ABSTRACT

Insomnia is defined as difficulty initiating or maintaining sleep and/or nonrestorative sleep which impairs daytime function. Self treatment with over-the-counter (OTC) sleep aids, herbal and dietary supplements, and/or alcohol is common. Problems associated with insomnia self treatment are ineffectiveness, tolerance, dependency, and potentially harmful side effects. Studies of OTC sleep aids and other non-prescription sleep aids such as antihistamines, valerian, melatonin, and L-tryptophan have inconsistent results and lack objective data on both their efficacy and safety. Lastly, alcohol should never be used as a sleep aid due to its abuse liability.

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision,1 defines primary insomnia as difficulty initiating or maintaining sleep and/or poor quality (nonrestorative) sleep for at least 1 month, which has some daytime consequences. The duration of insomnia can be transient (days to several weeks) or chronic (≥1 month). Insomnia is associated with impairments in social, occupational, and other areas of functioning. Sleep disturbances can have a significant negative impact on daytime function, evident by mental slowing, reduced concentration, memory lapses, and decreased motivation. Insomnia can be associated with medical conditions, medication use, psychiatric disorders, substance abuse, or other primary sleep disorders (eg, sleep apnea, restless leg syndrome). However, primary insomnia is a disorder independent of these other conditions.

Epidemiologic studies report varying estimates of insomnia prevalence. The estimates are dependent upon whether the
data come from patient care settings; female, elderly, or general populations; or the study’s definition of insomnia. Taking into consideration the various adult insomniac populations, prevalence estimates range from approximately 10% to 50%. When including only chronic insomnia the prevalence range decreases from 10% to 15%.

Insomnia predisposes one to psychiatric disorders, aggravates medical conditions, decreases the quality of life, and increases the risk of drug and alcohol abuse. Greater than 50% of those with depression, psychosomatic disorders, anxiety disorders, neuroses, dementia, and schizophrenia have insomnia complaints. In some cases, treating the underlying mental disease may not improve the insomnia.

Self treatment with over-the-counter (OTC) sleep aids, herbal and dietary supplements, and/or alcohol is common among insomniacs. It is thought that the availability of these products, decreased cost compared to prescription sleep aids, and importantly, perceived safety results in the great usage of OTC sleep aids. A metropolitan Detroit study showed that 25.9% of respondents reported using some substance to aid their sleep. Of those who used medications (either prescription, OTC sleep aids, or both) to improve sleep, 57% reported using OTC sleep aids. In a recent study, approximately 25% of patients with insomnia used OTC sleep aids, and 5% used these drugs several times a week. A study of insomniac women ≥85 years of age noted that the respondents reported they did not see a physician or nurse practitioner for insomnia until the self treatment (with alcohol, OTC sleep aids, or both) was no longer effective. The problems associated with insomnia self treatment are use at higher than recommended doses, tolerance resulting from loss of efficacy, and the development of dependency in at-risk populations. There are even greater concerns with alcohol used as a sleep aid. Ineffective and potentially harmful self treatment is not fully appreciated as a risk of not treating insomnia medically with drugs exhibiting efficacy and safety profiles. This article provides an overview of what is known regarding the efficacy and safety of popular nonprescription products used for insomnia.

ANTIHISTIMINES

Antihistamines consist of a broad class of pharmacologic agents that include the first-generation, central acting histamine (H1) receptor antagonists. The primary action of this drug class is to block the effects of histamine, which reduces congestion, sneezing, coughing, and allergy symptoms. Centrally, these drugs block histamine receptors, histamine being one of the major alerting central neurotransmitters. Due to the sedative action of antihistamines, they are widely used as non-prescription sleep aids. Evidence appears to suggest that antihistamines may be useful for insomnia for 1–2 nights, but not efficacious in treating chronic insomnia.

Diphenhydramine

In 1982, the Food and Drug Administration authorized the initial marketing of diphenhydramine HCl and diphenhydramine citrate as active ingredients in non-prescription sleep aids. Other general medical uses include relief of allergies, motion sickness, and coughing. Table 1 lists the various OTC products and their doses. For sleep, the available dose range of diphenhydramine is 25–50 mg, with 50 mg being the maximum dose to be taken 30–60 minutes before bed. While marketed for allergy relief, Benadryl, which contains 12.5 or 25 mg of diphenhydramine depending on the formulation, is commonly used for sleep. Diphenhydramine citrate is often combined with an analgesic; together they are advertised to provide pain relief and induce sleep (Table 1).

Diphenhydramine has a half-life of 5–12 hours and has significant anticholinergic activity. Consequently, its use is associated with next-day mild-to-moderate side effects, namely residual morning sedation, dry mouth, grogginess, and malaise. Importantly, it has not been determined which aspects of its pharmacologic activity are mediated by H1 receptors and which are mediated by cholinergic receptors. Despite the reported side effects of diphenhydramine, virtually all OTC sleep aids contain diphenhydramine as the active ingredient (Table 1).

The use of diphenhydramine is common, but the number of controlled trials that support its efficacy are limited and many lack objective data. Several studies show evidence of sedative properties. One-week administration of diphenhydramine (50 mg) significantly decreased self-reported sleep latency and improved sleep depth and quality. Similar results were reported in psychiatric patients with insomnia following nightly administration of 12.5–50 mg of diphenhydramine for 2 weeks. Sleep quality, duration of sleep, and severity of insomnia symptoms significantly improved as measured by self reports. Interestingly, global improvements in sleep were significantly greater in those who had not received previous treatment for insomnia. This finding suggests drug tolerance, cross-drug tolerance, or that the efficacy of diphenhydramine is not as robust as other pharmacologic treatments. Tolerance to the hypnotic effects of diphenhydramine was evident on both objective and subjective measures of sleepiness following 3–4 days of administration. Thus, only short-term use is recommended since physical tolerance, can develop.

For several reasons, it is advised that those with chronic medical conditions should not take diphenhydramine, and specific precautions should be considered in those with cardiovascular disease, hypertension, or lower respiratory disease. Diphenhydramine produces additive central nervous system effects when taken concomitantly with alcohol, hypnotics, anxiolytics, narcotic analgesics, and neuroleptic drugs. Similarly, significant interactions may occur if the drug is taken concomitantly with anticholinergic agents or tricyclic antidepressants.
Doxylamine

In 1978, the FDA approved doxylamine succinate as an active ingredient for OTC sleep aid use. Doxylamine succinate mediates its activity through the H₁ receptor. Doxylamine has minimal effects on sleep onset due to its relatively long time to maximum plasma concentration. The time for sleep to be achieved is 45–60 minutes after oral administration. The peak plasma concentration is not reached until 90 minutes after administration. Using patient report outcomes, doxylamine (25 mg) for 1 week significantly decreased sleep latency. The authors of this article are unaware of any further published OTC efficacy studies for doxylamine. The elimination half-life is 10.1 hours. Thus, upon waking, plasma levels of doxylamine are present; consequently, residual daytime sedation is a documented side effect. Doxylamine is also potentially dangerous in accidental or intentional overdose. Rhabdomyolysis and secondary acute renal failure are rare but potentially serious complications, making early recognition and treatment essential.

H₁ antihistamines are not recommended for the elderly due to potential adverse effects and drug interactions. Doxylamine shares the same mechanism of action as diphenhydramine and the potential for tolerance to doxylamine's sedative effects exists.

SUPPLEMENTS AND HERBS

In the United States, usage of complementary and alternative medicines showed a secular upward trend from 33.8% to 42.1% for treatment of any health condition between 1990 and 1997. In comparison, treatment for insomnia rose from 20.4% in 1990 to 26.4% in 1997. Supplements and herbs are perceived as “natural” and, therefore, a safe alternative to prescription medications and some OTC products. The FDA does not rigorously test or regulate manufacturing of supplements and herbs. Currently, no FDA regulations specific to dietary supplements require a minimum standard for manufacturing of dietary supplements. Thus, the manufacturer is responsible for the strength, purity, composition, and safety of their products. According to FDA regulations, supplement manufacturers are forbidden to market their product as a treatment, prevention, or cure, for any medical disorder, including insomnia.

Supplements and herbs have reported side effects and inconsistent clinical findings, so the risk to benefit is questionable. Care should be used when taking these substances because they still cause physiologic changes in the body and can interact with other medications (Table 2).

Valerian

Valerian is a flowering plant that includes >200 species. The species Valeriana officinalis is most often used in the treatment of anxiety and insomnia. Valerian preparation methods vary with several different extraction methods used. The aqueous
Valerian 400 mg administered on three nonconsecutive nights produced a significant decrease in self-reported sleep latency, which was notable in people >40, men, and those who considered themselves poor or irregular sleepers. Poor or irregular sleepers and those who considered themselves as having long sleep latencies also reported significant improvements in sleep quality.24 Significant decreases in self-reported sleep latencies were also found in healthy subjects without major sleep disturbances following one valerian dose of either 450 or 900 mg. Only the 900 mg dose reduced wake time after sleep onset using objective assessments of sleep latency have varied. Actigraphy, a series of randomized n-of-1 trials.26 Similarly, valerian (6.4 mg) for 28 days did not relieve insomnia or anxiety to a greater extent than placebo in an Internet-based study. Adverse events occurred with similar frequency between the treatment group and the placebo group except that significantly more reports of diarrhea (18% of 114) occurred in the valerian group compared to those receiving placebo (8%).27

Polysomnography (PSG), the concurrent recording of electroencephalograph (EEG), electromyogram, and electrooculogram, is the standard method of objectively assessing sleep. It is often combined with computer analyses of EEG frequency and power (ie, spectral analyses). PSGs and spectra analyses of sleep EEG showed no significant differences between a 900 mg valerian dose and placebo administration in healthy volunteers. No adverse events or side effects were reported.28 Results of objective assessments of sleep latency have varied. Actigraphy, recording movements of arms or legs, is a less labor-intensive and intrusive method of assessing sleep than PSG. Actographs, worn by eight mild insomniacs, showed decreases in sleep latencies following valerian 450 mg for 4 nonconsecutive nights. In contrast, 900 mg did not produce a further improvement in sleep latencies and the higher dose had significantly greater morning sleepiness associated with it.29 In a PSG study, no significant decrease in sleep latency was demonstrated following 8 consecutive days of valerian (405 mg on day 1 and 1,215 mg on days 2–8) in 14 elderly female insomniacs. On other sleep measures, this dosing produced selective effects on non-rapid eye movement (REM) sleep stages. Non-REM is characterized by slower brain activity, divided into sleep stages 1–4, and is not associated with dreaming. Relative to baseline, valerian decreased the percentage of stage 1 sleep on night 1 and further decreased it on night 8. No systematic change occurred in the placebo group. Slow wave sleep (SWS; sum of sleep stages 3 and 4) significantly increased from baseline to

### TABLE 2

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night 8. REM sleep (sleep stage characterized by active brain waves and dreams) was unaltered by valerian. 

Sixteen insomniacs given valerian 600 mg for 14 days showed significant decreases in SWS latency in comparison to placebo, and a significant increase in the percentage of SWS compared to baseline as measured by PSG. Other sleep parameters were not significantly altered. Only three independent side effects or adverse effects occurred following valerian administration, which included one episode of gastrointestinal complaints, migraine, and an accident associated with the PSG procedures. Subjective measures of sleep and other sleep parameters were not significantly altered. Overall, these double-blind data suggest that although valerian is safe it does not improve the symptoms of disturbed sleep. It would be interesting to pursue the question of the increase in slow-wave sleep, its clinical significance, and the degree to which this is mediated by GABA.

Valerian is frequently combined with other herbal extracts such as hops and lemon balm, each purportedly having their own sedative or tranquilizing effects. A valerian preparation (valerian 400 mg, hops 375 mg, and lemon balm 160 mg) was rated better than control following one night of administration. No side effects were reported with this preparation. In contrast, for 3 nonconsecutive nights a commercial preparation of valerian 120 mg and hops 60 mg produced no significant change in sleep latency or sleep quality on subjectively rated sleep measures in healthy normal volunteers. This valerian preparation resulted in significantly greater reports of “more sleepy than usual” responses in comparison to the placebo group. Similar results were reported in mild insomniacs administered a valerian (374 mg)-hops (83.8 mg) combination for 28 days. This dosing and duration failed to produce a significant effect in sleep parameters using sleep diaries and PSG.

St. John’s Wort

St. John’s wort (hypericum perforatum) is the medicinal herb used for a variety of ailments including depression, anxiety, and fatigue. The active components are thought to be hyperforin and hypericin, although different formulations vary in their level of constituents. Most clinical studies focus on the treatment of depression rather than insomnia. No published double-blind placebo controlled studies were found using St. John’s wort to ameliorate primary insomnia.

Kava

Kava (or kava kava) comes from the roots of the Polynesian plant Piper methysticum is indigenous to the South Pacific. Supplements containing kava are marketed to alleviate menopausal symptoms, anxiety, and insomnia. Liver damage may be a risk factor associated with kava, and the FDA issued an advisory to consumers of this important potential risk. A meta-analysis of kava in the treatment of anxiety reported adverse events such as stomach complaints, restlessness, tremor, headache and tiredness (Table 2). Stress-induced insomnia was ameliorated after 6 weeks of 120 mg of kava and further improved by 6 weeks of valerian (600 mg) as measured by sleep questionnaires. There was a 2-week wash-out period between both treatments and, importantly, sleep during the washout did not differ from baseline. Side effects of kava included, diarrhea, gastric disturbances, and dry mouth.

A frequent symptom associated with anxiety disorder is sleep disturbances. Kava 300 mg for 28 days did not significantly relieve anxiety or insomnia symptoms using the Insomnia Severity Index and State-Trait Anxiety Inventory, respectively. In contrast, significant improvements relative to placebo in sleep quality and the recuperative effects of sleep as well as decreases in anxiety were demonstrated in patients with sleep disturbances associated with anxiety of non-psychotic origin following kava 200 mg (WS1490) for 4 weeks. Sleep questionnaires such as the Hamilton Rating Scale for Anxiety, self-rating scales of well being, and the Clinical Global Impressions scale showed improvements in sleep and anxiety. No drug-related adverse events or changes in clinical or laboratory parameters were noted.

As is the case in many of these products, there are some non-controlled data suggesting efficacy. However, objective and/or other placebo controlled trials that further suggest efficacy for insomnia are limited. Further, the benefit has to balanced against the risk, and the potential of liver toxicity in the case of kava cannot be dismissed.

NEUROHORMONES AND TRANSMITTER PRECURSORS

Melatonin

The pineal gland produces the neurohormone melatonin (N-acetyl-5-methoxytryptamine). Synthesis and secretion occurs nocturnally by darkness and is inhibited by environmental light, which suggests that melatonin is involved in modulating circadian rhythm. Melatonin secretion starts at approximately 9:00pm and peaks between 2AM and 4AM. Melatonin supplements are commonly used to combat jet lag and sleep disturbances, to protect cells from free-radical damage, and for enhancement of immune function. The mechanism by which melatonin affects sleep, beyond its circadian signaling capability (phase shifting), is unknown, but it likely involves stimulation of melatonin receptors.

The half-life of melatonin ranges from 0.54–2 hours; with doses ranging from 0.3–5.0 mg, melatonin is less likely to cause residual daytime drowsiness. Side effects reported in the literature included headache, odd taste in mouth, and poor sleep quality (Table 2). Melatonin supplements are relatively safe
when used short term over days or weeks. However, the safety of melatonin over months has not been studied.

Riemann and colleagues showed significant decreases in nighttime melatonin concentrations in insomniacs, and others have shown delays in melatonin secretion. However, several double-blind, placebo-controlled studies have failed to show the effectiveness of supplemental melatonin in treating primary insomnia. Melatonin in doses that range from 0.3–5 mg showed no significant differences over placebo in sleep measures such as sleep efficiency; total sleep time; latency to sleep; number of nocturnal awakenings; average length of the non-REM-REM cycle; percent of stage 1, 2, delta sleep, and REM sleep; total minutes of each sleep stage; and in the latency to REM sleep. The lack of hypnotic activity was evident when measured by self reports or by PSG measures. MacFarlane and colleagues found a significant improvement in subjective assessments of sleep and daytime alertness in insomniacs given a much larger dose, 75 mg, in a single, crossover placebo-controlled study. It is important to recognize that this dose is dramatically higher than the physiologic doses of melatonin (0.5–1 mg) and hence the safety of this dose requires study.

Melatonin appears to ameliorate secondary and age-related insomnia. Increased sleep efficiency was noted in both populations after administration of melatonin. Improved sleep efficiency occurred in an elderly population with doses of 0.1–3.0 mg which elevated plasma levels within normal range. Overall, the present data would suggest that melatonin is not an effective treatment for the management of primary insomnia. However, it has clear phase shifting properties and hence it may have efficacy in elderly insomniacs with decreases in endogenous melatonin and insomnia associated with sleep circadian rhythm disorder.

**Tryptophan**

L-tryptophan is an essential amino acid that comes from food. Once absorbed, it can be converted to serotonin and melatonin. In the brain, serotonin is synthesized from tryptophan, which is the major metabolic route. Low levels of serotonin have been reported to be associated with depression, anxiety, and insomnia, and L-tryptophan supplements have been used to treat these disorders despite the absence of convincing data of its benefit.

The tryptophan-depletion model has been used to determine the association between tryptophan and sleep. Tryptophan depletion, following an ingestion of a tryptophan-free amino acid drink, significantly increased stage 1 sleep and decreased stage 2 sleep. However, indices of sleep induction and sleep efficiency were not affected. Indices of REM density (the frequency of eye movements per unit of time during REM sleep) were significantly increased, whereas REM latency remained unaltered.

L-tryptophan supplements appeared to be effective hypnotic agents in chronic insomniacs with sleep maintenance disturbances that were characterized by 3–6 discrete awakenings during the night. Insomniacs self-reported 100% improvement following 1 g nightly administration for 1 week. No consistent significant effects of L-tryptophan on sleep parameters determined by PSG were found in doses <1 g. Significant decreases in sleep latencies were observed following 1–3 g of tryptophan but inconsistent findings were noted on total sleep time, SWS, and REM sleep.

In a study by Schneider-Helmert and Spinweber, chronic insomniacs characterized by both sleep onset and sleep maintenance problems showed therapeutic improvement occurring over time with repeated administration of low doses of L-tryptophan. The hypnotic effects appeared late in the treatment period or, as shown in some studies, even after discontinuation of treatment. L-tryptophan is also effective in reducing sleep onset time on the first night of administration in doses ranging from 1–15 g in young situational insomniacs.

The treatment of depression with the selective serotonin reuptake inhibitor fluoxetine can exacerbate insomnia. The hypnotic effects of tryptophan in conjunction with an antidepressant were used to potentiate an improvement in insomnia. Tryptophan (2–4 g) and fluoxetine (20 mg) administered for 8 weeks significantly decreased depression scores and had a SWS protective effect. A significant decrease in SWS was noted in the fluoxetine placebo group but not in the fluoxetine-tryptophan group.

L-tryptophan administration has not been linked with impairments in visuomotor, cognitive, or memory performance. Some side effects of tryptophan can include drowsiness, tiredness/fatigue, nausea, loss of appetite, dizziness, headache, and dry mouth (Table 2).

**ALCOHOL**

In 2001, approximately 30% of chronic insomniacs in the general population reported using alcohol to induce sleep and 67% of those reported that alcohol was effective. However, in PSG studies insomniacs who used alcohol had significantly impaired measures of sleep continuity and had more severe alcohol dependence and depression. Males and those never married or those separated or divorced/widowed are approximately 1.5 times more likely to use alcohol as a sleep aid than females or those who are married.

Alcohol consumed at bedtime may decrease the time required to fall asleep and increase SWS. Because of alcohol’s sedating effect, many people with insomnia consume alcohol to promote sleep. However, alcohol consumed within an hour of bedtime appears to disrupt the second half of the sleep period. Alcohol affects the proportions of the various sleep stages with dose-dependent suppression of REM sleep. Higher
doses of alcohol increased nocturnal awakenings and/or lighter stages of sleep (stage 1) during the second half of the night. The second-half disruption of sleep continuity is referred to as a “rebound effect,” occurring as alcohol is metabolized or eliminated from the body. Overall, the use of alcohol as well as the discontinuation of alcohol is associated with disturbances of sleep. This is most clearly seen in alcoholics who exhibit profoundly disturbed sleep during active drinking and after months of abstinence. Finally, the relation of alcohol consumption to improve sleep to the evolution of chronic alcoholism warrants study.

### Conclusion

Much of the data on the efficacy and safety of OTC sleep aids is inconclusive and is associated with problems such as too few participants in the studies, little demographic and diagnostic information regarding study participants, inconsistency in demographic and diagnostic information among studies to allow comparisons, lack of placebo-control groups, subjective reports with a lack of objective data, and short-term treatment with study medication which provides little indication about long-term usage.56 Treatment of insomnia with antihistamine-containing OTC sleep aids may help occasional mild insomniacs. Prolonged use of some if not all antihistaminic drugs may result in tolerance and/or dependence and produce daytime sleepiness. The data on other non-prescription sleep aids is too limited or inconsistent in results to consider their use. While alcohol may have initial sedative effects, it is associated with rapid tolerance development and dose escalation (Table 2).

## References

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