Over-the-Counter Agents for the Treatment of Occasional Disturbed Sleep or Transient Insomnia:

A Systematic Review of Efficacy and Safety

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ABSTRACT

Objective: To investigate the level of evidence supporting the use of common over-the-counter (OTC) agents (diphenhydramine, doxylamine, melatonin, and valerian) for occasional disturbed sleep or insomnia.

Data sources: A systematic review of the literature was conducted on July 31, 2014, using MEDLINE (PubMed) and the search terms (*insomnia* OR *sleep*) AND (*over*the*counter* OR *OTC* OR *non*prescription* OR *antihistamine* OR *doxylamine* OR *diphenhydramine* OR *melatonin* OR *valerian*) with the filters English, human, and clinical trials.

Study selection: Identified publications (from 2003 to July 31, 2014, following previous published literature reviews) that met the inclusion criteria were selected. The criteria included randomized placebo-controlled clinical studies that utilized overnight objective (polysomnography) or next-day participant-reported sleep-related endpoints and that were conducted in healthy participants with or without occasional disturbed sleep or diagnosed insomnia.

Results: Measures of efficacy and tolerability were summarized for each study individually and grouped according to OTC agent: H_1 antagonists or antihistamines (3 studies, diphenhydramine), melatonin (8), and valerian or valerian/hops (7). Of the 3 sleep agents, studies conducted with melatonin, especially prolonged-release formulations in older individuals with diagnosed insomnia, demonstrated the most consistent beneficial effects (vs placebo) on sleep measures, specifically sleep onset and sleep quality, with favorable tolerability. In contrast, the clinical trial data for diphenhydramine, immediate-release melatonin, and valerian suggested limited beneficial effects.

Conclusions: A review of randomized controlled studies over the past 12 years suggests commonly used OTC sleep-aid agents, especially diphenhydamine and valerian, lack robust clinical evidence supporting efficacy and safety.

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Occasional disturbed sleep, consisting of difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and nonrestorative sleep, is frequently reported among individuals in the United States. Approximately one-fifth of the respondents in the 2008 Sleep in America Poll[1] experienced at least 1 of these symptoms 2–3 nights a week. Other studies[2–5] have likewise reported occasional disturbed sleep in up to one-third of various populations, although an objective definition of occasional disturbed sleep (regarding duration, frequency, and severity) is not available, possibly contributing to variability across studies.

With the transient nature of occasional disturbed sleep, individuals often turn to nonpharmacologic (cognitive-behavioral approaches, sleep hygiene) or over-the-counter (OTC) agents to improve sleep.[2,6,7] Nonprescription antihistamine-containing sleep aids (diphenhydramine hydrochloride, diphenhydramine citrate, or doxylamine succinate) as well as herbal and nutritional supplements (eg, valerian, melatonin, kava kava, dogwood, L-tryptophan, St John's wort) are often used for the treatment of "occasional sleeplessness" but are not indicated for the management of diagnosed insomnia due to the lack of specific safety and efficacy data.[8] Although OTC sleep aids claim to provide benefits for adults with occasional sleeplessness, established efficacy and safety in well-designed clinical trials in relevant populations are rare. Moreover, herbal and nutritional supplements (such as melatonin) are not required to undergo the same rigorous clinical testing as prescription medications.

The lack of scientific evidence supporting the efficacy and safety of OTC sleep aids for insomnia symptoms was highlighted in a comprehensive review by Meoli et al.[8] The authors conducted a systematic review of oral, nonprescription treatment for insomnia (1980–2002), excluding melatonin (which they stated had already undergone extensive evaluation), to determine the level of evidence regarding the safety and efficacy of nonprescription drugs for insomnia. The authors concluded that although placebo-controlled studies are available for some OTC sleep aids, rigorous scientific evidence supporting the efficacy and safety of nonprescription sleep aids, including herbal, dietary, or nutritional supplements, was not available.[8] In a systematic review[9] published in 2005 of melatonin in randomized controlled clinical trials of individuals with sleeping disorders (including but not limited to insomnia), it was concluded that melatonin had limited value in individuals with insomnia, but confirmation in large, well-designed clinical trials was needed. These evidence-based reviews are in agreement with clinical guidelines,[10,11] which do not recommend OTC sleep agents for the treatment of chronic or primary insomnia due to the lack of well-designed studies and supporting evidence. As a result, health care providers can only recommend sleep aids with caution until further evidence becomes available to support their efficacy and safety. As such, we undertook a review of more recent placebo-controlled randomized studies, including the past 12 years, to reevaluate treatment

Clinical Points

- Commonly used nonprescription sleep aids continue to lack robust clinical evidence supporting efficacy and safety in relevant populations.
- Further clinical investigations and novel treatments are needed to improve management of occasional disturbed sleep.

recommendations. This review was based on a systematic literature search of all published studies (up to July 31, 2014) supporting the efficacy and safety of nonprescription agents for the management of occasional disturbed sleep with a focus on summarizing only those studies conducted after 2002 (given the previous published reviews).

SYSTEMATIC REVIEW OF CURRENTLY AVAILABLE OTC SLEEP AIDS

We focused on common recommended OTC agents that are available in pharmacies in the United States and have been evaluated in controlled clinical studies: those including antihistamines (diphenhydramine, doxylamine) or natural supplements (melatonin, valerian) (Table 1).[10,13] As a result, we did not include information on other herbal or nutritional supplements. We also did not include combination products comprising pain relievers (eg, ibuprofen) and diphenhydramine because these products are only indicated for use when having difficulty sleeping due to associated pain.

A MEDLINE literature search (PubMed) was conducted using the search terms (*insomnia* OR *sleep*) AND (*over*the*counter* OR *OTC* OR *non*prescription* OR *antihistamine* OR *doxylamine* OR *diphenhydramine* OR *melatonin* OR *valerian*) and the additional filters English, human, and clinical trials. No date restrictions were imposed other than an end date of July 31, 2014. The resulting 926 articles were screened for relevance (ie, clinical trial that involved the collection of overnight measures of polysomnography [PSG] or next-morning participant-reported sleep assessments). Nonrelevant articles, including studies conducted in populations with underlying serious medical conditions (physical or psychiatric diseases or sleep disorders other than insomnia) and studies exclusively on sedative or cognitive effects following daytime administration (without an intervening period of bedtime), were excluded. A total of 126 articles (H_1 antagonists: 25, valerian: 25, melatonin: 78; multiple drugs were included in some articles) were identified as potentially relevant. These articles comprised all publications, including those prior to 2002, up to the end date of July 31, 2014 (Figure 1).

Bibliographies of identified articles also were reviewed to identify other potentially relevant placebo-controlled randomized studies for inclusion. Given the previous reviews by Meoli et al[8] and Buscemi et al,[9] we focused on those studies published after 2002. The studies were carefully selected to include only randomized placebo-controlled studies in healthy participants with or without diagnosed insomnia (using established diagnostic classification criteria) or occasional disturbed sleep (generally defined as mild symptoms of insomnia occurring 2–3 times per week) that included objective or subjective (ie, participant-reported) sleep-related endpoints.

EFFICACY AND SAFETY OF OTC DRUGS AND NATURAL SUPPLEMENTS

Diphenhydramine and Doxylamine

Although numerous OTC formulations are available to aid sleep, the majority contain diphenhydramine, a nonselective histamine H_1-receptor antagonist that has significant affinity at other receptor subtypes leading to nonspecific side effects, including anticholinergic effects (sedation, dry mouth, blurred vision). The US Food and Drug Administration (FDA) included diphenhydramine hydrochloride (up to 50 mg) and diphenhydramine citrate (up to 76 mg) as safe and effective nighttime sleep aids as part of the FDA Final Drug Monograph for OTC Use.[22] Doxylamine succinate (up to 25 mg) is not yet included in this monograph (on the basis of insufficient evidence), but specific formulations (eg, Unisom) have received FDA approval. Very few published studies have rigorously evaluated the hypnotic effects of H_1 antagonists as OTC sleep agents. In the Meoli et al[8] review, it was concluded that although short-term efficacy was demonstrated on subjective measures (participant self-reports) in some studies, the evidence should still be considered preliminary, largely owing to small sample sizes and lack of objective sleep measures (ie, PSG-derived parameters).

In the present review, 25 publications on diphenhydramine and other antihistamine products were identified as potentially relevant; this includes all publications, as well as those prior to 2002 (Figure 1). Several of these articles failed to meet the inclusion criteria and were eliminated, mostly owing to no overnight sleep-related endpoints, use of H_1 antagonists not available as OTC sleep agents, or the presence of an underlying medical condition in the study population. This elimination resulted in 7 publications meeting the inclusion criteria (randomized placebo-controlled with at least 1 specific sleep endpoint and conducted in healthy adults with or without primary insomnia or occasional disturbed sleep). Of these articles, 3[23–25] were published after 2002 and are summarized in Table 2.

Each of these studies used diphenhydramine 50 mg (although the specific salt, citrate vs hydrochloride, was provided in only 1 study[23]) administered either as a single dose or multiple dose over 2 weeks. Together, these studies failed to demonstrate consistent positive improvements on self-reported and objective (PSG-derived) sleep measures. Morin et al,[23] the largest of the 3 studies, reported significant improvements relative to placebo on self-reported sleep efficiency and the Insomnia Severity Index, but both Morin et al[23] and Katayose et al[24] failed to observe significant effects on key PSG-derived parameters (eg, sleep onset latency, sleep efficiency, total sleep time) among healthy individuals with and without occasional sleep disturbances, respectively.

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Table 1. Current Over-the-Counter Treatment Approaches for Occasional Disturbed Sleep[a]

Drug (chemical name), Dose	Mechanism of Action (if known)	Example Branded Products (manufacturer)	Overview of Pharmacokinetic Properties	Adverse Reactions (most frequent)	Drug-Drug Interactions[b]
Diphenhydramine HCl (2-[diphenylmethoxyl]-*N*, *N*-dimethylethylamine hydrochloride), 25 mg or 50 mg taken at bedtime	First-generation H_1 antagonist with nonspecific anticholinergic and sedative effects	ZzzQuil Nighttime Sleep-Aid LiquiCaps (P&G) Unisom SleepMelts (Chattem Inc) Simply Sleep (McNeil PPC Inc) Nytol (GlaxoSmithKline)	t_{max}: 1–4 h Half-life: 2.4–9.3 h Half-life and clearance are age-related[14]	Sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, thickening of bronchial secretions	Metabolized primarily by CYP2D6[15] 28 major drug interactions, including acetaminophen
Doxylamine succinate, 25 mg 30 min before bedtime	First-generation H_1 antagonist with nonspecific anticholinergic and sedative effects	Unisom SleepTabs (Chattem Inc) Medi-Sleep Sleep Aid (Various) Aldex AN (Pernix LLC)	t_{max}: ~2.4 h (25 mg) Half-life: 10–15 h Clearance reduced in elderly men[16–18]	Dizziness; drowsiness; dry mouth, throat, and nose; thickening of mucus in nose or throat	31 major drug interactions, including acetaminophen, aspirin
Melatonin (*N*-acetyl-5-methoxy-tryptamine), 5 mg 3–4 h prior to bedtime	Melatonin receptor agonist	Nature Made Melatonin	t_{max}: 30–60 min (2 mg) Half-life: 0.54–0.67 h[19]	Depression, dizziness, enuresis, excessive daytime somnolence, headache, nausea	Metabolized primarily by CYP1A2[20] 7 moderate drug interactions
Valerian (*Valeriana officinalis* L), 400–600 mg valerian extract 1–2 h before bedtime	Not fully understood; proposed central actions on GABA, serotonin, and adenosine receptors	Nature's Way Valerian Root GNC Herbal Plus Standardized Valerian Root	t_{max}: 1–2 h (600 mg) Half-life: 1.1 h[21]	Headache, upset stomach, thinking problems, dry mouth, feeling excited or uneasy, strange dreams, daytime drowsiness	3 major drug interactions, including sodium oxybate and buprenorphine

[a]Information obtained from http://www.drugs.com/pro/[12] unless otherwise referenced. Information is intended as a summary; health care providers should consult detailed, up-to-date product information.
[b]According to http://www.drugs.com, *major interaction* is defined as highly clinically significant, avoid combinations; the risk of the interaction outweighs the benefit. *Moderate interaction* is defined as moderately clinically significant, usually avoid combinations, use only under special circumstances.
Abbreviations: CYP = cytochrome P450, GABA = γ-aminobutyric acid, t_{max} = time of maximal (peak) plasma concentration.

In the third study, Glass et al[25] evaluated diphenhydramine 50 mg (over 2 weeks) in a small sample of older individuals (aged 70–89 years) with diagnosed insomnia. Diphenhydramine was associated with a small but significant decrease in participant-reported number of awakenings but with no significant effects on other key self-reported sleep parameters (eg, total sleep time, sleep latency, and sleep quality).[25] Together, these studies,[23–25] although few in number, indicate limited support of diphenhydramine for sleep efficacy.

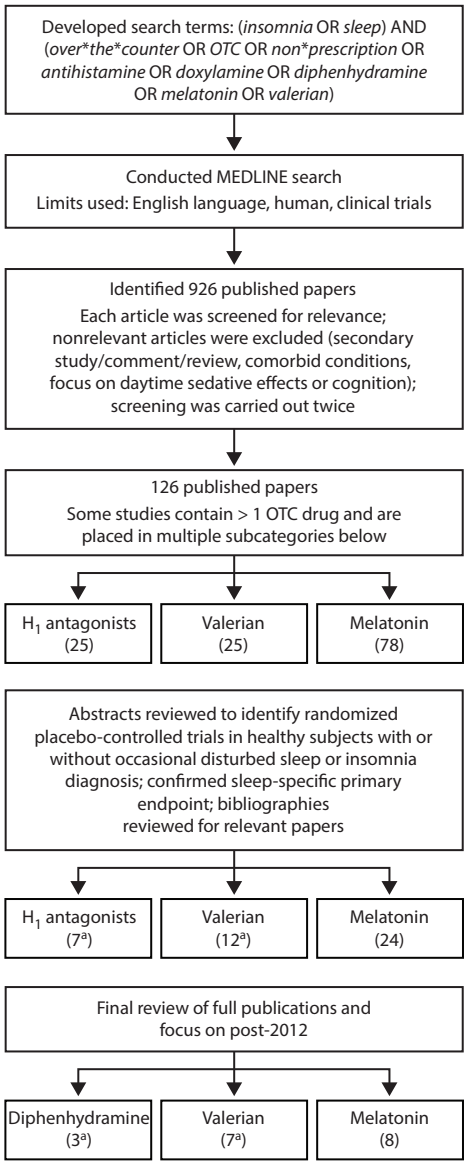
In terms of safety, 2[24,25] of the 3 studies examined next-day residual effects (a safety concern frequently associated with H_1 antagonists) using a battery of tests to measure psychomotor/cognitive functioning and sleepiness. Diphenhydramine (50 mg administered at 11:45 PM) was associated with significant psychomotor impairment on the 1-back test (a working memory task) and a decreased level of wakefulness as measured by the α attenuation coefficient during the morning and afternoon test sessions the following day (the effect on wakefulness represented an average across test times).[24] Adverse events and measures of withdrawal or rebound effects were collected in 2 studies.[23,25] Morin et al[23] reported no significant differences in adverse event frequency among the treatment groups (placebo and diphenhydramine 50 mg) and no evidence of rebound insomnia following treatment discontinuation. Likewise, in Glass et al,[25] the frequency and type of adverse events were similar among treatment groups, although a somewhat higher frequency of rebound insomnia in the diphenhydramine group was reported: signs of rebound insomnia were detected in 7 of 15 participants who discontinued diphenhydramine treatment versus 5 of 14 following placebo.

Melatonin

Melatonin (*N*-acetyl-5-methoxy-tryptamine) is a naturally occurring hormone produced by the pineal gland, which acts physiologically to regulate the circadian cycle. Exogenous melatonin is believed to promote sleep and is used as an herbal supplement in the United States. We identified 78 studies in total that referred to melatonin use in insomnia, of which 24 were placebo-controlled clinical studies that met our inclusion criteria (including those published in 2002 or earlier; Figure 1). Many of the excluded studies were conducted in the daytime or in individuals or patient populations with underlying illnesses or sleep disorders other than primary insomnia (eg, delayed sleep-phase disorder or sleep disturbances associated with jet lag or shift work).

Of the studies published after 2002, a total of 8[26–33] met the inclusion criteria (with 1 study resulting in 2 publications[33,34]) (Figure 1, Table 3). All but 3 studies used sustained- or prolonged-release melatonin. Of

Figure 1. Summary of the Systematic Search Strategy



[a]Morin et al[23] is listed for both diphenhydramine and valerian (see Tables 2 and 4).

the 8 studies, 2[26,27] were conducted in healthy volunteers with or without occasional disturbed sleep and 6[29–34] in individuals with a diagnosis of insomnia (*DSM-IV*). The 2 studies[26,27] conducted in healthy volunteers were small in size (n = 20–26; 1 was a crossover study) and showed little benefit of immediate-release melatonin compared with placebo on a variety of objective and self-reported sleep endpoints. In 1 study,[26] using both objective (actigraphy) and subjective sleep measures and considered sufficiently powered, 2 groups of older (aged ≥ 65 years) healthy participants categorized as either normal or problem sleepers treated nightly with immediate-release melatonin (5 mg) for 4 weeks showed no significant benefit on sleep measures, with the exception of reduced actigraphy-derived number of awakenings in normal sleepers. In the second study, which was considered a pilot study, Peck et al[27] evaluated the effects of melatonin 1 mg/d immediate-release for 4 weeks in older individuals (aged 64–89 years) and demonstrated significant improvements versus placebo on morning "restedness" and on a cognitive test (verbal recall on the California Verbal Learning Test) performed in the afternoon at week 4. Neither study[26,27] included PSG assessments.

In the 6 studies[29–34] (Table 3) that included participants with diagnosed insomnia, all but 1 were conducted using a sustained- or prolonged-release formulation. Four[29–32] of 6 studies were conducted exclusively in older individuals (aged ≥ 55 years). Overall, significant positive effects of immediate- (5 mg/d for 8 weeks) and prolonged-release formulation (2 mg/d for 3 weeks) were observed on participant-reported sleep quality,[29–33] sleep onset,[32,33] and morning alertness.[29,30] Not all endpoints were evaluated in each study, so consistency of treatment effects is not easily determined; furthermore, 1 small crossover study[28] (n = 10, mean age of 50 years) failed to show any significant effects of a "sustained-release" formulation (0.3 or 1.0 mg/d for 7 days) on either sleep quality or sleep onset or on any other participant-reported endpoint included in the study. A secondary analysis[34] of a large study (n = 722) suggested that age may be an important factor; a significant effect on sleep-onset latency was observed in the ≥ 55 years cohort but not in the younger cohort. These effects were sustained for up to 26 weeks of treatment.[34] Two of the 6 studies included PSG assessment; 1[32] observed a significant reduction (relative to placebo) in PSG-derived sleep-onset latency following prolonged-release formulation administration (2 mg/d for 3 weeks), whereas a smaller crossover study[28] (with 0.3, 1.0 mg/d for 1 week) showed no significant effects on any PSG parameters. A number of methodological differences (eg, dose, formulation, treatment duration, and study population) could account for this discrepancy. Neither study[28,32] showed any significant treatment effects on sleep architecture.

Next-day residual effects on psychomotor/cognitive functioning were evaluated in 1 relatively small study[32] (n = 40) of older individuals (aged ≥ 55 years) with insomnia. Nightly 3-week administration of prolonged-release formulation (2 mg 2 hours before bedtime) versus placebo resulted in no significant performance impairment (in some cases, significant improvements were observed) on next-day psychomotor tests (reaction time tests and critical flicker fusion were conducted at 9:00 AM).[32]

Immediate-release melatonin and prolonged-release formulation were well tolerated with a low incidence of mild adverse events, often comparable to placebo.[26,27,29–34] Studies[29,32,34] with prolonged-release formulation also reported no evidence of withdrawal or rebound effects following discontinuation after 3 or 26 weeks of nightly administration.

Valerian and Valerian/Hops

Valerian is a plant derivative that has long been used to aid sleep and anxiety.[35] Valerian can be marketed in powder

Table 2. Summary of Safety and Efficacy of Diphenhydramine

Study	Participant Characteristics	Outcome Measures	Principal Findings/Outcomes	Secondary Observations and Adverse Events	Interpretation and Limitations	Overall Assessment of the Data[a]
Healthy volunteers with or without occasional disturbed sleep						
Morin et al (2005)[23] Design: randomized, double-blind, placebo-controlled, multicenter, objective, self-report Arms: diphenhydramine 50 mg/d (Sominex) vs placebo (vs valerian/hops) Schedule: diphenhydramine for 2 wk followed by placebo for 2 wk	Occasional insomnia (sSL > 30 min and/or awake after sleep onset > 30 min 2–4 nights/wk) 25–65 y N = 184 (mean age: 44.3 y, 59.8% female)	Primary: sleep diary (active agent vs placebo, sleep latency, sleep efficiency, and total sleep time at wk 2) Secondary: overnight PSG (baseline to wk 2, subset n = 75), ISI, CGI, SF-36, withdrawal/rebound effects, adverse events	Diphenhydramine vs placebo: no treatment difference in sSL after 2 wk of treatment (21.6 vs 23.8 min); sSE improved with diphenhydramine vs placebo: 4.6% vs 2.5%*; no significant difference in sTST	Diphenhydramine vs placebo: ISI lower after 2 wk (9.39 vs 11.63**); PSG: no significant improvements on sleep latency, sleep efficiency, or TST vs placebo; no rebound insomnia vs placebo; no. of participants discontinuing due to adverse events and reporting adverse events: diphenhydramine > placebo	"Mild hypnotic effect" but no significant improvements on PSG parameters	U
Katayose et al (2012)[24] Design: randomized, double-blind, placebo-controlled, cross-over, objective Arms: diphenhydramine 50 mg vs placebo (vs zolpidem 10 mg vs ketotifen 1 mg) Schedule: single dose	Healthy Japanese volunteers N = 22 (mean age: 22.2 y, 0% female)	Primary: next-day measures of sleepiness (MSLT, AAT, visual analog scale) and psychomotor performance (DSST, reaction time tests, n-back test) Secondary: overnight PSG (active agent vs placebo)	Diphenhydramine vs placebo showed impaired psychomotor performance on 1-back test; % error rate: 6.3% vs 4.7%; reduced wakefulness on AAT: 2.2 vs 2.5*	Diphenhydramine vs placebo: longer REM latency (138.5 vs 99.9 min*) and reduced % REM (16.2 vs 20.5*) No significant differences in other PSG parameters Adverse events not captured	Minimal effects on PSG parameters; significant next-day psychomotor impairment	U
Diagnosed insomnia						
Glass et al (2008)[25] Design: randomized, double-blind, placebo-controlled, cross-over, self-report Arms: diphenhydramine 50 mg/d vs placebo (vs temazepam) Schedule: 2 wk	*DSM-IV* insomnia ≥ 70 y N = 20 (mean age: 73.9 y, 50% female)	Primary: sleep diary (active agent vs placebo) Secondary: rebound effects, next-day impairment (DSST, manual tracking task, memory assessment), adverse events	Diphenhydramine vs placebo: no treatment difference for sleep quality: 3.0 vs 2.9, SOL: 34.2 vs 36.8 min, or TST: 6.6 vs 6.3 min; significant decreased awakenings: 1.7 vs 2.0* Temazepam vs placebo: significant on all sleep diary measures	7 of 15 experienced rebound effects with diphenhydramine (5 of 14 for placebo); no changes in DSST, manual tracking task, or memory task with diphenhydramine; adverse events: diphenhydramine similar to placebo	No improvement in sleep quality Limitations: significant improvement in awakenings may not be clinically relevant (0.3/night)	–

[a]The last column provides overall assessment of the data: U = unclear (study interpretation is unclear with regard to use as a sleep aid); – = negative study (did not meet primary endpoint and does not support use as a sleep aid).

*$P < .05$. **$P < .01$. ***$P < .001$.

Abbreviations: AAT = α attenuation test, CGI = Clinical Global Impressions scale, DSST = Digit Symbol Substitution Test, ISI = Insomnia Severity Index, MSLT = Multiple Sleep Latency Test, PSG = polysomnography, REM = rapid eye movement, SF-36 = 36-Item Short-Form Health Survey, SOL = sleep onset latency/latency to persistent sleep via PSG, sSE = sleep efficiency by participant report, sSL = sleep latency by participant report, sTST = total sleep time by participant report, TST = total sleep time by PSG.

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Table 3. Summary of Safety and Efficacy of Melatonin or Prolonged-Release Melatonin

Study	Participant Characteristics	Outcome Measures	Principal Findings/Outcomes	Secondary Observations and Adverse Events	Interpretation and Limitations	Overall Assessment of the Data[a]
Healthy volunteers with or without occasional disturbed sleep						
Baskett et al (2003)[26] Design: randomized, double-blind, placebo-controlled, cross-over, self-report Arms: melatonin 5 mg/d (fast-release capsule) vs placebo Schedule: 4 wk	Normal vs problem sleepers ≥ 65 y N = 20/group (mean age: 71.1 y, 68% female)	Primary: actigraphy measures of sleep latency, sleep time, no. of awakenings, sleep efficiency Secondary: sleep diary, awakenings, LSEQ, alertness	Melatonin vs placebo: no significant differences in either group on any of the primary outcome measures, except fewer number of awakenings measured by actigraphy (36.4 vs 40.2*) in normal sleepers	Response to melatonin was not dependent on low vs high secretion of endogenous melatonin Very few adverse events were reported	Melatonin demonstrated no significant effects on sleep latency, maintenance, or quality in older individuals (≥ 65 y) Study was sufficiently powered	–
Peck et al (2004)[27] Design: randomized, double-blind, placebo-controlled, self-report Arms: melatonin 1 mg/d (Schiff) vs placebo Schedule: 4 wk	Healthy volunteers 64–89 y N = 26 (characteristics not provided)	Primary: 7-item Sleep Interview and 21-item sleep questionnaire VAS (melatonin vs placebo baseline to wk 4) Secondary: various cognitive assessments (conducted at end of study in afternoon)	Melatonin vs placebo: improved morning "restedness" (4.6 vs 3.6* VAS) No other significant effects on sleep-related measures	Melatonin vs placebo: improved CVLT verbal recall at wk 4 (9.3 vs 8.6*) No reported adverse events on exit interview with melatonin	Melatonin improved morning "restedness" and scores on the CVLT interference subtest Limitations: pilot study	U
Diagnosed insomnia						
Almeida Montes et al (2003)[28] Design: randomized, double-blind, placebo-controlled, cross-over, objective, self-report Arms: sustained-release synthetic melatonin 0.3, 1.0 mg/d (Cronocaps) vs placebo Schedule: 1 wk	*DSM-IV* primary insomnia N = 10 (mean age: 50 y, 40% female)	Primary: PSG, sleep diary, VAS	No significant differences among treatments on PSG parameters (including sleep architecture) and subjective reports of sleep onset, no. of awakenings, total sleep time, and sleep quality	No differences in reported adverse events among treatments	7-day treatment with melatonin did not produce any sleep benefits in patients with primary insomnia Limitations: small sample size and variable ages (30–72 y)	–
Lemoine et al (2007)[29] Design: randomized, double-blind, placebo-controlled, multicenter, self-report Arms: prolonged-release melatonin 2 mg/d (Circadin) vs placebo Schedule: 3 wk	*DSM-IV* primary insomnia ≥ 55 y N = 170 (mean age: 68.5 y, 66% female)	Primary: change in LSEQ quality and morning alertness (prolonged-release melatonin vs placebo baseline to wk 3) Secondary: sleep diary (quality), rebound and withdrawal effects, adverse events	Prolonged-release melatonin vs placebo: improved LSEQ sleep quality (–22.5 mm vs –16.5 mm*) and morning alertness (–15.7 vs –6.8 mm**)	Prolonged-release melatonin vs placebo: improved sleep quality (diary) (0.89 vs 0.46 unit improvement**) No rebound or withdrawal symptoms Well tolerated, treatment-emergent adverse events (9 subjects in each arm)	Prolonged-release melatonin improved sleep quality and morning alertness suggesting more restorative sleep, with no rebound or withdrawal symptoms after treatment discontinuation	+
Wade et al (2007)[30] Design: randomized, double-blind, placebo-controlled, self-report Arms: prolonged-release melatonin 2 mg/d (Circadin) vs placebo Schedule: 3 wk	*DSM-IV* or *ICD-10* diagnosis of primary insomnia 55–80 y N = 334 (mean age: 65.7 y, 60% female)	Primary: responder rate analysis on sleep quality and morning alertness of (baseline to wk 3) ≥ 10 mm on both outcomes Secondary: sleep diaries, PSQI, CGI, WHO-5 QoL, adverse events	Prolonged-release melatonin vs placebo: higher responder rate for change (sleep quality and morning alertness) from baseline to wk 3: (26% vs 15%*)	Prolonged-release melatonin vs placebo: improved sleep quality LSEQ (–8.6 vs –4.2*), next-day alertness LSEQ (–7.0 vs –4.1*), and QoL (1.7 vs 1.1*) scores Well tolerated, adverse events reported by 24% (prolonged-release melatonin) vs 21% (placebo)		+

(continued)

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Table 3 (continued). Summary of Safety and Efficacy of Melatonin or Prolonged-Release Melatonin

Study	Participant Characteristics	Outcome Measures	Principal Findings/Outcomes	Secondary Observations and Adverse Events	Interpretation and Limitations	Overall Assessment of the Data[a]
Diagnosed insomnia						
Garzón et al (2009)[31] Design: randomized, double-blind, placebo-controlled, cross-over, self-report Arms: melatonin 5 mg/d (Helsinn Chemicals SA) vs placebo Schedule: 8 wk	*DSM-IV* primary insomnia or transient insomnia ≥ 65 y N = 22 (mean age: 75 y, 68% female)	Primary: sleep quality (38-item NHSMI) (prolonged-release melatonin vs placebo wk 8); ability to discontinue hypnotic drug (benzodiazepine) treatment Secondary: VAS depression (GDS) and anxiety (GAS), adverse events	Melatonin vs placebo: improved sleep quality (1.78 vs 3.44*) and greater benzodiazepine discontinuation rate***	Melatonin vs placebo: reduced depression GDS (5.61 vs 7.06*) and anxiety GAS (0.5 vs 1.5**) scores No adverse events reported for melatonin; no significant changes in clinical laboratory tests	8-wk treatment with melatonin improved sleep quality, reduced depression and anxiety, and facilitated discontinuation of conventional hypnotic drugs in older individuals Limitations: potential interactions with concomitant benzodiazepine treatment	+
Luthringer et al (2009)[32] Design: randomized, double-blind, placebo-controlled, objective, self-report Arms: prolonged-release melatonin 2 mg/d (Circadin) vs placebo Schedule: 3 wk	*DSM-IV* primary insomnia ≥ 55 y N = 40 (mean age: 61 y, 40% female)	Primary: PSG (prolonged-release melatonin vs placebo wk 3); next-day effects (Leeds Psychomotor Test battery) and rebound effects Secondary: LSEQ, adverse events	Prolonged-release melatonin vs placebo: reduced SOL by 9 min (13.7 vs 22.6*) No change in other PSG variables/sleep architecture No next-day psychomotor impairment (prolonged-release melatonin significantly better than placebo) or rebound effects	Improvement on LSEQ sleep quality in prolonged-release melatonin compared with baseline (but not different from placebo) No treatment-related adverse events	Prolonged-release melatonin reduced time to sleep onset without affecting other PSG endpoints, including sleep architecture in insomnia patients aged ≥ 55 y, with no next-day impairment or rebound effects Limited effects on sleep quality	+
Wade et al (2010, 2011)[33,34] Design: randomized, double-blind, placebo-controlled, self-report Arms: prolonged-release melatonin 2 mg/d (Circadin) vs placebo Schedule: 3 wk followed by a 26-wk double-blind extension	*DSM-IV* primary insomnia (sleep latency > 20 min) 18–80 y N = 722 (mean age: 61.7 y, 68.8% female) Low melatonin excretors: n = 172 (mean age: 63.8 y, 74.4% female) Older individuals 65–80 y: n = 281 (mean age: 71.0 y, 64.8% female)	Primary: sSL (prolonged-release melatonin vs placebo change from baseline to wk 3) for low (≤ 8 µg) melatonin excretors and in older individuals (aged 65–80 y) Secondary: sleep diary, PSQI, CGI-I, WHO-5 Index, adverse events, includes 26-wk extension Wade et al (2011)[34]: sSL by age (18–54 y, 55–80 y)	Prolonged-release melatonin vs placebo: no change in sSL with low endogenous melatonin (–9.0 vs –9.0 min) Prolonged-release melatonin reduced sSL (–19.1 vs placebo –1.7 min**) in subjects 65–80 y regardless of melatonin levels Wade et al (2011)[34]: prolonged-release melatonin vs placebo: at 3 wk, significant reduction in sSL for 55–80 y (–15.4 vs –5.5 min*) but not for overall (18–80 y) (–14.6 vs –7.9 min) or 18–54 y (–11.0 vs –16.6 min) At 26 wk, significant reduction in sSL for subjects 55–80 y and overall 18–80 y	Some secondary outcomes favored prolonged-release melatonin in older individuals and low excretors over short (3 wk) and long-term (26 wk) Sustained long-term prolonged-release melatonin effects on sSL (65–80 y) Safety profile similar between placebo and prolonged-release melatonin Drug-related adverse events for 3 wk: prolonged-release melatonin (5.36% patients) vs placebo (6.1%); for 26 wk, prolonged-release melatonin (17.3%) vs placebo (12.9%) No withdrawal symptoms after discontinuation of prolonged-release melatonin Wade et al (2011): other secondary measures were significant, favoring prolonged-release melatonin in overall 18–80 y and subgroup 55–80 y at 3 wk and 26 wk	Low melatonin production regardless of age is not useful for predicting response to prolonged-release melatonin Prolonged-release melatonin promoted sleep onset in the older group, but not in low excretors Long-term, sustained effects on subject-reported sleep latency and other secondary measures with prolonged-release melatonin, particularly in insomnia patients aged ≥ 55 y Prolonged-release melatonin was well tolerated and did not cause withdrawal or rebound effects at discontinuation following 3 or 26 wk of treatment Limitations: no objective measures; lack of effect in low excretors may be due to high percentage of younger subjects Fewer number of subjects in study aged 18–54 y vs 55–80 y; study failed to meet statistical power requirements for subgroups	+

[a]The last column provides overall assessment of the data: + = positive study (met primary endpoint and supports use as a sleep aid), – = negative study (did not meet primary endpoint and does not support use as a sleep aid), U = unclear (study interpretation is unclear with regard to use as a sleep aid).

*$P < .05$. **$P < .01$. ***$P < .001$.

Abbreviations: CGI-I = Clinical Global Impressions–Improvement, CVLT = California Verbal Learning Test (recall after interference), GAS = Goldberg Anxiety Scale, GDS = Geriatric Depression Scale, LSEQ = Leeds Sleep Evaluation Questionnaire (10-cm visual analog scale to rate sleep quality), NHSMI = Northside Hospital Sleep Medicine Institute test, PSG = polysomnography, PSQI = Pittsburgh Sleep Quality Index, QoL = quality of life, SOL = sleep onset latency/latency to persistent sleep via PSG, sSL = sleep latency by participant report, VAS = visual analog scale, WHO-5 = World Health Organization 5-item Well-Being Index.

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form or sold as an extract in aqueous or alcoholic media. The method of extraction can influence the active components,[36] and, therefore, method of preparation is an important consideration and varies among published reports.

After a systematic review of the literature and subsequent screening (Figure 1), 25 studies of valerian were identified, of which 12 were verified as placebo-controlled randomized studies investigating the efficacy of valerian or valerian/hops. Thirteen studies were eliminated because they included individuals with underlying medical conditions, had study design limitations, or did not include overnight sleep measures, the latter the most common.

Of the 12 studies that met the inclusion criteria, 7[23,37–42] were published after 2002; all but 2 evaluated multiple doses over 2–4 weeks. Six studies[23,37–41] were conducted in healthy volunteers who reported occasional or mild insomnia symptoms and 1[42] in individuals with a diagnosis of insomnia (*ICD-10*) (Table 4). In agreement with Meoli et al[8] and a subsequent meta-analysis[43] published 1 year later, limited evidence is available regarding the efficacy of valerian in occasional disturbed sleep and insomnia. Of the studies reviewed here (Table 4), 3 of 7 met their primary endpoint, which included (1) participant-reported sleep quality (Pittsburgh Sleep Quality Index) in postmenopausal women with "mild insomnia" after 4 weeks of treatment,[41] (2) PSG-derived change in "sleep quantity" from baseline following single-dose administration of valerian/hops in participants with occasional disturbed sleep,[39] and (3) objectively defined sleep latency (home recorder system) in participants with insomnia treated with valerian/hops (but not valerian alone) for 4 weeks.[42]

In contrast, 4 studies[23,37,38,40] were negative on primary endpoints comprising self-reported (sleep diaries, questionnaires) and PSG-derived sleep parameters. Specifically, Diaper and Hindmarch[37] found no significant effects on any PSG parameter after a single dose of valerian versus placebo in a crossover study of 16 participants with mild sleep complaints. Likewise, no sleep-related improvements were found using self-reported and PSG-derived measures following multiple doses (2–4 weeks) of valerian or valerian/hops in individuals with occasional or mild insomnia,[23,40] with 1 study[40] conducted in older individuals (aged 55–80 years). In a large Web-based study[38] that randomized over 400 participants with self-reported insomnia, 14-day treatment with valerian did not result in significant improvement in sleep quality relative to placebo (primary endpoint), although small, yet significant, beneficial effects of valerian versus placebo were demonstrated on mean improvement in night awakenings (0.13 vs 0.03) and global self-assessment of change (9.1% vs 3.7% of valerian vs placebo-treated individuals, respectively, reporting their sleep as "better" or "much better"). Reasons for the inconsistent effects on sleep measures observed across studies may be related to small sample sizes (with some exceptions, including both negative and positive studies[23,38,41]) and different valerian preparations (with and without hops) and doses, which vary considerably among studies.

Few adverse events (relative to placebo) were reported in the 7 studies,[23,37–42] consistent with the conclusion of Meoli et al[8] that valerian is associated with a relatively benign side effect profile. Next-day effects were evaluated as secondary outcome measures in 2 studies.[23,37] Following 4 weeks of nightly treatment, Morin et al[23] reported no next-day residual effects on subjective ratings of sluggishness or drowsiness or rebound insomnia with valerian/hops (374 mg/83.8 mg) versus placebo. Likewise, Diaper and Hindmarch[37] observed no effects on next-day psychomotor performance (evaluated at 7:05 AM) following valerian 300 or 600 mg versus placebo (administered as a single dose at 10:00 PM on the evening prior to tests). Although these studies[23,37] are not comparable because of differences in valerian preparation, doses, and outcome measures, these observations broadly suggest that valerian may not cause noticeable significant next-day effects in healthy individuals with occasional disturbed sleep; however, neither study demonstrated beneficial effects on sleep.

DISCUSSION

The OTC landscape is evolving alongside research into improving our understanding of occasional disturbed sleep as an unmet clinical need. Our review highlights that over the past 12 years, there have been relatively few published reports of large, randomized placebo-controlled studies evaluating the efficacy (with self-report and PSG measures) and safety of OTC agents in the intended population (individuals with occasional sleep disturbances or mild insomnia), despite their widespread and frequent use[2–5] often without input from a health care provider. Studies on melatonin have been the most widely published, followed by valerian and then antihistamines, specifically diphenhydramine.

Three randomized placebo-controlled studies[23–25] on single- and multiple-dose (50 mg) diphenhydramine published in the past 12 years were identified. Although few in number, these studies represent progress over the past 12 years in terms of further evaluating the efficacy (by including objective PSG measures) and safety (by examining residual next-day effects and rebound insomnia) of diphenhydramine in randomized placebo-controlled studies. Of particular note is 1 relatively large, well-designed study[23] conducted in individuals with occasional disturbed sleep that included both participant-reported and objective (PSG) sleep measures; few significant treatment effects (diphenhydramine vs placebo) were observed and none were related to objective PSG measures, a general pattern consistent with smaller crossover studies.[24,25] In terms of safety, next-day residual effects and rebound insomnia were observed,[24,25] but not consistently, and adverse events (and discontinuations due to adverse events) following diphenhydramine were slightly higher relative to placebo in 1 study[23] but similar in another.[25] Together, the scientific evidence suggests limited beneficial effects of diphenhydramine on sleep, an increased risk of next-day performance impairments, and potential rebound insomnia

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Table 4. Summary of Safety and Efficacy of Valerian or Valerian/Hops

Study	Participant Characteristics	Outcome Measures	Principal Findings/Outcomes	Significant Secondary Observations and Adverse Events	Interpretation and Limitations	Overall Assessment of the Data[a]
Healthy volunteers with or without occasional disturbed sleep						
Diaper and Hindmarch (2004)[37] Design: randomized, double-blind, placebo-controlled, crossover, objective, self-report Arms: valerian 600 mg vs 300 mg (Li 156, Sedonium, Lichtwer Pharma) vs placebo Single dose	"Mild sleep complaint" (sleep questionnaire) 50–64 y N = 16 (mean age: 55.9 y, 68.8% female)	Primary: PSG Secondary: LSEQ, mood and psychomotor/memory tests, adverse events	No significant differences between valerian (300 or 600 mg) and placebo for any PSG-derived parameter	No difference in sleep, mood (depression, anxiety), or psychomotor/memory performance Adverse events of mild (valerian 300 mg, placebo) or moderate (valerian 600 mg) intensity, but no dose-related effect on frequency	Valerian 300–600 mg is ineffective as an acute dose for sleep problems Limitations: preliminary trial, single dose, alcoholic extraction	–
Morin et al (2005)[23] Design: randomized, double-blind, placebo-controlled, multicenter, objective, self-report Arms: 2 tablets of valerian/hops (each tablet containing 187 mg valerian native extracts and 41.9 mg hops native extracts) vs placebo (vs diphenhydramine) Schedule: 4 wk	Occasional insomnia (sSL 30 min and/or awake after sleep onset > 30 min 2–4 nights/wk) 25–65 y N = 184 (mean age: 44.3 y, 59.8% female)	Primary: sleep diary (active agent vs placebo, sSL, sSE, and sTST at wk 2) Secondary: overnight PSG (baseline to wk 2, subset n = 75), sleep diary (wk 4), ISI, CGI, SF-36, withdrawal/rebound effects, adverse events	Valerian vs placebo: no treatment difference in sSL after 2 wk of treatment (27.5 vs 23.8 min); no improvement in sSE or sTST	Valerian vs placebo: PSG: no significant improvements on SL, sleep efficiency, or TST vs placebo; sleep diary (wk 4): no significant effects; SF-36 (physical) improved at 4 wk (55.0 vs 53.3*); no next-day residual effects or rebound insomnia vs placebo; safety profile similar between groups	Valerian/hops produced some mild improvements, but only 1 observation vs placebo reached statistical significance (QoL measured by SF-36 physical) Limitations: below recommended dose of valerian	–
Oxman et al (2007)[38] Design: randomized, double-blind, placebo-controlled, Web-based Arms: *Valeriana officinalis* (Valerina Forte, Cederroth International AB) 3,600 mg vs placebo Schedule: 2 wk	Self-reported insomnia for at least 1 mo with a PSQI score > 5 18–75 y N = 434 (randomized) Valerian: n = 202 (mean age: 45.7 y, 62% female) Placebo: n = 203 (mean age: 41.8 y, 60% female)	Primary: sleep quality (valerian vs placebo) Secondary: other sleep diary measures (sleep onset, no. of awakenings, sleep duration, next-day energy level), adverse events	Valerian vs placebo: no treatment difference in sleep quality improvement; percentage of individuals showing ≥ 0.5: 28.7% valerian vs 21.2% placebo	Valerian vs placebo: no treatment differences on most secondary sleep measures except average improvement on awakenings and global self-assessment of change (better or much better) No treatment differences in adverse events	Limited beneficial effects of valerian on sleep efficacy in individuals with insomnia symptoms	–
Dimpfel and Suter (2008)[39] Design: randomized, double-blind, placebo-controlled, objective Arms: valerian/hops (*Valeriana officinalis* 460 mg and *Humulus lupulus* 460 mg) liquid extract (Dormeasan, Bioforce AG) vs placebo Schedule: single dose	Healthy, with occasional poor sleep (sleep questionnaire) 30–70 y N = 42 (males mean age: 48.2 y, females mean age: 50.2 y, % of females not provided)	Primary: PSG time spent in sleep (based on spectral frequency index) (baseline vs treatment night) Secondary: sleep quality (inventory) vs EEG sleep quantity	Time spent in sleep and deep sleep was higher for valerian/hops extract vs placebo**	PSG sleep quantity was correlated with subjective sleep quality ($r = 0.48$***)	Acute valerian/hops combination improves sleep quantity in subjects with mild sleep disturbance	+
Taibi et al (2009)[40] Design: randomized, double-blind, placebo-controlled, cross-over, objective, self-report Arms: valerian (*Valeriana officinalis*, Nature's Resource, Pharmavite, LLC) 300 mg vs placebo Schedule: 2 wk	Mild insomnia (PSQI ≥ 5, ISI < 22) 55–80 y N = 16 (mean age: 69.4 y, 100% female)	Primary: WASO, sleep efficiency (PSG, actigraphy, and self-report), sleep latency (PSG, self-report), sleep quality (self-report) in laboratory and at home Secondary: PSG (sleep architecture), adverse events	Valerian vs placebo: no treatment differences on self-reports or PSG measures after single dose or 2 wk of dosing or on actigraphy and self-reports during intervening days at home	No treatment differences on sleep architecture or adverse events	Valerian after a single dose or after 2 wk did not improve sleep in this sample of older women with insomnia	–

(continued)

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Table 4 (continued). Summary of Safety and Efficacy of Valerian or Valerian/Hops

Study	Participant Characteristics	Outcome Measures	Principal Findings/Outcomes	Significant Secondary Observations and Adverse Events	Interpretation and Limitations	Overall Assessment of the Data[a]
Healthy volunteers with or without occasional disturbed sleep						
Taavoni et al (2011)[41] Design: randomized, triple-blind, placebo-controlled, self-report Arms: valerian root extract 530 mg vs placebo, twice a day (time of day not provided) Schedule: 4 wk	Postmenopausal, healthy women with mild self-reported insomnia (PSQI) 50–60 y N = 100 (mean age: ~53 y, 100% female)	Primary: PSQI (valerian vs placebo at wk 4) Secondary: proportion of participants with PSQI improvement	Valerian vs placebo: significant improvement in PSQI score compared with placebo*** (valerian improvement: 9.8 to 6.02)	30% (valerian) vs 4% (placebo) of participants reported an improvement in sleep quality*** Adverse events not captured	Multiple-dose valerian improved sleep quality in postmenopausal women with mild insomnia	+
Diagnosed insomnia						
Koetter et al (2007)[42] Design: randomized, double-blind, placebo-controlled, multicenter, objective Arms: valerian extract (Ze 911) 500 mg/d vs valerian 500 mg/hops 120 mg (Ze91019) vs placebo Schedule: 4 wk	Nonorganic insomnia (*ICD-10*) with prolonged sleep latency ≥ 30 min (mean of 2 objective assessments) at baseline ≥ 18 y N = 30 (mean age: ~37.7 y, 53.3% female)	Primary: sleep latency on home recorder system (valerian vs placebo baseline to wk 4) Secondary: WASO, sleep efficiency, % sleep stages, REM latency, CGI, adverse events, safety laboratory tests (no details)	Valerian extract vs placebo: no treatment difference, SL: 22.1 vs 5.5 min (values represent change from baseline) Valerian/hops vs placebo: significant improvement in SL: 44.5 vs 5.5 min* (values represent change from baseline)	Slow-wave sleep and CGI showed significant "superiority" for valerian/hops; no other secondary outcomes were significant No adverse events reported for any individual across any treatment group; safety laboratory data within physiologic range	Valerian/hops, but not valerian alone, improved sleep latency in individuals with insomnia and was well tolerated	–/+

[a]The last column provides overall assessment of the data: + = positive study (met primary end point and supports use as a sleep aid), – = negative study (did not meet primary end point and does not support use as a sleep aid).
*$P < .05$. **$P < .01$. ***$P < .001$.
Abbreviations: CGI = Clinical Global Impressions scale, EEG = electroencephalogram, ISI = Insomnia Severity Index, LSEQ = Leeds Sleep Evaluation Questionnaire, PSG = polysomnography, PSQI = Pittsburgh Sleep Quality Index, QoL_=quality of life, SF-36 = 36-Item Short-Form Health Survey, SL = sleep latency, sSE = sleep efficiency by participant report, sSL = sleep latency by participant report, sTST = total sleep time by participant report, TST = total sleep time by PSG, WASO = wake after sleep onset by PSG.

following discontinuation, although additional studies are needed to confirm these safety risks.

Evaluating the efficacy and safety of melatonin in randomized controlled clinical trials also progressed in the past 12 years, with larger, better-designed clinical trials (eg, longer treatment duration up to 26 weeks), although most were limited to the prolonged-release formulation in older individuals (aged ≥ 55 years) with diagnosed insomnia. In general, significant positive effects on sleep-related measures, mostly self-reported sleep latency, sleep quality, and morning alertness, were observed, with the exception of 1 small study[28] of a sustained-release formulation that failed to show any effects (perhaps owing to variable ages and lack of statistical power). The novel prolonged-released formulation (Circadin, Neurim Pharmaceuticals Ltd, Tel-Aviv, Israel) used in 4 studies[29,30,32,33] is currently approved in Europe and other countries as a prescription drug for the short-term treatment of primary insomnia in individuals aged ≥ 55 years.[44] These studies were included in this review because they suggest that OTC sustained or prolonged-release melatonin formulations might provide beneficial effects, although further studies are needed, particularly across a wider age range and in individuals with occasional disturbed sleep (rather than diagnosed insomnia).

In contrast, the evidence remains less conclusive for immediate-release melatonin (versus prolonged-release melatonin). Of the 3 clinical trials[26,27,31] identified, isolated positive effects were observed on morning "restedness" and sleep quality, but 1 crossover study,[26] considered sufficiently powered (n = 20), failed to demonstrate any significant sleep-related benefits (based on actigraphy and self-reports). Thus, scientific evidence supporting the efficacy of immediate-release melatonin remains inconclusive; this may reflect the fewer number of randomized controlled studies conducted with this formulation (3) since 2002, relatively small sample sizes (n = 20–26), variations in population and study design, absence of objective PSG measures, and the use of concomitant medications in at least 1 study (eg, benzodiazepines in Garzón et al[31]). Scientific evidence regarding safety is more consistent. Melatonin, including the prolonged-release formulation, was well tolerated, with adverse events generally similar between the placebo and active treatment arms and no evidence of significant next-day impairment or rebound insomnia following treatment discontinuation.

For valerian, 7 randomized controlled studies[23,37–42] were conducted since 2002. The evidence supporting valerian's (or valerian/hops')

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efficacy is inconsistent. Less than half (3/7) of the studies reported significant effects on primary sleep endpoints, and the specific endpoints were different among the 3 studies.[39,41,42] The remaining negative studies, some with a large sample size, failed to show significant beneficial effects on primary sleep measures, including PSG-derived endpoints. These observations are in line with those generated over 10 years ago[8] and with a systematic review[45] conducted in 2007 and further confirm the paucity of data available to support valerian efficacy despite its widespread use. One important consideration that may account for some of the discrepant results, beyond differences in study design, dosing schedule, and participants, is the method of valerian extraction and preparation and whether it was combined with hops. To this point, 2 of 3 studies[39,42] that reported positive effects used a combination product (valerian/hops). Regarding safety, the studies suggest a favorable tolerability profile, with adverse events similar to placebo in most studies, and no evidence (albeit, based on a limited number of studies) suggesting next-day residual impairment or rebound insomnia after discontinuation.

In addition to the considerations summarized here regarding the efficacy and tolerability of OTC sleep agents, other concerns may pose significant risk, namely drug-drug interactions (Table 1). Given that many individuals with occasional sleep disturbance are older and may have significant comorbidities and take concomitant medications, possible drug interactions are an important safety element when considering OTC use. Significant drug interactions are evident for antihistamines based on in vivo and in vitro (metabolism) studies.[46–48] Likewise, drug interactions with melatonin and valerian may also present concerns.[49,50] Specific studies, comparing combination of OTC agents with alcohol (commonly used to promote sleep) and commonly prescribed therapies for insomnia, such as zolpidem, eszopiclone, and zaleplon, are needed. In addition to drug interaction studies, carefully designed safety studies are critical. This is particularly important for older individuals who are frequently more susceptible to side effects (eg, anticholinergic effects associated with diphenhydramine) and their potentially dangerous consequences (falls resulting from dizziness).

Limitations

Our systematic review of the OTC literature should be interpreted in light of certain caveats. We made the decision not to include agents with very limited clinical trial data. We therefore excluded studies on some herbal remedies such as kava kava, dogwood, and St John's wort that are used to treat occasional disturbed sleep. The exclusion of these agents should be considered when interpreting the evidence summarized in the present study. Meoli et al[8] included a range of herbal products and supplements in their systematic review but concluded that although specifically designed randomized controlled trials have been conducted on certain OTC sleep agents (other than valerian and antihistamines), evidence was in general limited with respect to efficacy. We also did not consider alcohol, although commonly used as an agent to promote sleep onset, potential harmful effects do not support its use. Finally, we focused on the treatment of either occasional disturbed sleep or diagnosed insomnia in otherwise healthy individuals and thereby did not include studies that examined insomnia symptoms that were secondary to other medical or psychiatric disorders (including other sleep disorders/symptoms resulting from jet lag/shift work, delayed sleep phase disorder, restless legs syndrome). The decision was made to review the effects of OTC agents in a generally healthy population (to the extent possible) and to minimize confounds associated with serious underlying medical conditions and concomitant medications.

CONCLUSIONS

Currently available literature suggests that commonly used OTC sleep agents, especially antihistamines and valerian, continue to lack robust clinical evidence supporting efficacy and safety in relevant populations. A prolonged-release formulation of melatonin appears to be efficacious for symptoms associated with sleep onset and shows a favorable tolerability profile, but the effects may be limited to older individuals (aged ≥ 55 years) with insomnia. Further clinical investigations on these and novel compounds are needed to improve management of occasional disturbed sleep. Moreover, continued educational efforts targeting health care providers, pharmacists, and the public to improve communication about sleep issues related to health and quality of life and their treatment with OTC sleep aids are needed.

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