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CLINICAL REVIEW

A systematic review of valerian as a sleep aid: Safe but not effective

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Summary Valerian is an herb that is widely available in a variety of commercial preparations and is commonly used as a sleep aid. A recent systematic review and meta-analysis of valerian concluded that evidence in support of the effectiveness of the herb was inconclusive. Therefore, in an effort to more closely examine this issue, a systematic review was conducted to examine the evidence on the efficacy of valerian as a sleep aid with specific attention to the type of preparations tested and the characteristics of the subjects studied. A comprehensive search of studies investigating valerian was conducted through computerized databases and hand searches of reference lists. Standardized forms were used to summarize findings and standardized criteria were used to assess study quality. Out of 592 articles initially identified, a total of 36 articles describing 37 separate studies met criteria for review: 29 controlled trials evaluated for both efficacy and safety, and eight open-label trials evaluated for safety only. Most studies found no significant differences between valerian and placebo either in healthy individuals or in persons with general sleep disturbance or insomnia. None of the most recent studies, which were also the most methodologically rigorous, found significant effects of valerian on sleep. Overall, the evidence, while supporting that valerian is a safe herb associated with only rare adverse events, does not support the clinical efficacy of valerian as a sleep aid for insomnia.

Introduction

Approximately one-third of the adults in the United States report symptoms of insomnia; including

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difficulty falling and/or remaining asleep at night.[1] Herbal therapies are commonly used for chronic symptoms of disturbed sleep. According to a recent survey, approximately 1.6 million Americans use complementary and alternative medical (CAM) therapies to treat their sleep disturbance.[2] Valerian is among the top-selling herbals in the US and is marketed as a promoter of restful sleep. In 2005, valerian was the 13th top-selling herb in US with estimated sales totaling $3.4 million.[3]

A previous systematic review[4] and a recent meta-analysis[5] both concluded that effects of valerian on sleep were promising, but inconclusive. Previous reviews have discussed various types of valerian products without specific attention to important differences in source species and in preparation techniques used (e.g., ethanol and water versus extractions with water alone). Because the chemical constituents in valerian products vary depending on species and extraction methods,[6,7] failure to evaluate the evidence based on the type of product used may have obscured an accurate assessment of valerian effects on sleep. The species used most commonly is *Valeriana officinalis*, although *V. edulis* (Mexican valerian) and *V. wallichii* (Indian valerian) are also used therapeutically. In general, extractions are prepared by soaking the dried root and rhizome (the underground portion of the stem) of valerian in a solution (called a menstruum), then centrifuging or drying the mixture to extract and concentrate plant constituents. The solutions used are typically: water alone, ethanol and water, or methanol and water. The ratio of alcohol to water affects the proportion of constituents obtained. According to the American Herbal Pharmacopeia, extraction of valerenic acids requires at least 30% alcohol, whereas extraction of valepotriates requires 70% alcohol.[7] The influence of extraction on the physiological effects of valerian remains unknown because the relative contributions of constituents responsible for to the plant's sedative effects have not been determined, and effects may depend on synergy of various compounds (e.g., valerenic acids, amino acids, valepotriates).[8]

In this review, we evaluate the research evidence on valerian as a sleep aid taking into account the types of products used. In addition, we considered whether the subjects in these studies were healthy, complained of general sleep disturbance, or met diagnostic criteria for insomnia: Diagnostic and Statistical Manual of Mental Disorders (DSM-III/IV); International Classification of Diseases (ICD-9/10); or International Classification of Sleep Disorders (ICSD). Finally, we make a recommendation about its usefulness as a sleep aid and clarify areas in which further research on valerian effects on sleep might be useful.

Materials and methods

The search strategy sought to obtain all relevant published data-based articles based on the following general criteria: (1) valerian root was administered orally, either alone or in combination with hops, lemon balm, or passion flower (herbs commonly combined with valerian in commercial preparations); and (2) a subjective or objective sleep measure (e.g., polysomnography or actigraphy) was at least one of the study's primary outcomes. A systematic computerized search of research databases was performed using the following keywords (where * is a wildcard): valerian*, valerenic, valepotriate*, and baldrian (''valerian'' in German). Databases included in the search were Pubmed, the Cochrane Central Register of Controlled Trials, EMBASE, PsychINFO, CINAHL, International Pharmaceutical Abstracts, and Dissertation Abstracts. The search was limited to human clinical trials in the databases that allowed this specification (Pubmed, Cochrane, and EMBASE). Reference lists from relevant articles, reviews, and book chapters were handsearched to identify additional studies. The search was not limited by language because numerous studies have been conducted in Europe, particularly in Germany, and reported in German-language journals.[9] In order to obtain the widest range of evidence on valerian, included studies were not limited to randomized clinical trials (RCTs), but only relevant full reports were evaluated (abstracts were excluded). Additionally, to fully explore the evidence on the sedative effects of valerian, studies of healthy persons without reported sleep disturbance were included.

Data were extracted onto standardized forms. A quality score based on the likelihood of bias was given to each study using the Jadad scoring system. In this system, studies are scored 0 (poor) to 5 (good) based on descriptions of randomization, double-blind methods, and reporting of dropouts.[10] Methodological features were also reviewed using the criteria of Stevinson and Ernst,[4] with the added criterion that adequate methods of blinding required masking of odor as well as appearance. These criteria included reporting of design elements of the study (e.g., randomization and blinding, effect size or power estimates); potential sources of bias and error (e.g., control of pre-bedtime variables); and measures to mask the

strong, distinctive odor unique to valerian. Studies were only assigned a point in the Jadad score for adequate description of blinding if both odor and appearance were addressed.

Results

Study characteristics and valerian products used

The computerized search yielded 592 article titles that were reviewed for relevance (see Fig. 1); 527 articles were excluded based on a review of the abstracts and 29 were excluded based on a review of the full text. These 556 articles were excluded for the following reasons: the articles (a) were not clinical studies (418 articles); (b) did not assess sleep as a primary outcome (65); (c) tested multiple herbs (other than hops, lemon balm, or passion flower) (6); (d) did not test an oral preparation of valerian (2); (e) were pediatric studies (2); (f) were not related to valerian at all (55); (g) were abstracts or incomplete reports (6); or (h) used a study design that did not permit assessment of valerian effects (2).

Thirty-six articles describing 37 studies of valerian (one article reported two studies)[11] for sleep in adults met criteria for inclusion in the review. Seventeen studies were published in German.[12–28] The German was translated into English and data extraction was checked against the articles in the original language by one of the co-authors (H, Petry), whose first language is German.

There was pronounced heterogeneity of study design, especially in regard to: sample inclusion and exclusion criteria; duration of treatment; preparation used (valerian species and extraction methods); dose given; dose timing (multiple daily doses versus bedtime only); and outcomes measured. Of the 37 included studies, 29 were clinical trials and 8 were open-label studies of clinical use. In the 29 clinical trials (see Table 1), the following preparations were tested: (a) valerian mono-preparations (without other herbs, 20 studies)[11,13,17,21,25–27,29–39]; (b) valerian with hops (6 studies),[15,22,24,40,41] of which one also investigated a mono-preparation[39]; (c) valerian with lemon balm (3 studies)[16,23,42]; and (d) valerian with both hops and lemon balm (1 study).[43] Eight open label trials tested: (a) valerian alone (1 study)[44]; (b) with hops (2 studies)[19,45]; (c) with hops and lemon balm (3 studies)[14,18,28]; and (d) with hops and passion flower (2 studies).[12,20] Open-label trials are discussed in regard to the safety and tolerability of the herb(s) but not for efficacy.

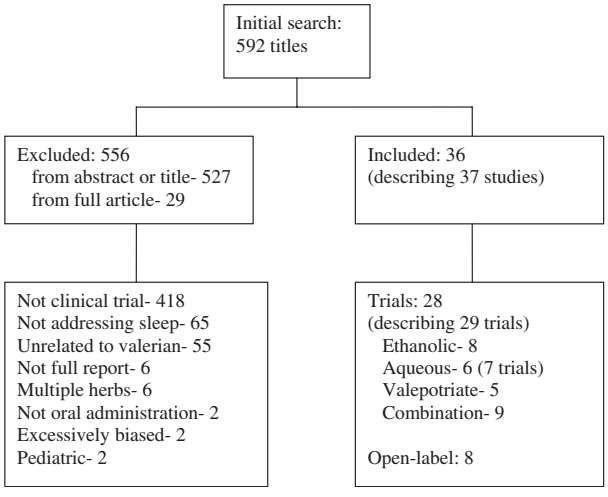

Figure 1 Search results.

In this review, studies are grouped by extraction type to allow for comparison of effects among preparations that are most likely to contain similar proportions of the various active constituents of valerian.

Ethanolic valerian extracts

Eight studies investigated ethanolic-aqueous *V. officinalis* extracts (see Table 2). All of these studies except one[34] tested valerian in persons who reported at least mild sleep disturbance, and most studies based inclusion on clinical diagnostic criteria for insomnia. Although some of the studies reported the proportions of the sample with different types of insomnia symptoms (e.g., sleep onset, sleep maintenance, or both), none of the studies analyzed the outcomes based on the specific insomnia symptom. Compared to the literature on other types of valerian preparations, studies of ethanolic extracts used the most rigorous standards for recruiting participants with primary insomnia (see Table 1). However, only three studies reported excluding persons with other primary sleep disturbances (e.g., sleep apnea, periodic limb movement disorder, restless legs).[13,33,34]

The commercial preparation of valerian most commonly studied is LI 156 (Sedonium®), an ethanolic extraction of *V. officinalis* (70% ethanol used for extraction). All six studies of this product tested 300–600 mg prior to bedtime (see Table 2). Only two of these studies measured polysomnographic (PSG) sleep outcomes.[30,33] In a double-blind randomized crossover trial, Diaper and Hindmarch[30] compared two doses (300 and

Table 1 Sample characteristics of valerian studies.

Study, year	Sample size	Sleep condition	Age	Female	Exclusions			
					Other sleep disorder	Medical conditions	Psychiatric problems	Medication affecting sleep
Ethanolic V. officinalis extracts								
Vorbach et al.[17] (1996)	121 (61 valerian, 60 placebo)	Insomnia, ICD-10 criteria	V: 47.2±11 P: 47.6±11.1	V: 62% P: 55%		+	+	+ (no use within 14 days)
Kuhlmann et al.[34] (1999)	102 (51 valerian, 51 placebo)	Insomnia, ICD-10 criteria	V*: 40.8±8.7 P*: 42.3±9.0	V: 51% P: 65%	+	+		+
Donath et al.[33] (2000)	16	Insomnia, ICSD criteria	All, Median: 49 (range: 22–55)	All: 75%	+	+	+	+ (14 days)
Dorn[13] (2000)	75 (39 valerian, 36 oxazepam)	Insomnia, ICD-10 criteria	V: 50.6±12.4 O: 53.9±12.0	V: 77% O: 61%	+	+	+	+ (4 weeks)
Ziegler et al.[32] (2002)	186 (93 valerian, 93 oxazepam)	Insomnia, ICD-10 criteria	V: 54.2±12.3 O: 50.6±12.6	V: 73% P: 61%		+	+ (past 3 months)	+ (4 weeks)
Coxeter et al.[31] (2003)	21	Diagnosed insomnia	All: 54±15	All: 54%		+	+	+
Jacobs et al.[29] (2003)	391 (135 valerian, 121 kava kava, 135 placebo)	Reported difficulty with sleep onset or maintenance within 2 weeks	V: 42.7±10 K: 41.1±10 P: 40.5±10	V: 79% K: 80% P: 88%			Anxiety required, depression allowed	+
Diaper and Hindmarch[30] (2004)	16	Mild sleep complaints	All: 55.9 ± 4.7	V: 62% P: 55%			+	
Aqueous V. officinalis extracts								
Leathwood et al.[46] (1982); Leathwood and Chauffard[39] (1982/1983)	166	General volunteers (no sleep problem required)	NR	NR				

Leathwood et al.[46] (1982); Leathwood and Chauffard[39] (1982/1983)	10	General volunteers (no sleep problem required)	All: 29±3.2	All: 0%				
Kamm-Kohl et al.[21] (1984)	78 (39 valerian, 39 placebo)	Elder home residents, behavioral sleep disturbance required	V: 70.6±4.4 P: 69.4±3.9	V: 76% P: 74%			Behavioral disturbance required	+
Balderer and Borbèly[11] (1985)	10	Healthy, no sleep disturbance	All: 32.5 (range: 22–44)	All: 50%				
Balderer and Borbèly[11] (1985)	8	Healthy, no sleep disturbance	All: 22.6 (range: 21–26)	All: 50%				
Leathwood and Chauffard[38] (1985)	8	Sleep onset problems	All: 45 (SD NR)	All: 37%				
Schulz et al.[37] (1994)	14	Elderly, insomnia	All: 61.6 ± 6.5	All: 100%		+	+	+ (14 days)
High-valepotriate preparations								
Jansen[27] (1977)	150 (74 valerian, 76 placebo)	Not specified, elder home residents	V: 78.4 (range 62–89) P: 78.8 (67–89)	V: 61% P: 51%				
Gessner et al.[26] (1983)	20 (11 valerian, 9 placebo)	Diagnosed sleep disturbance	All, range: 19–68	All: 57%				+
Gessner and Klasser[25] (1984)	11	Sleep disturbance and general nervous conditions	All: 26.1 (range: 20–38)	All: 45%		+		
Herrera-Arellano et al.[36] (2001)	20	Insomnia, DSM-III-R criteria	All: 45±7.8	All: 70%				+
Poyares et al.[35] (2002)	19 patients, 18 controls	Insomnia, DSM-IV criteria, chronic BZD use; healthy controls	All: 43.3±10.6	All: 80%	+	+ +		Required BZD use-withdrawn
Combination preparations: valerian and hops								
Müller-Limmroth and Ehrenstein[22] (1977)	12	Self-reported sleep disturbance	All, range: 22–27	All: 50%				
Rodenbeck et al.[24] (1988)	15 (8 valerian, 7 placebo)	Insomnia, ICSD criteria	V: 45.4±11.6, P: 47.6±12.5	NR		+	+	
Schmitz and Jackel[15] (1988)	46 (23 valerian, 23 bromazepam)	Insomnia, DSM-IV criteria	All: 50.3±13.6	All: 80%			+	+
Füssel et al.[41] (2000)	30	Mild to moderate insomnia	All*: 57.6±8.1	A: 70%		+		+
Morin et al.[40] (2005)	184 (59 valerian, 65 placebo, 60 diphenhydramine)	Mild insomnia, DSM-IV or ICSD criteria	V: 43.9±10.5 P: 45.2±10.2 D: 43.8±9.7	V: 59% P: 60% D: 60%	+	+	+	+

Table 1 (*continued*)

Study, year	Sample size	Sleep condition	Age	Female	Exclusions			
					Other sleep disorder	Medical conditions	Psychiatric problems	Medication affecting sleep
Combination preparations: valerian and lemon balm								
Lindahl and Lindwall[43] (1989)	27	Sleep disturbance and fatigue	All: 54 (range 25–68)	All: 30%				
Dressing et al.[23] (1992)	20	Not specified, healthy	All: 37.2±5.9	All: 50%		+	+	
Dressing et al.[16] (1996)	49 (25 valerian, 24 placebo)	Insomnia, DSM-III or ICD-10 criteria	V: 59.0 (range 31.2–86.8) P: 54.2 (range 22.1–81.4)	V: 26% P: 29%	+	+	+	+
Cerny and Schmid[42] (1999)	98 (66 valerian, 32 placebo)	No reported sleep problems	V: 33.4±12.5 P: 34.8±11.7	V: 42% P: 37%		+	+	+

*Mean±SD calculated from information given in the article. NR, not reported. *Insomnia diagnostic guides*: ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; ICSD, International Classification of Sleep Disorders.

Table 2 Studies of valerian for sleep.

Study, year	Sample with sleep disturbance	Study design	Intervention	Treatment duration	Outcome measures	Main valerian sleep outcomes	Adverse effects
Ethanolic extracts							
Vorbach et al.[17] (1996)	Yes	PDB, RCT	(a) Valerian 600 mg (b) Placebo	28 nights	SF-B	No significant difference from placebo	AE related to valerian: headache (n = 2), morning hangover (n = 1)
Kuhlmann et al.[34] (1999)	No	PDB, RCT	(a) Valerian 600 mg (b) Placebo	14 nights	VIS-M, VIS-A	No significant difference from placebo	AE differences between treatments not significant, no serious AE
Donath et al.[33] (2000)	Yes	PDB, RCT, C/O	(a) Valerian 600 mg (b) Placebo	14 nights	PSG, sleep diary, sleep questionnaire (VAS ratings)	No significant difference from placebo	AE related to valerian: headache (n = 1), GI complaints (n = 1)
Dorn[13] (2000)	Yes	DB, RCT	(a) Valerian 600 mg (b) Oxazepam 10 mg	28 nights	SF-B	Valerian versus baseline: ↑ SQ; no significant difference between valerian and oxazepam	Withdrawals related to treatment: valerian (n = 2), oxazepam (n = 3)
Ziegler et al.[32] (2002)	Yes	DB, RCT	(a) Valerian 600 mg (b) Oxazepam 10 mg	42 nights	SF-B	Valerian versus baseline: ↑ SQ; no significant difference between valerian and oxazepam	AE: valerian (n = 29), oxazepam (n = 36) Hangover effects: valerian (n = 2), oxazepam (n = 6)
Coxeter et al.[31] (2003)	Yes	PDB, n-of-1 design*	(a) Valerian 450 mg (b) Placebo	7 nights	Sleep diaries	No significant difference from placebo	AE differences between treatments not significant
Jacobs et al.[29] (2003)	Yes	PDB, RCT	(a) Valerian, 6.4 mg valerenic acid (b) Kava kava, 100 mg, Kavalactones (c) Placebo	28 nights	ISI	No significant difference from placebo	Significantly greater incidence of diarrhea with valerian

Table 2 (*continued*)

Study, year	Sample with sleep disturbance	Study design	Intervention	Treatment duration	Outcome measures	Main valerian sleep outcomes	Adverse effects
Diaper and Hindmarch[30] (2004)	Yes	PDB, RCT, C/O	(a) Valerian 300 mg (b) Valerian 600 mg (c) Placebo	1 night	PSG, LSEQ	No significant difference from placebo	AE possibly related to treatments: valerian 300 mg (n = 11), valerian 600 mg (n = 4), placebo (n = 8)
Aqueous extracts							
Leathwood et al.[46] (1982); Leathwood and Chauffard[39] (1982/1983)	No	PC, C/O	(a) Valerian 800 mg (b) Placebo	2 nights	PSG, sleep questionnaire	No significant difference from placebo	Not mentioned
Leathwood et al.[46] (1982); Leathwood and Chauffard[39] (1982/1983)	No	PDB, RCT, C/O	(a) Valerian 400 mg (b) Valerian–hops 400 mg (c) Placebo	3 nights	SQ and SL improvement ratings	Valerian versus placebo: greater proportions reported improved SQ and SL	No residual sedation
Kamm-Kohl et al.[21] (1984)	Yes	PDB, CCT	(a) Valerian 90 mg 3x/d (b) Placebo	14 nights	Sleep questionnaire (Likert scales)	Valerian versus placebo: greater proportions reported improved SL and sleep maintenance	Dizziness (4 total): valerian (n = 2), placebo (n = 2)
Balderer and Borbèly[11] (1985)	No	PDB, CCT, C/O	(a) Valerian 450 mg (b) Valerian 900 mg (c) Placebo	1 night	Sleep diary, sleep quality (VAS)	Valerian versus placebo: ↓ WASO and SL, both doses	No residual sedation
Balderer and Borbèly[11] (1985)	No	PDB, RCT, C/O	(a) Valerian 900 mg (b) Placebo	1 night	PSG	No significant difference from placebo	No residual sedation
Leathwood and Chauffard[38] (1985)	Yes	PDB, RCT, C/O	(a) Valerian 450 mg (b) Valerian 900 mg (c) Placebo	4 nights	Actigraphy, sleep questionnaire	Valerian versus placebo: Actigraphy: ↓ SL, both doses SR: No significant difference from placebo	Significantly greater morning sleepness with 900 mg dose, no other AE
Schulz et al.[37] (1994)	Yes	PDB, RCT	(a) Valerian, 1215 mg on night 1, 405 mg 3x/d days 2–8; (b) Placebo	8 nights	PSG, sleep diaries, SF-A, SF-B	Valerian versus placebo: PSG: significance NR SR: No significant difference from placebo	Not mentioned
Valepotriate preparations							
Jansen[27] (1977)	No	PDB, RCT	(a) Valerian, 100 mg valepotriates 3x/d (b) Placebo	30 nights	4-point symptom rating scales	↓ Sleep disturbance, valerian > placebo (statistical testing NR)	No AE occurred

Gessner et al.[26] (1983)	Yes	PDB, CCT, C/O,	(a) *V. edulis*, 240 mg valepotriates (b) Placebo	9 nights	VIS-M, VIS-A, SF-A , SF-B	Valerian versus placebo: ↑ SQ and ↓ SL	↓ bad dreams with valerian. No other significant AE differences between treatments
Gessner and Klasser[25] (1984)	Yes	PDB, RCT, C/O	(a) *V. edulis*, 60 mg valepotriates (b) *V. edulis*, 120 mg valepotriates (c) Placebo	1 night	PSG, sleep questionnaires	PSG: ↓ Stage 4 with 120 mg versus placebo SR: No significant difference from placebo	No hangover symptoms
Herrera-Arellano et al.[36] (2001)	Yes	DB, RCT, C/O	(a) *V. edulis*, 450 mg (b) *V. officinalis* 450 mg	1 night	PSG, sleepiness VAS	Versus baseline: *V. edulis* ↓ number of awakenings. No significant difference between valerian preparations	Dyspepsia (3 total): *V. edulis* (n = 1), *V. officinalis* (n = 2)
Poyares et al.[35] (2002)	Yes	PDB, RCT	(a) *V. wallichii*, 100 mg valepotriates 3x/d (b) Placebo	15 nights	PSG, sleep diaries, sleep quality (VAS)	Valerian versus placebo: PSG: ↓ WASO, ↑ SL SR: ↑ SQ	AE with valerian (n = 3 GI complaints)

Study design abbreviations: CCT: controlled clinical trial (non-randomized); C/O: crossover; DB: double-blind (no placebo condition); PC: placebo-controlled (not double-blind); PDB: placebo-controlled double blind; RCT: randomized clinical trial. *Outcome measures*: AE, adverse event; NR, not reported; PSG, polysomnography; SF-A, Gortelmeyer Schlaffragebogen A, assesses sleep quality for the past night; SF-B, Gortelmeyer Schlaffragebogen B, assesses sleep quality for the two weeks; SL, sleep latency; SQ, sleep quality; SR, self-report; VAS, visual analog scale; VIS–M, Visualanalogskala–Morgen (a standardized set of visual analog scales of sleep completed in the morning); WASO, wake after sleep onset.

600 mg) of LI 156 to a placebo after one night in a sample of persons with mild sleep complaints. No significant differences were found on PSG or subjective sleep outcomes (sleep efficiency, sleep latency, awakenings, sleep stages, and sleep quality ratings). Another double-blind randomized crossover study tested 600 mg LI 156 for 14 nights in persons with insomnia.[33] In the valerian group, percent slow wave sleep (SWS, NREM Stages 3 and 4 which are considered deep sleep) was increased compared to baseline. No differences between valerian and placebo were found in other PSG outcomes or subjective sleep quality ratings.

The other four double-blinded studies of LI 156 measured only subjective outcomes. Parallel-group randomized controlled trials (RCTs) compared repeated dosing of valerian versus placebo in healthy individuals for 14 days[34] or in persons with insomnia for 28 days.[17] Subjective sleep quality ratings improved in the valerian groups of both studies, but in neither case was sleep significantly improved when compared to placebo. Lack of significance in the healthy sample[34] may have resulted from a ceiling effect. One of these studies,[34] as well as two other RCTs,[13,32] compared LI 156 (600 mg dose) to benzodiazepines (flunitrazepam and oxazepam). In these studies, the effectiveness of the benzodiazepines was assumed, and comparable effects of valerian and benzodiazepines were presumed to confirm the effectiveness of valerian. Kuhlmann et al.[34] reported reduced subjective sleep latency and increased sleep quality ratings with both valerian and flunitrazepam compared to placebo after a single night in a sample of healthy persons, but did not report the statistical significance of these findings. Two other studies compared valerian and oxazepam for four weeks[13] or six weeks[32] in persons with insomnia. The studies reported significant improvement of subjective sleep quality ratings compared to baseline with both valerian and oxazepam. Improvement did not significantly differ between the treatments, indicating that the effects of valerian were equivalent to oxazepam.

Two studies investigated ethanolic valerian extracts other than LI 156. In a double-blind RCT, Jacobs et al.[29] compared 28 days of valerian extract (PureWorld Botanicals, 70% ethanolic extract), kava kava extract, or placebo in persons with both sleep disturbance and anxiety. Insomnia severity index (ISI) scores, subjective sleep latency, and subjective awakenings were reduced with all three treatments, but the magnitude of improvement was greatest in the placebo group and neither of the herbal treatments differed significantly from placebo. Another double-blind study used n-of-one methods (a within-subject repeated crossover design) to test a high-ethanol (96%) extraction of valerian.[31] Because this product used an ethanol concentration over 70% for extraction, the product contained significant amounts of valepotriates (valtrate) as well as valerenic acid. Each participant was tested for six one-week periods (three valerian, three placebo) in random order. Treatment was considered a success or failure within each individual based on whether the individual improved during the weeks of valerian compared to the weeks of placebo treatment. The analyses showed valerian to be equivalent to placebo on subjective outcomes of sleep quality, sleep latency, awakenings, total sleep time, and morning refreshment.

In sum, ethanolic extracts of *V. officinalis*, several of which were investigated using rigorous study designs, have not been shown to significantly affect objective[30,33] or subjective[17,29,31,33,34] sleep outcomes in comparison to placebo in subjects with and without insomnia. However, these preparations have been shown to improve subjective sleep quality ratings in a manner equivalent to benzodiazepines under the assumption that the benzodiazepines tested were superior to placebo.[13,32]

Aqueous valerian extracts

Seven studies (reported in six publications) investigated the effects of aqueous *V. officinalis* extracts (water alone is used for extraction) on sleep (see Table 2). These studies varied greatly in methodological quality, and several of the trials did not report randomization to treatment procedures. All of these studies reported using a double-blind design except for one.[39] Four of these studies were conducted in general volunteers who were not required to complain of a sleep disturbance,[11,39,46] one in persons with sleep onset difficulties,[38] and two in elderly persons with sleep disturbance.[21,37] None of the studies used insomnia diagnostic criteria as inclusion criteria, and none reported exclusion of persons with primary sleep disorders (see Table 1). Only one study excluded medical conditions that could contribute to sleep disturbance[37] and only two excluded concurrent use of sleep-altering medications.[21,37]

Two parallel-group clinical trials investigated a commercially available aqueous valerian extract (Valdispert®) in elderly individuals with insomnia. In a randomized trial, Schulz et al.[37] investigated 405 mg valerian extract or placebo given three times a day for eight days to elderly participants with sleep onset and sleep maintenance problems.

Objective (PSG) and subjective sleep outcomes (sleep efficiency, wake after sleep onset (WASO), sleep quality rating) did not differ significantly between valerian and placebo after one dose, but no statistical comparison of valerian and placebo is reported at the end of treatment (after eight nights). Another trial of elderly persons with sleep disturbances, Kamm-Kohl et al.[21] investigated 90 mg of Valdispert® or placebo three times daily for 14 days. When asked whether their sleep onset and maintenance difficulties improved, significantly greater proportions of persons on valerian reported that these conditions were "better" (versus "the same or worse") after treatment than those on placebo.

Several studies investigated a specific aqueous valerian extract (Dixa S.A., Switzerland) in general volunteers (only one of these studies required sleep disturbance for enrollment).[38] An early randomized crossover trial by Leathwood and colleagues[46] measured subjective sleep in general volunteers (no exclusions noted) with 400 mg aqueous valerian extract (Dixa S.A., Switzerland) or placebo taken on two nights each in random order (a 400 mg valerian/hops extract was also tested, discussed later). A significantly greater proportion of persons rated their sleep quality as "better than usual" and sleep latency as "shorter than usual" when given valerian than when given placebo. Improved sleep was more pronounced in the sub-sample of persons reporting habitually poor sleep. In a double-blind crossover trial (randomization not reported), Balderer and Borbèly[11] investigated 450 and 900 mg of valerian extract (Dixa S.A., Switzerland) in 10 healthy young persons. One night of valerian significantly decreased subjective sleep latency and WASO but not sleep quality ratings compared to the placebo. Two studies measured PSG sleep outcomes. In a small crossover trial, Leathwood and colleagues[39,46] investigated the effects of two nights of valerian extract (400 mg, Dixa S.A., Switzerland) on the sleep of 10 young, healthy men. No significant differences between the valerian and placebo were found on PSG sleep measures (total sleep time, % sleep stages). In another crossover trial, Balderer and Borbèly[11] tested two doses (450 and 900 mg) of the same extract (Dixa S.A., Switzerland) for one night of each dose (or placebo) in eight healthy young persons. Neither PSG nor subjective sleep outcomes (sleep latency, awakenings, WASO, time in sleep stages) differed significantly between valerian and the placebo. Finally, one study measured objective sleep using actigraphs (wrist-worn movement detectors that can discriminate waking from sleep behavior) in addition to subjective outcomes. In this double-blind crossover trial by Leathwood and Chauffard[38] each of three treatment conditions (450 mg valerian, 900 mg valerian, Dixa S.A., Switzerland, or placebo) was given randomly over 12 weeknights to individuals with difficulty falling asleep (recruited from the research staff and families), with the participants undergoing four nights per treatment condition. Both doses significantly reduced actigraphic sleep latency compared to the placebo. Subjective sleep latency and sleep quality ratings did not differ significantly from the placebo. Morning sleepiness was significantly greater with the 900 mg valerian dose than the placebo, suggesting dose-dependent effects.

In sum, studies testing the effects of aqueous valerian extracts produced mixed results. In older persons with sleep disturbance, one study reported that a significant proportion of the sample reported "better" sleep,[21] whereas another study did not show significant effects on either objective or subjective sleep outcomes.[37] Short-term supplementation (one to four nights) of valerian was not shown to affect PSG[11,39] or subjective sleep outcomes[11,38,39] in subjects without known sleep complaints, but valerian did reduce subjective sleep latency and WASO with sleep onset insomnia.[38] The findings of these studies of aqueous valerian extracts cannot be generalized to persons diagnosed with insomnia because this type of product has not been rigorously tested in clinic populations.

Valepotriate preparations

Five studies investigated valerian extractions standardized on valepotriate content (see Table 2). This constituent is minimally present in the *V. officinalis* species or extractions from this species. However, valepotriates are present in significant levels in other *Valeriana* species (*V. edulis* and *V. wallichii*) and are believed to be largely responsible for purported clinical effects of preparations from these species. The studies of valepotriates varied in the products used, samples studied, and timing of administration (e.g., several times/day and/or at bedtime). Information on valerian extraction method was only available from one study.[36] As with the studies of aqueous extracts, none of the studies used insomnia diagnostic criteria for inclusion (see Table 2). One study excluded subjects for primary sleep disorders (other than insomnia),[35] two excluded subjects for co-morbid sleep disturbance,[25,35] and three excluded subjects for current use of sleep-altering medications[26,35,36] (see Table 1).

Three studies investigated extracts of *V. edulis* species. Herrera-Arellano and colleagues[36] compared two types of valerian extracts, *V. edulis* (high-valepotriate, 450 mg, 62% ethanol extraction) and *V. officinalis* (high-valerenic acid, 450 mg, information on extraction method not available) in a double-blind crossover study of persons with diagnosed insomnia. There were no significant differences between the two species on any PSG outcome (sleep latency, sleep efficiency, sleep stages), but the overall effects of either preparation are uncertain because the study did not include a placebo group. Two of the studies were placebo-controlled, double-blind crossover trials (Gessner and Klasser; Gessner et al.)[25,26] and investigated the effects of *V. edulis* (Harmonicum Much®) on sleep in persons with general sleep disturbance. In one study[26] that assessed only subjective sleep outcomes, nine nights of valerian (standardized to contain 120 mg valepotriates) significantly improved subjective sleep quality ratings and reduced subjective sleep latency compared to placebo. In the other study, which assessed the effects of 60 or 120 mg valepotriates on PSG outcomes,[25] one night of valerian significantly reduced Stage 4 sleep in comparison to placebo. Neither dose significantly affected other PSG outcomes.

Two other studies tested a preparation standardized to valepotriate content. One study tested the effects of a *V. wallichii* extract (Valmane®) on rebound sleep disturbances in persons with insomnia following gradual cessation of chronic benzodiazepine use.[35] In this double-blind, placebo-controlled RCT, a 100 mg dose of valepotriates was given three times daily for 15 days. Subjective sleep quality ratings improved significantly with valerian compared to the placebo. PSG outcomes showed reduced WASO. A significant and substantial reduction in sleep latency occurred with placebo but not with valerian. The authors suggested that this may have been related to individual differences in withdrawal from benzodiazepines. In a placebo-controlled, double-blind RCT, geriatric clinic patients were given 100 mg valepotriates (species and preparation not reported) three times daily for 30 days.[27] When asked to rate whether their sleep disturbance was better, the same, or worse, both the valepotriate and placebo groups reported improvement. Improvement was greater in the valepotriate group, but no statistical comparisons were reported.

Overall, the literature on valepotriate preparations provides limited evidence that valepotriates may improve sleep, but these studies are highly varied. Compared to placebo, studies reported significantly improved sleep quality ratings in persons withdrawing from benzodiazepines[35] and persons reporting disturbed sleep.[25] One of these studies also reported reduced awakening versus baseline but used no placebo control.[36] These findings suggest that valepotriate preparations may mildly reduce sleep disturbances. Like aqueous valerian preparations, high-valepotriate preparations have not been rigorously tested in persons diagnosed with insomnia and extrapolation from the few studies available suggests such efficacy would be limited.

Valerian combination preparations

Many of the valerian products commercially available are combinations with other herbs including hops, lemon balm, and/or passion flower, all of which purportedly have their own sedating or tranquilizing effects. It is possible that these combinations produce synergy and thus are more effective than each of these component herbs alone. Controlled studies have investigated only combinations of valerian with hops and/or lemon balm. Most of these studies were in persons with insomnia[15,24,40,41] or those with a general complaint of sleep disturbance,[22,43] although three studies recruited healthy persons without requiring sleep disturbance.[16,23,42] The specificity of exclusion criteria was thorough in some studies, but not in others (see Table 1). Only two of 10 studies reported screening for primary sleep disorders other than insomnia as well as medical conditions affecting sleep, psychiatric problems, and medications affecting sleep.[23,40] Most of the other studies screened for some but not all of these criteria, but two studies did not report screening for any of these criteria.

Six studies investigated valerian–hops combinations (see Table 3). Three studies investigated the effects of the valerian–hops combination ZE 91019 (Alluna®, methanolic-aqueous extract, % alcohol proprietary) on sleep. Two of these studies were double-blind, placebo-controlled RCTs that compared four weeks of ZE 91019 (500 mg valerian/120 mg hops[24]; 374 mg valerian/82 mg hops)[40] to placebo in persons with insomnia (ICD or DSM-IV criteria). In these two studies, neither PSG outcomes[24,40] nor subjective outcomes (sleep efficiency, sleep latency, ISI scores)[40] improved or were substantially different between valerian–hops and placebo. In a one-group study of persons with mild to moderate insomnia, Füssel et al.[41] reported reduced sleep latency and increased sleep efficiency measured by PSG with ZE 91019

Table 3 Studies of valerian combination products for sleep.

Study, year	Sample with sleep disturbance	Study design	Intervention	Treatment duration	Outcome measures	Main sleep outcomes	Adverse effects
Valerian and Hops							
Muller-Limmroth and Ehrenstein[22] (1977)	Yes	PDB, CCT, C/O, Experimental sleep disturbance by traffic noise	(a) Valerian–hops 240 mg/400 mg (b) Placebo	1 night	PSG	No significant difference from placebo	Not mentioned
Leathwood et al.[46] (1982); Leathwood and Chauffard[39] (1982/1983)	No	PDB, RCT, C/O	(a) Valerian 400 mg (b) Valerian–hops 400 mg (c) Placebo	3 nights	Sleep questionnaire	No significant difference between valerian–hops and placebo	No residual sedation
Rodenbeck et al.[24] (1998)	Yes	PDB, RCT	(a) Valerian–hops 500 mg/120 mg (b) Placebo	28 nights	PSG	No significant difference from placebo	Not mentioned
Schmitz and Jackel[15] (1998)	Yes	DB, RCT	(a) Valerian–hops 200 mg/45 mg (b) Bromazepam 3 mg	14 nights	SF-A, SF-B	Valerian–hops versus baseline: ↑ SQ; no significant difference between valerian and bromazepam	No withdrawal symptoms Stomach complaint: valerian (n = 1), bromazepam (n = 1)
Fussel et al.[41] (2000)	Yes	One-group, pre-post-test	Valerian–hops 500 mg/120 mg	14 nights	PSG	Valerian–hops versus baseline: ↓ SL, ↓ wake, ↑ SE	No AE occurred
Morin et al.[40] (2005)	Yes	PDB, RCT	(a) Valerian–hops 374 mg/82 mg (b) Diphenhydramine 50 mg (c) Placebo	28 nights	Sleep diaries, sleep questionnaire (ISI); PSG ($n = 75$)	Valerian hops versus diphenhydramine or placebo: no significant difference	No residual effects, serious AEs, or rebound insomnia No significant group difference in AEs
Valerian and lemon balm							
Lindahl and Lindwall[43] (1989)	Yes	DB, RCT, C/O	(a) Valerian–hops–lemon balm 400 mg/375 mg/160 mg (b) Valerian–hops–lemon balm 4 mg/375 mg/160 mg	1 night	Sleep quality (4-point scale)	Valerian 400 mg versus 4 mg: Greater proportion reported ↑ SQ	No AE occurred
Dressing et al.[23] (1992)	No	PDB, RCT, C/O	(a) Valerian–lemon balm 160 mg/80 mg (b) Triazolam 0.125 mg (c) Placebo	1 night	PSG	No significant difference from placebo	No rebound effects occurred

Table 3 (*continued*)

Study, year	Sample with sleep disturbance	Study design	Intervention	Treatment duration	Outcome measures	Main sleep outcomes	Adverse effects
Dressing et al.[16] (1996)	Yes	PDB, RCT	(a) Valerian–lemon balm 320 mg/160 mg 2x/d (b) placebo	14 nights	VIS-M, SF-B	Valerian–lemon balm versus placebo: ↓ SL, ↑ SQ	No hangover, rebound, or withdrawals. AE: Valerian/lemon balm (n = 5), placebo (n = 1)
Cerny and Schmid[42] (1999)	No	PDB, RCT	(a) Valerian–lemon balm 360 mg/240 mg (b) Placebo	30 nights	Sleep quality VAS, SQ improvement ratings	Valerian versus placebo: VAS: No significant difference. A greater proportion reported SQ improvement	No serious AE, no significant group difference in AEs

Study design abbreviations: C/O, crossover, DB, double-blind (no placebo condition); PDB, placebo-controlled double blind; RCT, randomized clinical trial. *Outcome measures*: AE, adverse event; NR, not reported; PSG, polysomnography; SF-A, Gortelmeyer Schlaffragebogen A, assesses sleep quality for the past night; SF-B, Gortelmeyer Schlaffragebogen B, assesses sleep quality for the two weeks; SL, sleep latency; SQ, sleep quality; SR, self-report; VAS, visual analog scale; VIS–M, Visualanalogskala–Morgen (a standardized set of visual analog scales of sleep completed in the morning).

(500 mg valerian/120 mg hops) compared to baseline measurements.

Two other studies investigated the valerian–hops combination Hova® (information on extraction method not available).[15,46] In the previously described randomized crossover trial by Leathwood and Chauffard,[46] three random nights of Hova® (400 mg, proportions of valerian/hops not reported) did not improve sleep in comparison to a placebo in healthy persons. In a double-blind RCT of persons with insomnia, sleep quality ratings improved significantly with both Hova® (200 mg valerian/45 mg hops) and the benzodiazepine bromazepam (3 mg).[15] The two treatments did not significantly differ, although only small improvement was seen with either treatment. Finally, in a double-blind controlled clinical trial, Müller-Limmroth and colleagues[22] investigated whether or not a valerian–hops combination (240 mg valerian/400 mg hops, Seda-Kneipp®) would attenuate sleep disturbances experimentally induced by traffic noise. No significant differences were found between valerian–hops and placebo on the PSG outcomes.

Valerian–lemon balm (also called lemon melissa) combinations were investigated in four clinical trials; two tested the herbal combination in healthy persons and two recruited persons with sleep disturbance (see Table 3). In a double-blind RCT of healthy persons, 30 nights of a valerian–lemon balm combination (360 mg valerian, 70% ethanol extraction/240 mg lemon balm, 30% methanol extraction, Songha Night®) had no effect on sleep quality ratings on a 0–100 visual analog scale (VAS) compared to a placebo.[42] However, a significantly greater proportion of those on valerian–lemon balm than those on placebo (33% versus 9%) reported that their sleep quality was "better" (versus "unchanged" or "worse") even though the VAS ratings did not reflect this change. Another double-blind study of healthy persons investigated the effects of one night of the valerian–lemon balm combination (160 mg valerian, 70% ethanol extraction/80 mg lemon balm, 30% ethanol extraction; Euvegal®).[23] In this double-blind crossover study of healthy individuals the herbal combination did not improve PSG-measured sleep efficiency, sleep latency, or WASO compared to a placebo. The same research group conducted a 14-day trial of Euvegal® (320 mg valerian, 70% ethanol extraction/160 mg lemon balm, 30% ethanol extraction) given twice a day in persons with insomnia. The herbal combination significantly improved subjective sleep quality ratings and reduced subjective sleep latency compared to the placebo.[16] Finally, in a placebo-controlled, double-blind crossover study of persons with sleep disturbance, a significantly greater proportion of participants reported that their sleep quality was "perfect" after one night of a valerian–hops–lemon balm combination (400 mg valerian/375 mg hops/160 mg lemon balm, information on extraction method not available; Valeriana natt®) than a night of hops–lemon balm alone.[43]

In summary, in subjects with insomnia, placebo-controlled studies of valerian–hops combinations did not improve PSG or subjective sleep outcomes,[24,40] but a valerian–lemon balm combination reduced subjective sleep latency and increased subjective sleep quality.[16] A one-group trial of valerian–hops reported improved sleep compared to baseline,[41] and another trial of valerian–hops reported improvement of sleep quality ratings that was similar to improvement with a benzodiazepine.[15] Neither of the two studies of valerian–lemon balm in healthy individuals showed significantly improved sleep.[16,42] Overall, these findings are similar to results of studies of valerian alone. These mixed, but predominantly negative, findings concerning the effects of valerian combinations on sleep outcomes indicate that combination products are no more effective than valerian alone; that is to say not effective at all.

Side effects and safety

No serious adverse effects occurred in these reported clinical trials of valerian (see Tables 2 and 3). The number of side effects with ethanolic valerian extracts did not differ significantly from placebo,[31,34] and tended to be fewer than benzodiazepines.[13,32] Specific side effects reported with ethanolic valerian extracts included headache, gastrointestinal (GI) complaints, morning "hangover," diarrhea, drowsiness, exaggerated feeling of well-being, mental dullness, difficulty sleeping, depression, irritability, dizziness, feeling remote, nausea, and sweating.[17,29,30,32,33] Studies of aqueous extracts reported two cases of dizziness with valerian[21] and one case of nausea possibly related to valerian.[46] Additionally, Leathwood and Chauffard[38] reported evidence of dose-dependent hangover effects, with morning sleepiness ratings significantly higher after valerian than placebo for the 900 mg dose but not the 450 mg dose. In the clinical trials of valepotriate preparations only five participants reported adverse effects, and in all cases these were GI (diarrhea, stomach discomfort, bitter taste in mouth).

Eight open-label clinical studies with sample sizes ranging from 20 to 830 participants investigated the tolerability of valerian or valerian combination products. In several studies, no adverse events occurred,[19,20,44] and in another study only three minor events occurred.[14] When asked to rate the tolerability of the herbal products, participants (70–90%) rated them as ''good'' or ''very good''.[12,14,18,20,28]

Discussion

Evaluation of the effectiveness of valerian as a sleep aid is difficult given the considerable variation among the studies in duration, design, and herbal preparation. Originally, we had intended to perform a meta-analysis of the literature available on valerian, but concluded that such an analysis was not appropriate given the variability in the research quality. In particular, evidence on valerian from both parallel-group and crossover trials should not be combined in the same meta-analysis because inclusion of crossover trials does not account for lack of independence of the group data and increases the risk of Type I error. Other features of valerian trials that preclude use of meta-analytic procedures are use of different types of products (species, extraction methods, and herbal combinations) and differing characteristics of the samples studied (healthy versus insomnia). There is insufficient data on specific sleep outcomes to conduct separate meta-analyses on the literature divided into categories based on product and sample. Therefore, to fully evaluate the current state of the evidence of valerian effects on sleep outcomes, we decided that a descriptive synthesis of the literature with specific attention to product and sample characteristics was most appropriate.

Issues related to dose and treatment duration were not emphasized in this review because there are no current standards for an optimal dose or recommended treatment duration. Given the lack of dose-response studies, it is unclear whether any of the studies used an optimal dose, although most were consistent with expert recommendations. Additionally, it is commonly recommended that at least two weeks of valerian treatment is necessary for effects to manifest,[8] but this recommendation has not been specifically investigated. Although a few placebo-controlled studies of two weeks or longer treatment duration reported significant improvement with valerian,[16,21,35] a greater number found no significant improvement.[17,24,29,33,34,40,42]

Quality of the research evidence

The quality of the studies reviewed was rated using the Jadad scoring criteria for potential sources of bias (higher scores = higher quality)[10] (see Table 4). The studies of ethanolic extracts were conducted most recently and were of the highest quality; most studies had Jadad scores ranging from 3 to 5.[13,17,29–32,34] Studies of aqueous extracts and valepotriate-containing extracts were mostly conducted in the 1970s and 1980s, and tended to be of mixed quality; few studies had a Jadad score $\geqslant 3$.[21,36,38,46] The studies of highest quality did not find valerian (ethanolic extracts or valerian–hops combination) to be significantly superior to placebo for improving outcomes in insomnia.[17,29,31,40]

In a previous systematic review,[4] the authors evaluated several criteria (e.g., randomization and blinding, power estimates, potential sources of bias) in addition to the Jadad score that were important to the validity of clinical trials of the effects of herbs on sleep. None of the studies reviewed addressed all of the important trial design elements, although the number of elements included did increase in the more recent studies examined. Few of the studies described the randomization procedures or reported data on group equivalence, which could bias the findings if the groups differed on baseline characteristics. Perhaps more problematic was the failure to calculate sample size, and thus, many studies were likely underpowered to detect group differences. The majority of studies had sample sizes between 11 and 21 participants, with only six studies having moderately large sample sizes (78–391).[17,27,29,32,34,46] Nevertheless, the studies generally used statistical methods that were liberal in assigning statistical significance to findings (e.g., paired tests with no alpha rate correction for multiple testing), which makes the lack of statistical significance more compelling evidence against the clear effectiveness of valerian as a sleep aid. On the other hand, failure to control pre-bedtime variables such as caffeine use or exercise may have allowed these factors to influence sleep outcomes, confounding any potential effects of valerian on sleep.

Of particular methodological concern in the studies reviewed was the considerable failure to ensure that the placebo (or comparison medication) and valerian were adequately masked. Valerian has a very distinctive, unpleasant odor. Failure to adequately mask the valerian treatment or 'odorize' the comparison treatment may increase expectations that valerian pills will be effective.

Of the 28 studies that were trials with a comparison group, 10 matched treatments on appearance, while seven matched on odor (two described the matching procedures).[29,31] Only one study reported the success of the employed masking procedure[29] (see Table 4). In two recently completed studies by the authors of this review (C.A. Landis and D.M. Taibi, unpublished), researchers used valerian to confer the odor of valerian on the placebo capsules. In one study, valerian capsules were stored in proximity to the placebo pills. In the other study, the placebo was stored in plastic containers that had been ''odorized'' by containing active valerian for a week. Although it is possible that these methods may contaminate the placebo, the amount of valerian transferred is likely to be minimal and not clinically effective. In each of these studies, participants were not able to identify which treatment condition they had received, indicating that both masking procedures were successful.

The specificity of the sample characteristics, including subject inclusion and exclusion criteria were evaluated (Table 1). Little consideration was given to age and gender, although few studies specifically investigated valerian in older adults. It was evident that many of the studies did not report exclusion of potentially confounding variables, including co-morbid insomnia, psychiatric diagnoses, and concurrent use of sleep-altering medications. In particular, a serious omission was the failure to report exclusion of other sleep disorders (e.g., sleep apnea and restless legs syndrome), even in several of the high-quality studies. The findings from studies of ethanolic extracts and valerian–lemon balm combinations are the most reliable in relation to controlling for potential confounding variables. Finally, none of the studies of insomnia patients differentiated between types of insomnia symptoms in the analysis. It is possible that valerian products may have differential efficacy for sleep initiating versus sleep maintenance symptoms.

Evaluation of the effects of valerian on sleep

Only a limited number of studies were available on each type of valerian product. Although some of these studies reported improvement over time, often no direct comparisons of valerian and placebo groups were reported.[27,37,34] Given that several studies of valerian reported improvement of sleep under the placebo condition (e.g.,[17,29,33]), improvement over time in the valerian group is insufficient to exclude the possibility of placebo effects or to conclude that the herb is effective.

Valerian effects on subjective sleep outcomes

The research findings to date do not support the efficacy of valerian or valerian combinations for improving subjective sleep outcomes. Most of the evidence of improved sleep with valerian preparations is from studies using non-specific outcomes for clinical trials (i.e. proportion improvement)[21,38,42,43] or studies in which placebo effect was not addressed.[13,29,32,41] Research evidence of high-quality is available for ethanolic *V. officinalis* extracts, and the findings do not support the efficacy for the treatment of insomnia. The quality of research evidence for other valerian products is mixed, but few studies have been conducted with these products in samples with insomnia. Although there is some evidence that suggests valerian may improve sleep outcomes, placebo effects cannot be ruled out in many of these trials. Therefore, the evidence is insufficient to recommend clinical use of valerian for treating disturbed sleep.

Recently, Bent and colleagues[5] published a meta-analysis of subjective sleep quality and sleep latency outcomes of valerian treatment, concluding that evidence suggests potential beneficial effects of valerian on sleep. In this analysis, the authors did not consider type of valerian product, and they included combination products with as many as eight other herbs. Two types of sleep quality outcomes have been used in valerian studies: (1) sleep quality *improvement*—whether participants rate their sleep as ''improved'' or ''not improved'' or (2) sleep quality *ratings*—e.g., 0–10 numeric scale, 0 = poor, 10 = excellent. Bent and colleagues conducted their meta-analysis on sleep quality *improvement* ratings (''improved versus ''not improved''). This analysis favored valerian, but inspection of the studies included revealed a publication bias towards small, positive studies. Additionally, in two of the six studies in which sleep quality *improvement* favored valerian, sleep quality *ratings* showed no significant differences between valerian and placebo.[17,42] Therefore, the clinical utility of assessing subjective sleep quality improvement is questionable. Bent et al. reported that results for subjective sleep latency were mixed, and, as discussed in our review, variation in study quality and lack of control for confounding variables influenced the outcomes of many of the studies. Given the limited scope of outcomes and studies considered in the Bent et al. review, the

Table 4 Quality, methodological features, and significance of primary outcomes of clinical trials of valerian for sleep.

Study	Jadad Score	Random procedure described	Blinding of appearance described	Blinding of odor described	Success of blinding checked	Compliance checked	Sample size calculated	Subject inclusion/ exclusion criteria	Dropouts reported	Control of pre-bedtime variables	Validated outcome measures	Intent-to-treat analyses	Primary sleep outcomes significant
Muller-Limmroth and Ehrentstein[22]	1							(+)					
Jansen[27]	3	+											NA*
Leathwood and Chauffard,[39] Leathwood et al.[46] (lab)	0										(+)		
Leathwood and Chauffard,[39] Leathwood et al.[46] (home)	4	+							+	+			$+^{P}$
Gessner et al.[26]	2							+			+		(+)
Gessner and Klasser[25]	2							(+)			(+)		
Kamm-Kohl et al.[21]	3								+				$+^{P}$
Balderer and Borbèly[11] (home)	1							+		+			(+)
Balderer and Borbèly[11] (PSG)	2							+		+	+		
Leathwood and Chauffard[38]	4	+	+			+			+				(+)
Lindahl and Lindwall[43]	2		+					(+)					$+^{P}$
Dressing et al.[16]	2							+			+		
Schulz et al.[37]	2							+			+		NA*
Dressing et al.[6]	3					+		+	+		+	+	+
Vorbach et al.[17]	5	+	+	(+)		+	+	+	+		+	+	
Rodenbeck et al.[24]	2							+			+		
Schmitz and Jackel[15]	3							+	+		+		$+^{=}$
Cerny and Schmid[42]	3		+					+	+				
Kuhlmann et al.[34]	3		+					+	+		+		
Donath et al.[33]	2							+			(+)		
Dorn[13]	5	+	+	(+)				+	+		+		$+^{=}$
Herrera-Arellano et al.[36]	4		+	(+)				+			+		(+)
Poyares et al.[35]	2							+		+	+		(+)
Ziegler et al.[32]	4		+	(+)			+	+	+		+	+	$+^{=}$
Coxeter et al.[37]	5	+	+	+		+	NA	+	+			NA	
Diaper and Hindmarch[30]	3		+	(+)			+				+		
Jacobs et al.[29]	5	+	+	+	+	+	+	+	+		+	+	
Morin et al.[40]	4	+	(+)		+		+	+	+	+	+	+	

Items related to quality: Studies listed chronologically. +: item was adequately addressed; (+): item was partially addressed; NA: item was not applicable to the study. *Primary outcomes* (*based on outcomes reported in Tables 1 and 2*): +: outcomes significant (versus placebo); (+): only part of main outcomes were significant; NA*: statistical analyses comparing valerian to the placebo were either not done or not reported; $+^{P}$: a statistically significant proportion of the sample improved, but the study did not compare mean scores; $+^{=}$: equivalence of valerian and a benzodiazepine (hypothesis was met if differences were non-significant).

preponderance of negative findings was neglected, and the author's conclusions that valerian, as it has been tested to date, is a promising therapy are unsupported in the broader context of the literature reviewed here.

Valerian effects on objective sleep outcomes

Current evidence suggests that the investigated valerian preparations do not significantly affect objective sleep outcomes, although very few studies have actually recorded sleep. Of the studies administering *V. officinalis* mono-preparations, only two of the studies that measured PSG outcomes investigated valerian administration for longer than three days in persons with sleep disturbance,[33,35] one showed no significant outcomes,[33] and the other reported reduced WASO.[35] Studies of valerian combinations reporting PSG outcomes after either one night[22,23] or 28 days[24,40] found no outcomes significant compared to placebo. One study of an aqueous valerian extract showed reduced sleep onset latency by wrist actigraphy in persons with sleep onset insomnia.[38] However, sleep latency was not longer than 30 min at baseline (15 min) and on average was reduced only four to six minutes, providing only weak evidence of valerian sedation. Overall, these findings do not support the effectiveness of valerian or valerian combinations for improving objective sleep outcomes. Additionally, when considering that the tested valerian preparations did not clearly show improved subjective sleep ratings, any evidence of improved objective sleep outcomes is of questionable relevance.

Safety of valerian

The studies reviewed support the safety of valerian. The most common side effects were mild and tended to be either mild neurological symptoms (dizziness, headache, drowsiness) or gastrointestinal (GI) symptoms (nausea, diarrhea). Although valerian has been implicated in a few case reports of transient liver dysfunction,[47,48] no hepatic symptoms or changes in liver function were reported in the research literature reviewed.[13,42] Valerian had been shown to cause little to no impairment of performance, especially in comparison to benzodiazepines.[30,34,49–51]

Concerns have been raised regarding the safety of ingesting valepotriates. These constituents have been shown *in vitro* to be cytotoxic and to inhibit DNA synthesis.[8] A recent *in vitro* study demonstrated that DNA damage of human epithelial cells occurred with high doses of valepotriates, but not with low doses.[52] It has been suggested that the GI tract is at particularly high risk for adverse effects of valepotriates because of the chemical degradation of these substances in the stomach.[8] While GI symptoms were reported in the reviewed studies on high-valepotriate preparations, these symptoms likely were related to purported muscle-relaxant effects of valepotriates.[8] No report was found in the literature directly linking valepotriates to the occurrence of serious adverse events in humans, but caution in the use of these products is warranted until more is known about potential adverse effects.

There is little evidence on potential herb–drug interactions of valerian. *In vitro* studies have demonstrated mild to moderate inhibition of the drug-metabolizing enzymes in the small bowel and liver that are involved in first-pass drug metabolism.[53,54] Although inhibition of these enzymes theoretically increases the risk of excessive levels of certain medications in the blood, an *in vivo* study of humans showed no significant effects of one valerian preparation on circulating levels of medications given to test enzyme inhibition.[55] Although evidence indicates that valerian is unlikely to significantly affect drug metabolism, caution may be advised with medications that are metabolized by cytochrome P450 enzyme subtype 3A4, and to a lesser extent subtypes 2C19 and 2D6, if the medications have high toxicity and a narrow therapeutic range (e.g., digoxin). Additionally, synergistic effects of valerian with medications are potentially problematic. In animal studies, valerian had been shown to potentiate barbiturate induced sleeping time.[6] Valerian should not be taken with benzodiazepines and other sedating substances, such as antihistamines and alcohol, due to the risk of over-sedation.

Conclusion

Although valerian is commonly used in the United States and Europe as a sleep aid, current evidence on the efficacy of valerian for improving sleep outcomes does not support such use. However, valerian is an apparently safe herb, with few reported side effects. Despite the lack of evidence for efficacy, these products are unlikely to cause harm other than perhaps delaying individuals from seeking the effective treatment for insomnia symptoms.

Although current evidence fails to support efficacy of valerian for relief of insomnia, the

widely variable and methodologically mixed nature of the extant literature clearly leaves room for further clarification. First, it is important to note that the source valerian plant material used in most studies was extracted from dried, rather than fresh, root and rhizome. The concentration of certain constituents of valerian varies between fresh and dried products, and study findings on dried root extracts should not be generalized to fresh root preparations. Second, valerian preparations were administered in pill form rather than as a liquid, which is the preferred method recommended by herbalists (personal communication Robin DePasquale, January, 2007). No studies were found that tested valerian tinctures for sleep; although one tested cognitive impairment with a syrup.[50] This is an important distinction because the presence and availability of active constituents varies between pills and tinctures. Finally, rigorous studies testing different doses of valerian and types of valerian products in well-defined samples of persons with insomnia are needed. It remains possible that valerian may be a useful, mild treatment for sleep disturbance, but current evidence does not support its use, and research is needed to determine which products and doses of valerian might be efficacious.

Practice points

- Current evidence does not support the efficacy of valerian or valerian combinations with other herbs for reducing general sleep disturbance or insomnia symptoms.
- Valerian has been shown to be a safe product and is unlikely to cause harm in the majority of patients. Healthcare providers should advise patients of potential herb–drug interactions (e.g., additive sedation, possible alteration of drug metabolism).
- Caution should be exercised in the use of valerian by patients who have a history of liver disease, those at risk for liver dysfunction, and taking other herbs linked to liver dysfunction.

Research agenda

- Future studies of valerian should specifically exclude persons with primary sleep disturbances other than insomnia (e.g., restless legs syndrome, sleep apnea).
- Future studies should use greater specification of inclusion/exclusion criteria, especially in defining the type of sleep disturbance in the sample. Study methods should also plan for greater control of potential sources of bias (see Table 4).
- Matching of valerian and placebo odor is critical to ensure adequate masking and to reduce potential placebo effects.
- Evidence on valerian preparations in tincture form is lacking. Given that this is a formulation preferred by herbalists, research on such preparations may provide new information on potential effects of valerian.

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