

Evaluation of effectiveness and safety of a herbal compound in primary insomnia symptoms and sleep disturbances not related to medical or psychiatric causes

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Background and purpose: Sleep disturbances and related daytime activities impairment are common diseases nowadays. General practitioners are often the first health care professional asked to alleviate sleep disturbances and primary insomnia symptoms. Beyond a wide class of hypnotic drugs, botanicals can represent an alternative treatment for those kinds of symptoms. The scope of the present study is to evaluate safety and effectiveness of a herbal compound composed of valerian, hop, and jujube (Vagonotte®) on primary insomnia symptoms and sleep disturbances not related to medical or psychiatric causes.

Patients and methods: One hundred and twenty subjects with sleep disturbances symptoms were randomized in two branches of 60 persons each, receiving the herbal compound or placebo at dosage of two pills per day 30 minutes before their scheduled bedtime. All subjects were screened for precise items related to sleep quality and daytime activity at the beginning, after 10 days, and after 20 days of consecutive dietary supplement (or placebo) consumption. The participants remained blind to group assignment until all of them completed the trial.

Results: Sleep onset, numbers of nocturnal awakenings, and overall nocturnal slept time were assessed. A statistically significant difference between the two groups emerged. The group receiving the herbal compound showed a lower time of sleep onset compared to placebo group, the same result was obtained for total slept time and night awakenings frequency ($p < 0.001$). Daily symptom improvement in subjects receiving the herbal compound showed significant reduction in tension and irritability, difficulty in concentration, and fatigue intensity, if compared to placebo scores ($p < 0.001$). None of the 60 subjects in the verum group reported adverse reaction related to the herbal compound, and 98% of subjects judged the product as having from good to excellent safety and tolerability.

Conclusion: Botanicals dietary supplement with relaxing and soothing properties can help practitioner to treat primary insomnia, especially when the risk/benefit profile of a patient does not sustain hypnotic drugs prescription. This clinical investigation on safety and effectiveness of a herbal compound made of valerian, hop, and jujube opens interesting perspectives on usage of herbal compound to manage primary insomnia. Further investigations could help in understanding herbal compounds' effectiveness on sleep disturbances.

Keywords: insomnia, sleep disturbance, fatigue, tension

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Introduction

Sleep-related disorders are a heterogeneous cluster of disturbances varying from restless legs syndrome to insomnia, including more than 70 different and specific diagnoses.¹ Sleep-related disorders affect from 25% to 33% of people all over the world, this is according

to different definitions, and at least 10% of population suffer from sleep disturbances that require therapeutic treatment.²

Insomnia is one of the most common sleep disturbances, defined as the experience of a poor sleep and described by specific symptoms like difficulty to fall asleep, difficulty to maintain sleeping, early awakening, and nonrestoring sleep. Primary insomnia can be defined as sleeplessness or the perception of poor sleep quality that cannot be attributed to medical, psychiatric, or environmental causes. Primary insomnia is characterized by 1 month or longer history of difficulty initiating or maintaining sleep and/or a nonrestorative sleep. Daytime symptoms like fatigue, sleepiness, difficulty in concentrating, and irritability are often present along with nocturnal disturbances. Daily disturbances can negatively affect health and quality of life by causing significant distress or impairment in social, occupational, or other important areas of activities. Most of the primary insomnia symptoms can be prevented and treated by adopting a proper lifestyle and sleep hygiene rules.³

To maintain healthy sleep habits, a wide variety of sleep medications exists. Hypnotic drugs are regularly used for insomnia and other sleep disorders, with over 95% of insomnia patients being prescribed hypnotics in some countries.⁴ When prescribed, hypnotic medication should be continued for the shortest period of time.⁵ Elderly people are more sensitive to potential side effects of drugs, and a meta-analysis found that the risks generally outweigh any marginal benefits of hypnotics in the elderly.⁶ Another review of the literature on hypnotics concluded that these drugs can have adverse effects, such as dependence and accidents, and that optimal treatment uses the lowest effective dose for the shortest therapeutic period, with gradual discontinuation in order to improve health without worsening of sleep.⁷

Botanical drugs with relaxing and soothing properties can help the practitioner to treat primary insomnia, especially when the risk/benefit profile of a patient does not allow for hypnotic drugs prescription.

Valerian (*Valeriana officinalis*), hop (*Humulus lupulus*), and jujube (*Ziziphus jujuba*) are among most widely and effective botanicals used to ameliorate chronic and non-restorative sleep.^{8–14}

Valerian extract (*Valeriana officinalis*) has been used for centuries to alleviate restlessness and anxiety, albeit with an unknown mechanism of action. Recent in vivo and in vitro studies brought to light that the mechanism of action of valerian is by a specific binding site on GABA(A) receptors that have affinity for valerenic acid.⁸

Hop (*Humulus lupulus*) has different properties: calming, sleep inducing, gastric secretion stimulating, and spasmolytic. The sedative characteristics of the hop plant

have been confirmed in a clinical trial where in association with valerian, sleep quality and sleep onset were improved.⁹ Increasing GABAergic activity seems to be the main mechanism of action, thus inhibiting the central nervous system.¹⁰ Moreover, hop has demonstrated binding affinities to some of the melatonin (ML1 and ML2) and serotonin (5-HT_{4e}, 5-HT₆ and 5-HT₇) receptor subtypes that are involved in circadian rhythm and sleep regulation.¹¹

Jujube (*Ziziphus jujuba*) has a long tradition of use in Chinese medicine for anxiety and sleep disturbance disorders. The main biologically active components are phenolics, flavonoids, and triterpenic acids.¹² Modulation of monoaminergic system related to triterpenic saponins activity in vitro could be the main bioactive factor for sleep disturbance reduction.¹³ In vivo results suggest that the hypnotic effect of saponins may involve serotonergic system.¹⁴

The aim of the present randomized, single-blind, placebo-controlled study was to investigate safety and effectiveness of a herbal compound made of valerian, hop, and jujube (Vagonotte®) in subjects with primary insomnia and sleep disturbances characterized by sleep onset difficulties with frequent night awakenings and overall poor sleep quality not related to main underlying pathologies.

Methods

One hundred and twenty subjects with self-reported symptoms of primary insomnia were recruited by general practitioners belonging to ANARDI association; all the practitioners were selected and coordinated by the internal scientific committee of the association. All eligible subjects were informed of the clinical trial aims and roll out and gave written informed consent.

Inclusion criteria were the following: generally healthy subject; no medical or psychiatric condition that would cause sleep disturbance; difficulty in sleep onset; more than two night awakenings; early morning awakening; not-restoring sleep; daily sleepiness; fatigue; difficulty in attention and concentration, anxiety, and irritability. These eligibility criteria for insomnia are generally consistent with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition and research criteria for insomnia. Exclusion criteria were the following: age <18 years old, pregnancy and/or breast-feeding; intolerance to at least one of the ingredients of the herbal compound; significant current major illness (eg, cancer, heart failure, asthma); current major psychiatric disease; alcohol dependence; and generally all clinical conditions that can be referred to as secondary insomnia.

Subjects were screened using a self-assessment questionnaire to measure intensity of symptoms at three experimental

times: T0 (baseline assessment), T1 (after 10 days), and T2 (after 20 days). At T1 and T2, tolerance and self-perceived efficacy questionnaires were filled in the presence of the general practitioner. Time of sleep onset, total slept time, and number of night awakenings were some of the variables monitored together with sleep satisfaction, tension and irritability, difficulty to concentrate, and fatigue. Those latter items describing daytime symptoms subsequent to insomnia were described by an intensity score varying from 0 (none) to 4 (very severe).

Subjects were randomized into two branches of 60 persons, each receiving the herbal compound (group A) or placebo (group B) at a dosage of two pills per day 30 minutes before their scheduled bedtime. The participants remained blind to group assignment until all of them completed the trial.

The herbal dietary supplement used in this study is a Cristalfarma registered trademark, freely provided for the clinical trial.

Herbal supplement composition: Valerian (*Valeriana officinalis*) root dry extract containing 0.8% of valerenic acid; Hop (*Humulus lupulus*) cone dry extract, containing 0.4% minimum of total flavonoids; Jujube (*Ziziphus jujuba*) seeds dry extract, containing 2% min. triterpene saponins; bulking agents: corn maltodextrin; anticaking agents (cross-linked sodium carboxymethylcellulose, magnesium stearate, silicon dioxide); coating agents (hydroxypropyl methylcellulose, cellulose, stearic acid, glycerol); colorant (titanium dioxide). Placebo composition: corn maltodextrin; anticaking agents (cross-linked sodium carboxymethylcellulose, magnesium stearate, silicon dioxide); coating agents (hydroxypropyl methylcellulose, cellulose, stearic acid, glycerol); colorant (titanium dioxide). Both verum and placebo pills were of identical appearance. The producer provided a certificate of analysis confirming product standardization and the absence of microbial contaminants. The research was approved by ANARDI scientific and ethical review board.

Statistical analyses

χ^2 test (or Fisher's Exact test when necessary) was used to compare gender and clinical parameter distributions between groups. Mann–Whitney test was used to match age between groups. Mixed models with robust error were used to evaluate score variations during time and between groups, considering subjects as random effect and time and groups as fixed effects. p -value <0.05 was considered statistically significant. All statistical analyses were performed with STATA 14.0 (StataCorp LLC, College Station, TX, USA) program.

Results

Descriptive data analysis

Participants were randomized into two groups (A receiving the herbal compound and B receiving placebo) of 60 subjects each. Demographical and clinical data of all subjects are summarized in Table 1. There were no significant differences of gender and age distributions in the two groups; all subjects fit inclusion criteria clinical parameters.

Comparison of sleep quality and day activity items at different experimental times

As previously described, all subjects were screened for different items related to sleep quality and daytime activity at the beginning (T0), after 10 days (T1), and after 20 days (T2) of consecutive dietary supplement (or placebo) consumption. Sleep onset, numbers of nocturnal awakenings, and overall nocturnal slept time are reported in Table 2. No statistically significant differences between group A and B were observed at baseline.

Baseline intensity score of sleep satisfaction does not differ in the two groups; we can notice similar distribution of symptom intensity, mostly of the subjects (41%) perceiving poor quality of sleep in both groups (Table 3).

Table 1 Demographical and clinical parameters

	Group		p-value
	A (Verum), n (%)	B (Placebo), n (%)	
	n=60	n=60	
Age, median (25th–75th percentile), years	55 (43–63.5)	54.5 (43.5–65.5)	0.944
Sex, Female	33 (55%)	32 (53.3%)	0.855
Family history for sleep disorders, No	60 (100%)	57 (95%)	0.079
Secondary insomnia, No	60 (100%)	60 (100%)	
Severe ongoing disease, No	60 (100%)	60 (100%)	
Alcoholism, No	60 (100%)	60 (100%)	
Hypnotics or similar drugs usage, No	60 (100%)	60 (100%)	
Pregnancy or breast-feeding, No	60 (100%)	60 (100%)	
Allergy, No	60 (100%)	60 (100%)	
Normal medical examination, Yes	60 (100%)	60 (100%)	

Diurnal symptoms score and distribution at baseline are shown in Table 4. Tension and irritability, difficulty in concentration, and fatigue do not differ in the two groups. In both groups, the majority of subjects perceive from “moderate” to “severe” the intensity of all the daytime monitored items.

After 10 days (T1), a statistically significant difference between the two groups started to emerge. At the end of the experimental period (T2) all the sleeping symptoms in group A were significantly improved if compared to placebo result ($p < 0.001$), as reported in Table 5. Group A showed a lower time of sleep onset (40 minutes) compared to placebo group (65 minutes), the same trend is described by night awakenings frequency and total slept time (Table 5).

After 20 days (T2), sleep satisfaction was perceived as very improved by 50% of group A subjects, while in placebo subjects this percentage was 5% (Table 6).

Differences in sleep satisfaction and daily symptoms intensity started to be evident after 10 days, (following sleeping symptoms improvement): at T1, group A scores significantly ameliorate if compared to placebo results (Tables 6 and 7).

Daily symptom improvement after 20 days followed the same trend discussed earlier, with increasing percentage of subjects referring a reduction in tension and irritability, difficulty in concentration, and fatigue intensity, if compared to placebo scores ($p < 0.001$, Table 7).

Results after 10 days (T0–T1) and after 20 days (T0–T2), expressed as average variations at considered experimental intervals, are reported in Table 8.

A statistically significant variation in all parameters related to sleeping symptoms was observed.

The same trend is shown in the questionnaire items results related to sleep satisfaction, tension and irritability, difficulty in concentration, and fatigue, $p < 0.001$ vs placebo.

Table 2 Baseline sleeping symptoms distributions, (T0)

Variables		Group		p-value
		A (Verum)	B (Placebo)	
Sleep onset, minutes	Median (25th–75th percentile)	90 (75–120)	100 (70–110)	0.236
N of night awakenings	Average (sd)	2.33 (0.63)	2.22 (0.76)	0.361
Slept time, minutes	Median (25th–75th percentile)	330 (300–360)	330 (300–360)	0.606

Note: T0 (baseline assessment).

Table 3 Baseline score and distribution of sleep satisfaction (T0)

	Group	1= very	2= modestly	3= poorly	4= not at all	p-value
Sleep satisfaction, n (%)	A (Verum)	0 (0%)	12 (20%)	41 (68.33%)	7 (11.67%)	0.162
	B (Placebo)	0 (0%)	17 (28.33%)	41 (68.33%)	2 (3.33%)	

Note: T0 (baseline assessment).

Table 4 Diurnal symptoms score distributions at baseline (T0)

Variables intensity	0= none	1= mild	2= moderate	3= severe	4= very severe	p-value
Tension and irritability, n (%)						
Group A (Verum)	0 (0%)	2 (3.33%)	32 (53.33%)	25 (41.67%)	1 (1.67%)	0.319
Group B (Placebo)	0 (0%)	6 (10%)	35 (58.33%)	16 (26.67%)	3 (5%)	
Difficulty to concentrate, n (%)						
Group A (Verum)	0 (0%)	5 (8.33%)	44 (73.33%)	11 (18.33%)	0 (0%)	0.278
Group B (Placebo)	0 (0%)	11 (18.33%)	37 (61.67%)	11 (18.33%)	1 (1.67%)	
Fatigue, n (%)						
Group A (Verum)	0 (0%)	2 (3.33%)	32 (53.33%)	25 (41.67%)	1 (1.67%)	0.164
Group B (Placebo)	0 (0%)	6 (10%)	35 (58.33%)	16 (26.67%)	3 (5%)	

Table 5 Sleeping symptoms distributions after 10 days (T1) and 20 days (T2)

Variables	T1			T2		
	Group					
	A (verum)	B (placebo)	p-value	A (verum)	B (placebo)	p-value
Sleep onset, minutes median, (25th–75th percentile)	60 (60–85)	75 (60–90)	0.024	40 (30–60)	65 (50–90)	<0.001
N of night awakenings average (ds)	1.43 (0.56)	1.78 (0.67)	0.002	0.8 (0.61)	1.62 (0.74)	<0.001
Slept time, minutes, median (25th–75th percentile)	360 (350–390)	360 (330–370)	0.005	398 (365–420)	360 (315–380)	<0.001

Table 6 Score and distribution of sleep satisfaction (T1 and T2)

Group		T1					T2					p-value
		1	2	3	4	p-value	1	2	3	4		
		very	modestly	poorly	not at all		very	modestly	poorly	not at all		
Sleep satisfaction, n (%)	A (Verum)	0 (0%)	12 (20%)	41 (68.33%)	7 (11.67%)	0.162	30 (50%)	29 (48.33%)	1 (1.67%)	0 (0%)	<0.001	
	B (Placebo)	0 (0%)	17 (28.33%)	41 (68.33%)	2 (3.33%)		3 (5%)	46 (76.67%)	11 (18.33%)	0 (0%)		

Notes: T1 (after 10 days), and T2 (after 20 days).

Table 7 Daytime symptoms score distributions after 10 days (T1) and 20 days (T2)

	T1						T2					
	0 none	1 mild	2 moderate	3 severe	4 very severe	p-value	0 none	1 mild	2 moderate	3 severe	4 very severe	p-value
Tension and irritability, n (%)												
Group A (Verum)	2 (3.33%)	28 (46.67%)	30 (50%)	0 (0%)	0 (0%)	0.001	13 (21.67%)	41 (68.33%)	6 (10%)	0 (0%)	0 (0%)	<0.001
Group B (Placebo)	1 (1.67%)	13 (21.67%)	36 (60%)	10 (16.67%)	0 (0%)		2 (3.33%)	17 (28.33%)	34 (56.67%)	7 (11.67%)	0 (0%)	
Difficulty to concentrate, n (%)												
Group A (Verum)	1 (1.67%)	37 (61.67%)	22 (36.67%)	0 (0%)	0 (0%)	0.011	15 (25%)	38 (63.33%)	7 (11.67%)	0 (0%)	0 (0%)	<0.001
Group B (Placebo)	0 (0%)	23 (38.33%)	32 (53.33%)	5 (8.33%)	0 (0%)		1 (1.67%)	30 (50%)	24 (40%)	5 (8.33%)	0 (0%)	
Fatigue, n (%)												
Group A (Verum)	14 (23.33%)	18 (30%)	27 (45%)	1 (1.67%)	0 (0%)	<0.001	26 (43.33%)	27 (45%)	7 (11.67%)	0 (0%)	0 (0%)	<0.001
Group B (Placebo)	1 (1.67%)	5 (8.33%)	43 (71.67%)	11 (18.33%)	0 (0%)		1 (1.67%)	16 (26.67%)	34 (56.67%)	9 (15%)	0 (0%)	

Table 8 Sleeping items and daily symptoms variations at considered experimental intervals

Variables			Group		p-value
			A (Verum)	B (Placebo)	
Sleep onset	T0-T1	Average (sd)	-28.9 (23.92)	-14.3 (14.98)	<0.001
	T0-T2	Average (sd)	-55.7 (28.6)	-18.8 (23.3)	<0.001
Slept time	T0-T1	Average (sd)	36.2 (24.38)	14.8 (17.18)	<0.001
	T0-T2	Average (sd)	64.3 (32.89)	18.7 (21.46)	<0.001
Sleep satisfaction	T0-T1	Average (sd)	-1 (0.6)	-0.5 (0.54)	<0.001
	T0-T2	Average (sd)	-1.4 (0.72)	-0.6 (0.64)	<0.001
Tension and irritability	T0-T1	Average (sd)	-0.9 (0.58)	-0.4 (0.48)	<0.001
	T0-T2	Average (sd)	-1.5 (0.62)	-0.5 (0.54)	<0.001
Difficulty to concentrate	T0-T1	Average (sd)	-0.8 (0.54)	-0.3 (0.54)	<0.001
	T0-T2	Average (sd)	-1.2 (0.62)	-0.5 (0.68)	<0.001
Fatigue	T0-T1	Average (sd)	-1.2 (0.69)	-0.2 (0.61)	<0.001
	T0-T2	Average (sd)	-1.7 (0.78)	-0.4 (0.77)	<0.001

Notes: T0 (baseline assessment), T1 (after 10 days), and T2 (after 20 days).

Considering the whole experimental time (T0-T2), a statistically significant variation in all parameters related to monitored sleeping variables (sleep onset, numbers of nocturnal awakenings, overall nocturnal slept time, and sleep satisfaction) was observed. Group A presented a further decreased time to fall asleep, fewer night awakenings, and further increased total slept time; all variations are statistically significant if compared with group B (Table 8).

A remarkable result was obtained in frequency of night awakenings reduction, with a final value of 0.8 for group A whose value was 2.33 at baseline; $p < 0.001$ vs placebo variations.

A similar performance was shown by all day-time symptoms describing tension and irritability, difficulty in concentration, and fatigue where an intensity score reduction of more than one point is observed, $p < 0.001$ vs placebo (Table 8).

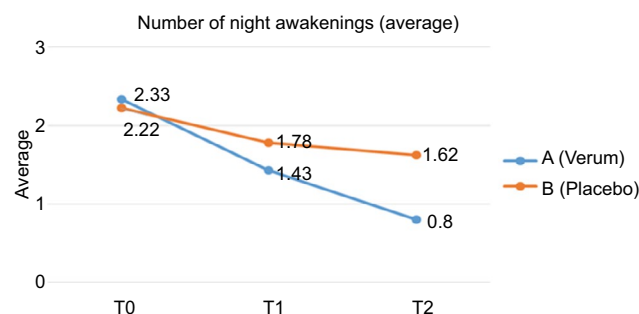


Figure 1 Average number of night awakenings during experimental time.
Notes: T0 (baseline assessment), T1 (after 10 days), and T2 (after 20 days).

Discussion

In this randomized, single-blind, placebo-controlled study, we investigated safety and effectiveness of a herbal compound made of valerian, hop, and jujube (Vagonotte, Cristalfarma) in subjects with sleep disturbances, such as difficulties falling asleep with frequent night awakenings, not related to main underlying pathologies.

Subjects in therapy with the herbal compound (group A) showed amelioration of all sleep parameters in a statistically significant way. Sleep onset decreased by 60 minutes at the end of the study, while placebo group showed a 15 minutes reduction; we noticed that time saved in sleep onset went to increase total slept time, 64 minutes of slept time increasing in group receiving the herbal compound vs 18 minutes in the placebo group (average value, Table 8). Moreover, decreasing of night awakenings frequency is consistent within 10 days in verum subjects (group A), with a further improvement at the end of the study, as shown in Figure 1. Sleep quality self-assessment results are consistent with the findings abovementioned. More in detail, subjects treated with the herbal supplement showed statistically significant improvements in sleep satisfaction and significant reduction in tension and irritability, difficulty to concentrate, and fatigue scores, compared to placebo group.

At the end of the study, the effectiveness of the herbal supplement was judged from good to excellent by 98% of subjects in group A, while 62% of group B (placebo) reported poor efficacy, ($p < 0.001$).

None of the 60 subjects reported adverse reaction related to the herbal compound at any experimental time, and 98% of subjects in the group A judged the safety and tolerability of the product to be from good to excellent.

Conclusion

Insomnia is a frequent disturbance in the Italian primary care population, often associated with high risk of comorbid conditions, and results in increased use of health care resources. Individuals who complain of sleep disturbance

are more likely to use the health care system, and the general practitioner is usually the first aide asked for intervention.¹⁵

The burden of insomnia is much more than financial; insomnia has a negative impact on the psychological and physical health of those who suffer from it, and this is in relation with self-report of depression,¹⁶ fatigue,¹⁷ and overall quality of life deterioration.¹⁸

Botanicals dietary supplement with relaxing and soothing properties can help practitioners to treat primary insomnia, especially when the risk/benefit profile of a patient does not sustain hypnotic drugs prescription. This clinical investigation on safety and effectiveness of an herbal compound made of valerian, hop, and jujube (Vagonotte, Cristalfarma) opens interesting perspectives on usage of herbal compounds to manage primary insomnia. The present study lacks quantitative diagnostic parameters because it is based on self-assessment questionnaires. Further investigations, providing quantitative data, could help in understanding herbal compounds' effectiveness on primary insomnia and sleep disturbances.

Acknowledgment

ANARDI group is a non-profit organization of scientific, social, and cultural interest. Special thanks to Pierluigi Coppola and all medical doctors and general practitioners of ANARDI medical and scientific association who played an essential role in supporting the project.

Disclosure

Professor Giancarlo Palmieri has a role of scientific consultant in Mediolanum Farmaceutici S.p.a.; Cristalfarma belongs to Mediolanum Pharmaceutical Group. The authors report no other conflicts of interest in this work.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: APA; 2000.
2. Costa e Silva JA, Chase M, Sartorius N, Roth T. Special report from a symposium held by the World Health Organization and the World Federation of Sleep Research Societies: an overview of insomnias and related disorders: recognition, epidemiology, and rational management. *Sleep*. 1996;19:412–416.
3. Hajak G. Insomnia in primary care. *Sleep*. 2000;23(Suppl 3):S54–S63.
4. National Prescribing Service. NPS News 67: Addressing hypnotic medicines use in primary care. *NPS*. 2010 Feb 2. Available from: <http://www.nps.org.au/publications/health-professional/nps-news/2010/nps-news-67>. Accessed March 19, 2010.
5. Mendels J. Criteria for selection of appropriate benzodiazepine hypnotic therapy. *J Clin Psychiatry*. 1991;52(Suppl):42–46.
6. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ*. 2005;331(7526):1169.
7. [No authors listed]. What's wrong with prescribing hypnotics? *Drug Ther Bull*. 2004;42(12):89–93.

8. Becker A, Felgentreff F, Schröder H, Meier B, Brattström A. The anxiolytic effects of a Valerian extract is based on valerenic acid, A1. *BMC Complement Altern Med*. 2014;14:267.
9. Morin CM, Koetter U, Bastien C, Ware JC, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep*. 2005;28(11):1465–1471.
10. Franco L, Sánchez C, Bravo R, Rodríguez A, Barriga C, Juárez JC. The sedative effects of hops (*Humulus lupulus*), a component of beer, on the activity/rest rhythm, *Acta Physiol Hung*. 2012;99(2):133–139.
11. Abourashed EA, Koetter U, Brattström A. In vitro binding experiments with a valerian, hops and their fixed combination extract (ze91019) to selected central nervous system receptors. *Phytomedicine*. 2004;11(7–8):633–638.
12. Gao QH, Wu CS, Wang M. The jujube (*Ziziphus jujuba* Mill.) fruit: a review of current knowledge of fruit composition and health benefits. *J Agric Food Chem*. 2013;61(14):3351–3363.
13. Jiang JG, Huang XJ, Chen J. Separation and purification of saponins from Semen *Ziziphus jujube* and their sedative and hypnotic effects. *J Pharma Pharmacol*. 2007;59(8):1175–1180.
14. Cao JX, Zhang QY, Cui SY. Hypnotic effect of jujubosides from Semen *Ziziphi Spinosae*. *J Ethnopharmacol*. 2010;130(1):163–166.
15. Terzano MG, Parrino L, Cirignotta F, et al; Studio Morfeo Committee. Studio Morfeo: insomnia in primary care, a survey conducted on the Italian population. *Sleep Med*. 2004;5:67–75.
16. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. *Am J Epidemiol*. 1997;146(2):105–114.
17. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry*. 1997;154(10):1417–1423.
18. Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med*. 1998;158(10):1099–1107.

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