.71 (21.19)	22.11 (13.83)
Week 6	25.71 (25.48)	24.50 (17.90)	20.70 (13.80)
Polysomnography			
Baseline	19.48 (21.61) 22	36.04 (43.30) 26	17.77 (19.40) 26
Week 1	15.94 (17.69)	19.50 (29.25)	15.65 (22.64)
Week 2	9.06 (4.95)	18.35 (22.82)	10.46 (9.57)
		Sleep Efficiency, %	
Sleep diary			
Baseline	81.32 (8.84) 58	80.13 (9.81) 65	82.59 (7.30) 58
Week 2	84.32 (9.68)	82.57 (11.53)	87.17 (6.55)
Week 4	86.37 (10.17)	83.38 (10.14)	85.62 (8.30)
Week 6	85.00 (10.48)	82.92 (9.67)	86.96 (6.90)
Polysomnography			
Baseline	76.33 (20.39) 22	75.76 (14.62) 26	77.34 (17.77) 26
Week 1	84.97 (13.13)	80.83 (15.84)	84.30 (9.01)
Week 2	84.68 (10.54)	83.72 (10.56)	86.31 (10.94)
		Total Sleep Time (min)	
Sleep diary			
Baseline	392.91 (67.66) 58	384.46 (74.71) 65	389.99 (74.95) 58
Week 2	404.88 (67.14)	401.76 (78.35)	419.59 (60.62)
Week 4	418.82 (66.49)	405.75 (71.07)	399.96 (77.04)
Week 6	411.06 (73.62)	399.17 (76.74)	412.85 (82.10)
Polysomnography			
Baseline	340.69 (98.29) 22	335.02 (61.17) 26	347.93 (82.73) 26
Week 1	373. 73 (65.01)	362.69 (74.80)	375.21 (41.09)
Week 2	381.36 (65.95)	370.40 (45.49)	382.77 (49.21)

Data are presented as mean (SD). Sleep diary data are based on 1 week of self-monitoring at each assessment phase. Polysomnographic data are based 1 night at baseline, 1 night after 1 week of treatment, and 1 night after 2 weeks of treatment. Numbers following parentheses indicate the number of subjects in the group.

Sleep Diary

ANCOVAs were computed on sleep latency, sleep efficiency, and total sleep time. Sleep latency was reduced from baseline to Week 2 in all 3 groups, with reductions of 7.4 minutes in the valerian-hops group, relative to 4.1 minutes in both the placebo and diphenhydramine groups. Those differences were not statistically significant. Comparison of baseline to Week 4 differences between valerian (9.5 minutes) and placebo (3.9 minutes) was nearly significant (P = .0795).

Sleep efficiency was increased from baseline to Week 2 in all 3 conditions, with significantly larger gains made in the diphenhydramine (4.6%) condition relative to placebo (2.5%) (P = .039). Valerian-hops produced an average increase of 3.1%, which was not significantly different from either of the other 2 groups. Changes from baseline to Week 4 averaged 5% for the valerian-hops relative to 3.3% for the placebo (NS).

Average gains in total sleep time from baseline to Week 2 were 12.9, 17.8, and 29 minutes for the valerian-hops, placebo, and diphenhydramine groups, respectively, with the comparison of di-

Table 3—Clinical Outcome Ratings

	Group		
	Valerian-Hops	Placebo	Diphenhydramine
Insomnia Severity Index			
Baseline	15.28 (4.39) 58	15.03 (4.38) 65	15.05 (4.31) 58
Week 2	10.51 (4.94)	11.63 (4.02)	9.39 (4.43)
Week 4	9.44 (5.25)	9.84 (5.11)	10.02 (4.78)
Week 6	10.75 (5.31)	10.34 (5.22)	9.84 (5.07)
SF-36 (Physical)			
Baseline	53.64 (5.94) 59	53.89 (6.69) 65	54.74 (6.52) 60
Week 2	54.46 (5.34)	53.46 (7.63)	56.12 (7.09)
Week 4	55.03 (4.42)	53.34 (7.76)	55.47 (6.54)
SF-36 (Mental)			
Baseline	48.75 (10.47) 59	48.22 (8.58) 65	48.25 (10.01) 60
Week 2	49.66 (7.67)	48.28 (9.02) 64	47.41 (10.05)
Week 4	49.28 (9.55)	48.29 (9.37)	49.21 (8.24)

Data are presented as mean (SD). Numbers following parentheses indicate the number of subjects in the group.

phenhydramine and placebo approaching statistical significance (P = .078). The average gain in total sleep time at Week 4 was 27.5 minutes for valerian and 22.1 for placebo subjects (NS).

Polysomnography

PSG group means and SD at baseline, Week 1, and Week 2 are shown in Table 2. ANCOVAs were computed on differences between baseline and Week 2 scores. There was no significant difference for any comparisons. All 3 groups showed average reductions in sleep latency of 8 minutes and an average increase of 8% to 9% in sleep efficiency. Total sleep time was increased by an average of 40 minutes in the valerian condition, compared with 35 minutes for diphenhydramine and placebo. There was no significant change in the percentages of time spent in any of the sleep stages (Stages 1-4 and REM sleep).

Clinical Outcome Ratings

All 3 conditions reduced their total Insomnia Severity Index scores from baseline to Week 2 (see Table 3). Comparisons of baseline and Week 2 differences using ANCOVAs (treatment, center, and the interaction treatment-by-center) showed that diphenhydramine (P = .003), but not valerian-hops (P = .06), produced greater changes than placebo. There was no significant difference between the 2 treatment groups (P = .24). Differences between Baseline and Week 2 scores averaged 4.9 for valerian-hops, 3.3 for placebo, and 5.6 for diphenhydramine. Comparisons between valerian-hops and placebo for baseline to Week 4 differences were not significant. χ^2 analyses revealed no significant group differences in the clinicians' ratings of therapeutic effect on the Clinical Global Impression scale at Week 1, Week 2, or Week 4 (all P values > 0.2).

Quality of Life

Table 3 shows group means for the 2 SF-36 component scores (Physical and Mental) at baseline, Week 2, and Week 4. ANCOVAs were computed on those 2 aggregate scores to examine differences among the 3 groups at Week 2 and between valerian and placebo at Week 4; baseline scores were used as the covariate. On the Physical component score, there was a significant difference at Week 4 (P = .028) in favor of valerian-hops over placebo but no significant difference on the Mental score for the same period. At week 2, there was a 1-point difference favoring valerian-hops (NS) and a 1.3-point difference favoring diphenhydramine (NS) over placebo on the Physical component score; for the same period, differences of 1.3 and 1.9 points favoring valerian over placebo and diphenhydramine, respectively, were obtained on the Mental score (NS)

Adverse Events

A total of 204 subjects used medication at least once and were available for safety analyses, including 87% (n = 182) who completed the entire study. Of the 28 subjects who did not complete the study, 6 withdrew due to adverse events. One of those subjects received valerian-hops, 1 placebo, and 4 received diphenhydramine. One hundred eleven subjects (54%) had at least 1 adverse event during the study (valerian-hops = 33; placebo = 34; diphenhydramine = 44). These 111 subjects reported a total of 216 adverse events (valerian = 63; placebo = 76; diphenhydramine = 77). There was no significant difference between valerian-hops and placebo, whereas the comparison between valerian and diphenhydramine approached significance (Fisher exact test, P < .08). There was no serious adverse event.

Next-Day Residual Effects and Rebound Effects

Subjects' ratings of drowsiness and sluggishness on their sleep diaries were examined as potential residual effects. There was no significant difference among the 3 groups at Week 2, and no difference between valerian-hops and placebo at Week 4. Rebound effects were evaluated by examining changes in sleep parameters after discontinuation of the medication, which involved changes from Week 2 to Week 4 for diphenhydramine and from Week 4 to Week 6 for valerian-hops. Table 2 shows a small increase of sleep latency (3.5 minutes) and a decrease of total sleep time (20 minutes) for the diphenhydramine subjects from Week 2 to Week 4, whereas the valerian-hops subjects experienced minimal changes on those 2 sleep parameters from Week 4 to Week 6.

DISCUSSION

The results indicate that a valerian-hops combination and diphenhydramine produce a mild hypnotic effect in the treatment of insomnia. Sleep improvements were obtained on subjective measures of sleep latency, sleep efficiency, and total sleep time. Both treatments produced reductions of patient's Insomnia Severity Index scores relative to placebo, and the valerian-hops combination improved quality of life relative to placebo. There were no significant residual effects and no rebound insomnia after treatment discontinuation, confirming the safety of the investigated valerian-hops combination and diphenhydramine when taken on a daily basis for 4 and 2 weeks, respectively. Overall, these findings indicate that a valerian-hops combination and diphenhydramine might be useful adjuncts in the treatment of mild insomnia.

Changes in sleep continuity parameters, as measured by PSG, were in the expected direction of improvements, and the magnitude of those changes was similar to those obtained on diary measures. However, comparisons between conditions were not statistically significant, partly because of the smaller sample size (and reduced statistical power) and because improvements were

obtained with placebo as well as with treatments. These findings should be interpreted cautiously, however, as only 1 night of PSG recording was conducted at each assessment, and a first-night effect (or reverse first-night effect) was a potential confound.

There was no significant change in the sleep architecture of patients treated with valerian-hops or diphenhydramine. Previous studies using PSG assessment have reported either an increase[16,19] or no change[15] in slow-wave sleep with valerian. Although the clinical significance of the suppression of slow-wave sleep, which has been well documented with the use of benzodiazepine hypnotics, is not entirely clear, the absence of such a change with either valerian-hops or diphenhydramine can be interpreted as a positive finding.

The relatively mild hypnotic effects obtained with valerian-hops and diphenhydramine were expected. Several possibilities might explain the lack of a statistically significant effect on the primary endpoint of sleep latency. First, the sample presented fairly mild sleep disturbances compared with patients who typically enrolled in insomnia clinical trials,[32,38] hence, leaving little room for improvement. Second, the lack of homogeneity at baseline and significant differences across centers produced noise and reduced statistical power on the primary endpoint. Third, sleep latency as single outcome measure might not capture all aspects of sleep improvements. It may be useful in future studies to incorporate, as a primary endpoint, outcome measures such as the Insomnia Severity Index that might more broadly capture the impact of sleep on daytime functioning rather than just focusing on 1 specific sleep parameter. Another possibility is that some outcome measures (eg, PSG) were not sensitive enough to detect treatment effects in a sample of subjects with mild insomnia. Despite these limitations, the results are in line with previous findings on the effects on sleep of herbal or dietary and over-the-counter products.[10,39,40]

The time required to produce sleep improvements was longer with valerian than with diphenhydramine, a finding consistent with those of previous studies using the same valerian-hops combination.[41,42] Although an acute treatment effect was not evaluated in this study, previous studies have shown few benefits on sleep latency with a single-dose treatment of valerian.[25] It may be useful in future clinical trials to incorporate outcome measures that would be more sensitive to changes that may be slower to emerge than with traditional hypnotics and also to capture changes not only in terms of absolute improvements on sleep parameters, but also in terms of reduction in the night-to-night variability that characterizes insomnia.[43]

There were few adverse events in patients treated with valerian and diphenhydramine, and reported adverse events were mild and similar to those experienced with placebo. In addition, there were minimal residual daytime effects, and those were similar in frequency and intensity as those reported with placebo. While the absence of significant adverse and residual effects for valerian is consistent with previous findings, diphenhydramine has been associated with residual effects in previous studies.[40,44,45] Rebound insomnia is also frequently observed with abrupt discontinuation of benzodiazepine hypnotics,[46,47] but no such rebound effect was observed with either valerian-hops or diphenhydramine for the doses tested. This finding is important, since rebound insomnia is likely to perpetuate long-term use of hypnotics. In the absence of such effects, it may be easier for patients to discontinue sleep aids, even after 2 and 4 weeks of nightly use.

Some methodologic limitations of this study were the inclusion of participants with mild insomnia, exclusion of those with significant comorbid medical or psychiatric conditions, and the use of only 1 night of PSG monitoring at each assessment period.

In summary, the present findings extend those from previous studies in documenting the effects of valerian and diphenhydramine on sleep. Although alternative medicines such as these are not widely endorsed by health-care practitioners and sleep clinicians, there is certainly an increasing use of those complementary and alternative therapies among the general population. Their safety and health benefits can be documented further with additional randomized clinical trials.[48]

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