

## Oral Nonprescription Treatment for Insomnia: An Evaluation of Products With Limited Evidence

Clinical Practice Review Committee, American Academy of Sleep Medicine

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**Purpose:** To evaluate the level of evidence regarding the safety and efficacy of nonprescription therapies used for insomnia.

**Reviewers:** Members of the American Academy of Sleep Medicine's Clinical Practice Review Committee.

**Methods:** A search of the World Wide Web was conducted using the terms insomnia, herbal remedies, and alternative treatments to develop a list of therapies. Therapies in this review include passionflower, valerian, Jamaican dogwood, hops, California poppy, chamomile, lemon balm, St. John's wort, kava kava, wild lettuce, scullcap, Patrinia root, first-generation histamine-1-receptor antagonists, alcohol, calcium, vitamin A, nicotinamide, magnesium, vitamin B12, l-tryptophan, 5-hydroxytryptophan, dietary changes, Natrum muriaticum, and Yoku-kan-san-ka-chimpi-hange. A search of the PubMed database was conducted in October 2002 using MeSH terms insomnia and each product listed in this paper, including only articles published in English between 1980 and 2002. Additional relevant articles from reference lists were also reviewed. Given the paucity of pediatric publications, this age group was excluded from this review.

**Results and Conclusions:** Although randomized, placebo-controlled studies were available for a few compounds, rigorous scientific data supporting

a beneficial effect were not found for the majority of herbal supplements, dietary changes, and other nutritional supplements popularly used for treating insomnia symptoms. Nevertheless, such treatments are described as alternative remedies for insomnia. Studies are limited by small numbers of participants and, in some instances, inadequate design, lack of statistical analysis, and sparse use of objective measurements. Sparse or no scientific data were found to support the efficacy of most products as hypnotics, including chamomile and St. John's wort. There is preliminary but conflicting evidence suggesting Valerian officinalis L. and first-generation histamine-1-receptor antagonists have efficacy as mild hypnotics over short-term use. There are significant potential risks associated with the use of Jamaican dogwood, kava kava, alcohol, and l-tryptophan. Physicians may find this information useful in counseling their patients.

**Key Words:** Herbal sedatives, dietary supplements, hypnotics and sedatives, herbal medicine, sleep disorders, insomnia.

**Citation:** Meoli AL; Rosen C; Kristo D et al. Oral nonprescription treatment for insomnia: an evaluation of products with limited evidence. *J Clin Sleep Med* 2005;1(2):173-187

The treatment of primary insomnia may include cognitive-behavioral therapies, sometimes in association with judicious use of hypnotic agents. While the efficacy of behavioral treatments is well established,<sup>1-5</sup> the evidence supporting popular nonprescription or nutritional supplements has received less attention.<sup>6</sup> Expenditures on alternative medical therapies are substantial.<sup>7-9</sup>

### Disclosure Statement

Dr. Rosen was the medical director for a centralized pediatric PSG and actigraphy reading center for a phase I study looking at pediatric labeling for a prescription hypnotic medication; has received research support from Sanofi-Synthelabo. Dr. Townsend has received research support from Medtronic. Dr. Meoli has participated in speaking engagements supported by Sanofi-Synthelabo. Dr. Fayle has received honoraria from Cephalon, Orphan, and Novartis. Drs. Aguillard, Hoban, Gooneratne, Claman, Troell, Kristo, Kohrman, and Mahowald have indicated no financial conflicts of interest.

Submitted for publication July 2004

Accepted for publication July 2004

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Further, if these treatments are ineffective or harmful, the costs of treating a disease may increase. The assumption that nutritional supplements are inherently safe is dangerous. There are several examples of lethal toxicity associated with some products.<sup>10-13</sup> Prescription drugs are subject to significant control of the manufacturing process, so that the active component is standardized between different drug preparations. In contrast, nutritional supplements are not regulated, so efficacy with 1 specific product may not be generalized to other commercially available products purporting to be the same compound. For some products, the active component may not be known. This article provides a review of most of the available scientific data on the safety and efficacy of nonprescription therapies popularly used to treat insomnia symptoms. (NOTE: Melatonin, marketed as a nutritional supplement, has undergone extensive evaluation as to its hypnotic properties and circadian-shifting effects and is not included in this review.)

### METHODS

A search of the World Wide Web was conducted using the terms *insomnia*, *herbal remedies*, and *alternative treatments*. A

list of nutritional supplements, dietary changes, and nonprescription medications that were listed by more than one Web site is included in the review (see Table 1). Medications, such as analgesics, that are not approved by the Federal Drug Administration (FDA) for use as nonprescription hypnotics or listed by public-oriented Web sites were not included. Literature searches (PubMed) limited to English language from 1980 to 2002 were conducted for each list item. Additional relevant articles from reference lists were also reviewed. Members of the Clinical Practice Review Committee, an American Academy of Sleep Medicine committee comprising a multidisciplinary group of clinicians, extracted the data from the search results. Given the limited number of publications for each therapy, studies were reviewed regardless of scientific caliber. In the case of first-generation histamine-1 (H<sub>1</sub>)-receptor antagonists, studies of antihistamines unavailable in the United States market were included because of the potential similarities in mechanism of action. Given the paucity of pediatric publications, this age group was excluded from this review. A consensus of committee members was used to formulate the conclusions.

## HERBS

### Passionflower

The aerial parts of passionflower are cultivated and used for its sedative and anxiolytic effects. The main components of passionflower are flavonoids, indole alkaloids, maltol, ethyl-maltol, and cyanogenic glycosides. A dose-dependent sedative effect of an aqueous extract has been found in mice.<sup>14</sup> A double-blind randomized trial of passionflower and oxazepam in 36 patients with generalized anxiety disorder showed no significant difference in Hamilton Anxiety Rating Scale between treatment groups after

30 days, although oxazepam had a more-rapid onset of anxiolytic effect.<sup>15</sup> No scientific studies regarding efficacy for insomnia were found. Safety is also not well established, based on the reviewed literature. A case of a woman suffering prolonged QT interval and nonsustained ventricular tachycardia after ingestion of passionflower has been reported.<sup>16</sup>

### Valerian

#### Mechanism of Action

Valerian is derived from plants of the species *Valeriana*, most commonly *V. officinalis* L. It is used as a sedative and anxiolytic in addition to having purported uses in other conditions. It can be marketed in powdered form, but it is most commonly sold as an aqueous, alcohol, or dilute alcohol extract. However, the extraction method can strongly influence the active components in a particular formulation. These components can be divided into the following categories: sesquiterpenes (volatile oil components that account for valerian's unpleasant odor), valepotriates, and amino acids (such as GABA and glutamine). The valepotriates, for example, are not present in aqueous extracts, are most common in dilute alcohol extracts, and tend to have a more prominent anxiolytic than sleep-inducing effect.<sup>17</sup> Because they degrade quickly, they are usually present in dry formulations. Most likely, the effects of valerian are due to the individual effects of each of these constituents on different pathways, along with possible interactions among them. This was extensively reviewed by Houghton.<sup>17</sup> Recent in vitro research suggests that an additional mechanism of action may be related to binding at A<sub>1</sub> adenosine receptors.<sup>18</sup>

#### Efficacy and Safety

Several studies have examined the effects of valerian on sleep, many of which have used a randomized placebo-controlled design. Only placebo-controlled studies will be included in this discussion because of the more extensive literature base. Most studies have administered valerian 30 to 60 minutes before bedtime at doses ranging from 400 to 900 mg. An aqueous extract of valerian, comprised predominantly of sesquiterpenes and without valepotriates, was given to 18 subjects without sleep disturbances in a randomized, crossover, double-blind, placebo-controlled trial.<sup>19</sup> Eight of these subjects had attended polysomnographic studies and received placebo or valerian 900 mg for 1 night; 10 had wrist-activity measured at home and received placebo, valerian 450 mg, or valerian 900 mg over 2 nights. During the laboratory study, when treatment response on 3 nights of placebo was compared to 1 night of valerian 900 mg, polysomnographic-measured latency to stage 2 sleep was reduced from an average of 25.4 minutes to 19.2 minutes and wakefulness after sleep onset decreased from an average of 29.6 minutes to 19.0 minutes. These findings were not statistically significant, possibly due to the small sample size. During the home study, subjective sleep latency and wake time after sleep onset significantly improved in a dose-dependent manner when comparing valerian doses of 450 and 900 mg ( $P < .05$ ). However, subjective sleep quality did not change, and objective measures, such as wrist activity, were less conclusive. Subjects had a statistically significant increase in nighttime activity in the middle third of the night when they used valerian 900 mg, relative to placebo, but decreased nighttime activity in the latter third of the night. A significant limitation of

**Table 1**—Oral Nonprescription Treatments for Insomnia Included in Review\*

Herbs (3.0)
Passionflower (3.1)
Valerian (3.2)
Jamaican dogwood (3.3)
Hops (3.4)
California poppy (3.5)
Chamomile (3.6)
Lemon balm (3.7)
St. John's wort (3.8)
Kava kava (3.9)
Wild lettuce (3.10)
Scullcap (3.11)
Patrinia root (3.12)
First-generation histamine-1-receptor antagonists (4.0)
Alcohol (5.0)
Vitamins and supplements (6.0)
Calcium (6.1)
Vitamin A (6.2)
Nicotinamide (6.3)
Magnesium (6.4)
Vitamin B12 (6.5)
Tryptophans (6.6)
Dietary changes (7.0)
Miscellaneous (8.0)

\*Section numbers are in parentheses

the study was the use of valerian for only 1 or 2 study nights in a study population without sleep problems. A second study that compared valerian aqueous extract (450-mg and 900-mg doses) and placebo in 8 insomniacs using objective measures (wrist actigraphy) found that 450 mg of valerian significantly reduced sleep latency (from  $15.8 \pm 5.8$  minutes to  $9.0 \pm 3.9$  minutes,  $P < .01$ ).<sup>20</sup> In contrast to the prior study, an increased dose of 900 mg had no additional benefit. In addition, the 900-mg dose was associated with a statistically significant increase in subjective morning sleepiness, a possible “hangover” effect.

The effects of 1 night of valerian in comparison to a 14-day regimen were assessed by Donath et al<sup>21</sup> using polysomnographic measures in a randomized, double-blind, placebo-controlled trial in 16 insomniacs using 600 mg of valerian-root extract. A single dose of valerian had no significant effects on subjective or objective measures of sleep. However, a 14-day course was associated with the following significant changes ( $P < .05$ ): a shorter subjective sleep latency (60 minutes with placebo vs 45 minutes with valerian) and a shorter objective latency to slow-wave sleep relative to placebo (21.3 minutes with placebo vs 13.5 minutes with valerian). There were no significant changes in subjective sleep quality and no changes in other objective parameters such as sleep efficiency (88.4% with placebo vs 89.6% with valerian). While slow-wave sleep time increased with valerian relative to baseline values (8.1% to 9.8%), slow-wave sleep time also increased with placebo (8.1% to 9.2%), and there was no statistically significant difference between valerian and placebo in this regard.<sup>22</sup>

The largest study ( $n = 128$ ) of valerian found in the English literature evaluated the effects of 400 mg of aqueous valerian extract on self-rated “good sleepers” (52%) and “poor sleepers” (48%) in a randomized, double-blinded, placebo-controlled crossover design.<sup>23</sup> Statistically significant improvements in subjective sleep latency (22% on placebo vs 36% on valerian) and sleep quality (28% on placebo vs 41% on valerian) were found ( $P < .05$ ). In subgroup analysis, the population that reported the largest improvement (63%) in sleep quality was older adult poor sleepers. However, 43% reported subjective improvement with placebo, and the difference was not statistically significant. In young poor sleepers, there was a statistically significant improvement with valerian treatment (45% reported better sleep with valerian vs 16% with placebo;  $P < .01$ ). There was no significant difference in subjective daytime sleepiness between placebo and valerian. This study is limited by the lack of objective measurement of sleep parameters.

Lindahl and Lindwall<sup>24</sup> studied valerian (400 mg, predominantly sesquiterpenes) in 27 insomniacs using a double-blind, crossover design. Subjective sleep quality improved in 78% after 1 night of valerian treatment, which was greater than that reported with placebo ( $P < .001$ ). The study is limited, however, by the short duration of treatment, limited sample, and lack of objective measurement.

Alternative sleep-related uses for valerian have also been explored. Poyares et al<sup>25</sup> considered the possible role of valerian as a method to facilitate benzodiazepine withdrawal. In a double-blind study of 19 chronic benzodiazepine users, subjects were asked to taper their benzodiazepines while being randomly assigned to receive either a placebo or valerian compound (predominantly valepotriates, 100 mg 3 times daily). Sleep patterns, after a course of either placebo or valerian, were also compared to those of healthy controls. Subjective reports of sleep quality

using a visual analogue scale were  $7.4 \pm 0.9$  on valerian compared to  $5.4 \pm 0.8$  on placebo ( $P < .001$ ). While the placebo group had a significant decrease in objective sleep latency from baseline to posttreatment, the valerian group had a slight increase in sleep latency after treatment. Wakefulness after sleep onset, however, decreased in the valerian group while it increased in the placebo group such that the overall sleep efficiency remained similar in both groups after treatment. The authors postulated that the decreased wakefulness after sleep onset explained the improved subjective interpretation of sleep with valerian, despite the increased sleep latency.

Another placebo-controlled study, using polysomnography, sought to further clarify the role of valerian in older adults with sleep problems.<sup>26</sup> Eight elderly insomniacs were randomly assigned to receive valerian and were compared to 6 elderly insomniacs given placebo in a parallel-group design. Subjects took valerian (450 mg) or placebo 1 hour before bedtime on study day 1, and on study days 2 through 8, they took valerian or placebo 3 times daily with meals but not at bedtime. When compared to pretreatment baseline, subjects on valerian had no significant change in sleep efficiency but did have an increased slow-wave sleep time (7.7% compared to 12.5%,  $P = .027$ ), a finding similar to that noted by Donath et al,<sup>21</sup> and an increased total sleep time (319 minutes compared to 370 minutes,  $P = .039$ ). However, when valerian treatment was compared directly to placebo, there were no differences in these or other polysomnographic parameters and there was no change in self-reported sleep quality and day or evening alertness.<sup>26</sup> This study is limited by its small sample size and the fact that several essential sleep parameters, such as sleep latency, were not similar between the subjects randomly assigned to placebo or valerian.

An additional special population studied with valerian was that of children with intellectual deficits ( $IQ < 70$ ) and sleep disturbances.<sup>27</sup> Five children were studied in a randomized, double-blind, placebo-controlled trial relying on the parents' report of their children's sleep. There were statistically significant improvements in time spent awake, total sleep time, and sleep quality with valerian at a dose of 20 mg/kg. The greatest benefit was noted during the second week of treatment. While promising, the lack of physiologic measurements limits the clinical utility of this study.

These and other studies have found that valerian has a relatively benign side-effect profile. Rarely reported side effects are gastrointestinal upset, contact allergies, headache, restless sleep, and mydriasis.<sup>28</sup> Although one study reported increased subjective morning sedation after ingesting 900 mg of valerian the prior evening,<sup>20</sup> a randomized double-blind, placebo-controlled, parallel-group study in 99 subjects specifically designed to identify “hangover” cognitive/vigilance effects found no difference between evening placebo and valerian 600 mg.<sup>29</sup> Valepotriates also have the potential to alkylate DNA, thus raising the concern that they may have cytotoxic and carcinogenic potential.<sup>17</sup> For this reason, valerian is not recommended for use during pregnancy.<sup>30</sup> One case report of a postoperative patient who had been taking high doses of valerian, 530 mg to 2.0 grams per dose up to 5 times daily for several years, cited valerian withdrawal symptoms characterized by delirium and high-output cardiac failure. Symptoms improved with benzodiazepine treatment.<sup>31</sup> In one study of 23 overdose cases with a valerian-containing compound (dose range 0.5-12 g), the main side effects noted were drowsiness or confusion, which may have been in part due to the anticholinergic properties of the other components of the product.<sup>32</sup>

Of note, no patients developed hepatotoxicity; another study in which 4 cases reported hepatotoxicity from valerian may have had scullcap-induced hepatotoxicity.<sup>33</sup> Valerian may potentiate sedative effects when taken concomitantly with other central nervous system depressants.<sup>30</sup>

### Jamaican Dogwood

The use of Jamaican dogwood has been associated with a sedative effect in animals, but, according to Jellin et al,<sup>34</sup> there are no scientific studies demonstrating this effect in humans. More importantly, it is toxic to humans and is no longer available in many areas.<sup>34</sup>

### Hops

Common hops are used orally for insomnia, although no scientific evidence was found to support their efficacy in humans. A sedative effect was shown in rats related to the constituent 2-methyl-3-butene-2-ol.<sup>35</sup> There is no scientific literature evaluating safety.

### California Poppy

The family *Papaveraceae* includes more than 100 species of poppy. California poppy has been used for sedation but should not be confused with the Oriental poppy (*P. somniferum*), which is a source of crude opium and alkaloids, including morphine, heroin, and codeine. No published English literature regarding safety or efficacy of California poppy was found.

### Chamomile

#### Mechanism of Action

There are 2 types of chamomile plants used in herbal preparations, German chamomile (*Matricaria recutita*) used for restlessness and insomnia and Roman chamomile (*Chamaemelum nobile*) used orally for a variety of digestive, menstrual, and nasal-oral mucosal symptoms and topically for eczema, wounds, and inflammation. Sedative effects of German chamomile may be due to the benzodiazepine-like compound in the flowerhead.<sup>6</sup>

#### Efficacy and Safety

Although chamomile tea has a popular reputation as a relaxing tea that facilitates sleep, clinical studies are lacking. German chamomile is thought to possess multiple actions, including mild sedative properties.<sup>36</sup>

Chamomile, when used orally as highly concentrated tea, can induce vomiting.<sup>37</sup> Chamomile can also cause an allergic reaction in individuals sensitive to the *Asteraceae/Compositae* family that includes ragweed, chrysanthemums, marigolds, daisies, and other herbs. Theoretically, German chamomile may interact with anticoagulant and antiplatelet drugs, benzodiazepines, or other drugs with sedative properties and may inhibit cytochrome P (CYP) 450.<sup>36,38</sup> Therefore, patients taking other drugs metabolized by this enzyme system (eg, lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam, and a number of others) should use caution or avoid German chamomile. There are no known interactions with foods, laboratory tests, or specific diseases or conditions.<sup>39</sup>

### Lemon Balm

Lemon balm is a perennial herb alleged to have efficacy as a hypnotic. A randomized, double-blind, crossover study of lemon balm versus placebo evaluated the effect on cognitive performance. The highest dosage of lemon balm (900 mg) was associated with decreased subjective alertness assessed by a visual analog scale.<sup>40</sup> No studies on its efficacy and safety in the treatment of insomnia were found.

### St. John's Wort

#### Mechanism of Action

St. John's wort is a flowering herb used orally for a variety of ailments, such as depression, anxiety, and sleep disturbances. Preparations may include naphthodianthrones (hypericin, pseudohypericin, isohypericin), flavonoids (kaempferol, hyperoside, quercetin), phloroglucinols (hyperforin, adhyperforin), tannins, pro-cyanidins, essential oils, amino acids, and other components.<sup>41, 42</sup> The most active components are thought to be hyperforin and hypericin, although other components have bioactivity. Different formulations of St. John's wort vary in their levels of these constituents,<sup>43</sup> although many commercial preparations are standardized as to the hypericin content. Hypericin was previously thought to be the active ingredient. Early work suggested hypericin acted via monoamine oxidase inhibition,<sup>44</sup> the significance of which was discounted by later studies.<sup>45-48</sup> More recent attention has been focused on the role of hyperforin. Hyperforin inhibits the reuptake of serotonin, norepinephrine, dopamine, GABA, and L-glutamate.<sup>49-52</sup> However, the exact mechanism of action of St. John's wort is unknown. It is possible that other components, either in isolation or combination, also contribute to effects.<sup>51</sup>

#### Efficacy and Safety

Most clinical studies of St. John's wort that were reviewed focused on treatment of depression rather than insomnia. Several studies have found St. John's wort to be more effective in short-term treatment of mild or moderate depression than placebo and to have similar efficacy as some tricyclic antidepressants<sup>53-57</sup> or selective serotonin reuptake inhibitors.<sup>58-60</sup> However, these findings should be viewed with caution because patient groups were heterogeneous, extracts varied in their constituents, and the doses of comparison antidepressants were frequently low.

No published scientific studies of St. John's wort for insomnia not associated with depression were found. However, limited data on the effects of St. John's wort on sleep were located. A double-blind, placebo-controlled, polysomnographic study of 11 young healthy subjects free of mood or sleep disturbances assessed the effect of St. John's wort on sleep (age range 20-44 years). A dose of 0.9 mg was found to significantly increase rapid eye movement (REM) sleep latency versus placebo (84 vs 69 minutes, respectively,  $P = .03$ ).<sup>61</sup> A second group of 10 different subjects was studied in similar fashion, though using a higher dose of St. John's wort (1.8 mg). Mean REM latency in this group was not significantly increased in the active-treatment group versus placebo (104 vs 64 minutes, respectively,  $P = .15$ ).<sup>61</sup> No other effect on sleep architecture, including REM sleep duration, was found, but details were not included. Another placebo-controlled, double-blind, randomized crossover study of 11 older female volunteers (mean age 59.8 ± 4.8 years) analyzed the effects on sleep electroencephalogram.<sup>62</sup> There was an increase in slow-wave activity in 10 of 11 subjects

taking St. John's wort and 5 of 11 taking placebo. Statistical significance was not given. Median percentage of slow-wave sleep increased from 1.5% to 6.0% during active-treatment phase, while values decreased during placebo treatment from 4.1% to 2.5%. Notably, the baseline amount of slow-wave sleep was much lower in the active-treatment group. No other changes were noted in sleep duration or architecture, including REM-sleep variables. It is unknown if the demonstrated changes in sleep architecture were associated with clinical improvement in insomnia. Moreover, the studies used healthy volunteers, and the results cannot be generalized to persons with insomnia symptoms. The studies cited used specially formulated extracts of St. John's wort, and it is unknown what effect would occur with commercially available products. Also, the constituents and method of extraction varied from study to study, hampering the generalization of results.

Side effects associated with St. John's wort during clinical trials included gastrointestinal complaints, dizziness, fatigue, anxiety, and headaches.<sup>41,42,49,56,59,60,63</sup> In an observational study of 3250 patients using a commercially available preparation of St. John's wort, gastrointestinal symptoms, allergic reactions, tiredness, anxiety, and confusion were most often reported.<sup>64</sup> Photosensitivity and phototoxicity have been reported.<sup>65-67</sup>

St. John's wort has potentially severe drug interactions. In vivo studies have shown that St. John's wort induces CYP450, including isoenzyme CYP3A4.<sup>68-73</sup> Many drugs on the market are metabolized by CYP3A4; thus, drug interactions are frequent. The component probably most responsible for CYP3A4 induction is hyperforin.<sup>74</sup> One potential problem in predicting interactions is related to the fact that most commercially available St. John's wort is standardized for hypericin content. St. John's wort also induces intestinal P-glycoprotein levels.<sup>73,75</sup> The most significant interactions potentially involve patients with cardiovascular disease, HIV, cancer, and depression. Serum digoxin levels are reduced by 18% to 25%,<sup>73,76,77</sup> a mechanism that could account for potential interactions with calcium channel blockers, lidocaine, quinidine, warfarin, and amiodarone.<sup>78</sup> Absorption of indinavir, a nonnucleoside reverse-transcriptase inhibitor, is reduced.<sup>77</sup> Serum cyclosporine levels are reduced, and cases of acute organ rejection have been reported after kidney, heart, and liver transplants.<sup>70,72,79-82</sup> Levels of amitriptyline and its metabolite nortriptyline are reduced.<sup>83</sup> Cases of serotonin syndrome have been reported in patients taking concomitant sertraline, nefazodone, or paroxetine.<sup>84,85</sup> This may be related to the serotonin-promoting effects of St. John's wort, and St. John's wort should not be used in combination with selective serotonin reuptake inhibitors. Breakthrough menstrual bleeding has occurred in a few women on oral contraceptives, possibly related to increased CYP induction and reduced hormone levels.<sup>86</sup>

### Kava Kava

Kava kava is an herbal product derived from *Piper methysticum*, a shrub indigenous to the South Pacific. In the United States, kava-containing products are sold as dietary supplements and marketed for the treatment of anxiety, occasional insomnia, premenstrual syndrome, and stress. These supplements are often in the form of raw plant material or concentrated extracts. Since 1999, health-care professionals in Europe and the United States have reported the occurrence of severe hepatotoxicity (including liver failure requiring liver transplantation) associated with the consumption of products containing kava.<sup>87</sup> On March 25, 2002,

the FDA issued an advisory for consumers and health-care providers about the potential risk of hepatotoxicity associated with the use of kava-containing products.<sup>88</sup> The CDC issued the results of its investigation in the United States of the cases of liver failure associated with kava-containing dietary supplements and summarized the European cases.<sup>89</sup> Several European countries have restricted the sale of kava-containing products based on the occurrence of adverse hepatic events. Given the potential for severe toxicity, especially in persons with pre-existing liver disease or who are at risk for liver injury, recommendation of kava-containing products for insomnia should be avoided.

### Wild Lettuce

Wild lettuce has been used orally for insomnia, although its efficacy has not been established. Caution should be used because a hallucinogenic effect has been reported when the substance is inhaled. Jellin et al reported 3 cases who experienced a febrile reaction associated with headache, nausea, abdominal pain and transaminase elevation after intravenous injection.<sup>90</sup> However, the possibility that the reaction was related to contaminants in the injectate could not be excluded.<sup>91</sup>

### Scullcap

Scullcap has been used for insomnia, but efficacy has never been shown, based on the literature obtained for this paper. Oral use of scullcap in larger doses may cause seizure activity.<sup>90</sup> Additionally, several cases of hepatotoxicity have been reported, though it is not known whether this was due to scullcap or another constituent.<sup>33,90</sup>

### Patrinia Root

*Patrinia Scabiosaefolia* Fisch is a member of the *Valerianaceae* family, which includes *Valerian officinalis* L. (Valerian root). An unblinded, uncontrolled observational study of Patrinia root in patients with neurasthenic syndromes predominated by insomnia found statistically significant decreases in insomnia symptoms after 10 to 14 days of treatment with various Patrinia formulations.<sup>92</sup> *Marked improvement* was defined as "definite" improvement or disappearance of symptoms. *Improvement* was defined as any reduction in symptoms. The method of symptom rating was not given. A 20% extract of Patrinia, which contained 10% to 15% alcohol, reduced insomnia symptoms in 91.9% of 62 patients, with marked improvement in 30.6%. A tablet containing a dry extract of the root reduced insomnia in 80.0% of 284 patients, with marked improvement in 33.5%. Finally, a capsule containing a volatile oil of Patrinia root reduced symptoms in 81.7% of 60 patients, with marked improvement in 50.0%. All formulations were associated with adverse effects, most frequently nausea. However, the method of adverse event documentation was not given.

## FIRST-GENERATION H<sub>1</sub>-RECEPTOR ANTAGONISTS

### Mechanism of Action

The FDA has limited the active ingredients in over-the-counter sleep aids to diphenhydramine hydrochloride, diphenhydramine citrate, and doxylamine succinate,<sup>93</sup> which are in the ethanamine class of H<sub>1</sub>-receptor antagonists.<sup>94</sup> Older prepara-

tions containing methapyrilene alone or in combination with scopolamine have been taken off the market due to safety concerns. Histamine is a wake-promoting neurotransmitter, and inactivation or suppression in various animal models has led to sedation and disrupted wakefulness patterns.<sup>95</sup> Several reviews have summarized the sedative effects of first-generation H<sub>1</sub>-antagonists in humans.<sup>96-100</sup> In a study of 16 healthy volunteers, significant increases in daytime sleepiness, measured by Multiple Sleep Latency Tests, occurred with the use of diphenhydramine (50 mg 3 times daily) versus placebo ( $6.7 \pm 2.6$  vs  $10.3 \pm 3.3$ ;  $P < .02$ ).<sup>101</sup>

## Efficacy and Safety

Observational data from a drug-surveillance program at three urban hospitals were used to evaluate the efficacy of the four most commonly prescribed hypnotics: chloral hydrate, diphenhydramine hydrochloride, secobarbital, and pentobarbital.<sup>102</sup> Of 4177 consecutive patients monitored, 2405 (58%) received one or more of these drugs during a single hospital admission. The length of neither individual nor average hospitalization was given. Diphenhydramine was given to 512 patients, although 213 (42%) also received one or more of the other hypnotics. Dosages used were 100 mg ( $n = 46$ ), 50 mg ( $n = 440$ ), 25 mg ( $n = 24$ ) and other ( $n = 2$ ). Physician ratings of efficacy were good in 259 (50.6%), fair in 42 (8.2%), poor in 54 (10.5%), and undetermined in 157 (30.7%). The potential additive effect of other hypnotic agents was not explored. Subjective reports of sleep quality, sleep latency, and sleep duration were significantly better with pentobarbital (180 mg) than with 2 doses of diphenhydramine (50 and 150 mg) in male subjects in 2 urban Veterans Administration hospitals, although the study was associated with a high rate of protocol incompleteness.<sup>103</sup>

There are several randomized, placebo-controlled studies of the hypnotic effects of centrally acting antihistamines. Some of the antihistamines discussed are no longer sold as over-the-counter sleep aids. Methapyrilene fumarate was used in a randomized, double-blind, placebo-controlled trial of postpartum patients.<sup>104</sup> Interviews conducted the following morning were used in 2 phases of the trial and self-completed questionnaires in a third. Interviews were conducted with 142 subjects who received either 50 mg of methapyrilene and 975 mg aspirin ( $n = 47$ , Treatment C), 42 mg methapyrilene and 925 mg acetaminophen ( $n = 46$ , Treatment D), or placebo ( $n = 49$ , Treatment P). The method of dosage selection was not given. Of 9 questions asked regarding pain relief and sleep quality, seven were answered by the patient and two by the treating nurse. Treatment C was significantly more likely than Treatment P ( $P = .001$ ) and Treatment D ( $P = .01$ ) to be rated as helpful in falling asleep, whereas there was no significant difference between Treatments D and P. Nurses' evaluation of hypnotic efficacy was significantly greater with Treatment C ( $P = .001$ ) and D ( $P = .02$ ) than with Treatment P, although C was more effective than D ( $P = .01$ ). A second study phase including 111 postpartum subjects similarly assessed the efficacy of 50 mg of methapyrilene fumarate, 390 mg of aspirin, 260 mg of salicylamide, and 325 mg of acetaminophen ( $n = 55$ , Treatment E) versus placebo ( $n = 56$ , Treatment P). Both subjects and nurses rated Treatment E as more effective ( $P = .001$ ). Treatment E ( $n = 42$ ) was also compared to placebo ( $n = 31$ ) in a third study phase using a self-completed questionnaire given to 73 postpartum subjects. Twenty-seven subjects receiving Treatment E and 16 receiving

Treatment P (NS) regarded the medication as effective as a sleep aid. Using a visual analog scale of treatment efficacy from 0 ("no effect") to 5 ("terrific"), mean response scores were 3.12 for Treatment E and 2.00 for Treatment P ( $P = .001$ ). It is unknown what contribution the analgesic additives played in a potential sedative effect. The effect of methapyrilene HCL (50 mg) combined with scopolamine (0.5 mg) was compared to placebo in five male subjects (24-25 years of age) undergoing in-laboratory nocturnal sleep monitoring.<sup>105</sup> Subjects received placebo (baseline) for three nights followed by active treatment for three nights and two placebo (withdrawal) nights. All subjects had a history of moderate to severe insomnia, characterized by sleep-initiation difficulty in one, sleep-maintenance difficulty in one, and both symptoms in three. There was little difference in group mean and individual sleep latencies between placebo and drug nights. The method of statistical analysis and  $P$  values were not given. Additionally, no significant reduction in wake time was found. The percentage of REM sleep was less during the first active-treatment night (20.4%) than baseline placebo night (23.3%). The next 2 drug nights were similar to baseline (23.1% and 22.8%), as were the withdrawal nights (24.3% and 24.0%). These results were not statistically significant.

In one study, no significant difference in total hourly observational wake versus sleep readings were found between placebo and diphenhydramine hydrochloride (25 mg) in geriatric insomniac subjects (mean age 77 years, range 58-92).<sup>106</sup> Significant improvement occurred with the use of Mandrax (250 mg methaqualone base and 25 mg diphenhydramine); chloral hydrate, 600 mg; and methaqualone base, 250 mg. Each treatment was given for one week without a washout period between. Subjects were in either a residential ( $n = 10$ ) or psychiatric section ( $n = 15$ ) of an elder care facility. All subjects suffered from psychiatric disturbances or "chronic brain syndrome." The frequent concomitant use of hypnotics, neuroleptics, or antidepressants could have also affected study results.

The use of diphenhydramine (50 mg) was studied in a double-blind, placebo-controlled, crossover design in 111 patients, 15 of whom were eventually excluded because of protocol violations.<sup>107</sup> Each treatment leg lasted one week. All patients (mean age  $45 \pm 13$  years) complained of sleep-initiation difficulty. The majority of patients were women (78%), white (73%), married (58%), and high-school graduates (72%). Based on self-completed, daily, sleep-log responses, diphenhydramine was significantly more effective than placebo in improving all sleep parameters, including sleep latency ( $P < .010$ ), frequency of awakenings ( $P < .01$ ), wake time ( $P < .001$ ), sleep duration ( $P < .001$ ), and quality of sleep ( $P < .001$ ). Physician ratings of efficacy at the end of each treatment week were similar to patient responses. Upon study completion, 57 of the 96 patients preferred diphenhydramine, whereas 21 preferred placebo ( $P < .001$ ), and 18 had no preference. Doxylamine succinate (25 mg) was studied with the same study protocol.<sup>108</sup> Of 111 insomniacs enrolled, 83 (mean age  $46 \pm 14$  years) completed the study, and 27 did not because of protocol violations or early dropout. Patients also tended to be women (88%), white (88%), and high-school graduates (55%). Patient ratings were significantly more positive for doxylamine with regard to sleep latency ( $P < .001$ ), nocturnal awakenings ( $P < .001$ ), sleep duration ( $P < .001$ ) sleep quality ( $P < .001$ ), and morning restfulness ( $P < .001$ ). Physician ratings were similar to those of the patients. More patients preferred doxylamine than placebo (43 vs 15, respective-

ly,  $P < .001$ ), while 24 had no preference.

A double-blind, placebo-controlled, crossover trial compared diphenhydramine hydrochloride (1 mg/kg) and placebo in 50 pediatric subjects (mean age 5.2 years, range 23.5 months to 12 years), with nine subjects not completing the two-week study period.<sup>109</sup> There was a significant reduction in subjectively reported sleep latency ( $P < .05$ ) and frequency of awakenings ( $P < .01$ ) during 1 week of diphenhydramine treatment versus placebo, while there was a statistical trend in increased sleep duration ( $P = .07$ ).

In one study, inpatient and outpatient psychiatric patients ( $n = 144$ ) complaining of insomnia symptoms were randomly assigned to receive various doses of diphenhydramine (12.5 mg, 25 mg, and 50 mg) or placebo over a two-week period.<sup>110</sup> The use of diphenhydramine was associated with an overall improvement in the severity of insomnia versus placebo ( $P = .0002$ ), although, individually, only the 12.5-mg dose achieved statistical significance ( $P = .042$ ).

A randomized, double-blind, crossover trial of temazepam (15 mg), diphenhydramine (50 mg), and placebo given to 17 nursing-home patients for five consecutive nights interspersed with 3 wash-out nights found patient reports of sleep latency were shorter with the use of diphenhydramine than with placebo ( $P < .05$ ). Diphenhydramine was reported to increase sleep duration more than temazepam on the fifth night only ( $P < .05$ ). Three subjects did not complete the study.<sup>111</sup>

In Shapiro's series, adverse effects were reported in nine subjects (1.8%), and treatment was discontinued in 8.<sup>102</sup> Most patients were given 50 mg of diphenhydramine ( $n = 7$ ), and two received 100 mg. Side effects included vomiting ( $n = 1$ ) and depression ( $n = 8$ ). A possible dose-dependent occurrence of side effects was found by Kudo et al.<sup>110</sup> No side effects were reported in 95.8% of the 12.5-mg group, 88% of the 25-mg group, and 82.6% of the 50-mg group. The most-reported side effect was malaise. Doxylamine succinate was rated by patients to have significantly more side effects than placebo ( $P < .05$ ).<sup>108</sup> The most frequently reported reactions were drowsiness, grogginess, tiredness, dry mouth, and weakness. Diphenhydramine was associated with more drowsiness, dizziness, grogginess, dry mouth, tiredness, and weakness than placebo, although statistical significance was not given.<sup>107</sup> In a prospective cohort study of 426 hospitalized patients over the age of 70, 114 (27%) received diphenhydramine for sleep, prophylaxis for blood transfusions, or allergic reactions. There was a 70% increased risk for impaired cognition in diphenhydramine-treated patients (42% vs 24%,  $P < .05$ ), which appeared to be dose related.<sup>112</sup> Mild drowsiness was reported as the only possible adverse reaction associated with the use of diphenhydramine hydrochloride in children, occurring in 1 out of 41 reported subjects.<sup>110</sup> Dimenhydrinate, a preparation composed of diphenhydramine and 8-chlorotheophylline, has been abused due to hallucinogenic and excitatory properties at higher than recommended doses.<sup>113</sup> Other central nervous system side effects include sedation, dizziness, stimulation, euphoria, nervousness, and extrapyramidal reactions.<sup>94</sup> A variety of gastrointestinal complaints, voiding difficulties, impotence, and headaches may also occur.<sup>94</sup> Antihistamines may increase intraocular pressure and should be avoided in patients with narrow angle glaucoma.<sup>114</sup> Symptoms of overdosage include flushing, excitement, and convulsions. Coma may ensue, with death usually related to hypotension or cardiac arrest.<sup>94</sup> Doxylamine

overdose has been associated with rhabdomyolysis and acute renal failure.<sup>115, 116</sup>

## ALCOHOL

### Mechanism of Action

Alcohol is a well-known central nervous system depressant. Several effects on sleep architecture have been described after acute alcohol consumption in nonalcoholic subjects, though results are variable. A reduction in sleep latency has been found by some investigators<sup>117-119</sup> but not others,<sup>120-122</sup> which is probably dose dependent.<sup>118</sup> Increases in stages 3 and 4 non-REM (NREM) sleep may occur in the first several hours of sleep<sup>118-122</sup> with a reduction in the latter portion of sleep.<sup>119,122</sup> The whole-night duration of slow-wave sleep is not significantly changed.<sup>118,121,122</sup> Changes in slow-wave sleep may also be dose related,<sup>118</sup> and one study using lower doses of alcohol found a whole-night reduction in stages 3 and 4 sleep.<sup>120</sup> REM-sleep alterations have been variably described. In several studies, higher doses of alcohol (0.9-1.0 g/kg of body weight) led to a reduction in REM sleep in the first half of the night and an increase in the second half.<sup>117,123,124</sup> One study using lower doses of alcohol (0.6 g/kg) found no significant change in REM sleep duration either throughout the night or in the first two hours.<sup>121</sup> In another study, a significant reduction ( $P < .03$ ) in REM sleep occurred in subjects with and without insomnia symptoms after consuming alcohol at a dose of 0.5 g/kg.<sup>122</sup> Stone reported no changes in REM sleep with three different alcohol doses (0.16, 0.32, and 0.64 g/kg), although there was a trend toward increasing REM sleep latency at the 2 highest doses.<sup>120</sup> Another study of the dose effects of alcohol on sleep (at 0.00, 0.25, 0.50, 0.75, and 1.00 g/kg) found no significant changes in percentage of REM sleep through either the entire night or the first three hours.<sup>118</sup> However, REM sleep for both time periods was reduced with increasing alcohol dose, and the small study size ( $N = 10$ ) may have led to a Type 1 error. A dose-dependent increase (doses of 0.00, 0.50, and 0.75 g/kg) in REM sleep percentage ( $P < .05$ ) was found in 11 young women volunteers.<sup>119</sup> Tolerance to these effects occurs after one to three nights of continued alcohol consumption.<sup>117,123,124</sup> In another study, significant increases in stage 1 sleep were found between hours four and six of the study night with two doses of alcohol (0.05, 0.75 g/kg) relative to placebo ( $P < .05$ ).<sup>119</sup> Further, the amount of wake time was also significantly increased during 6 hours in bed ( $P < .05$ ). In Stone's series, a significant ( $P < .05$ ) increase in total sleep time occurred with a low dose of alcohol (446.0 minutes) versus placebo (431.1 minutes).<sup>120</sup> However, at higher doses (0.32 and 0.64 g/kg), total sleep time was reduced nonsignificantly (442.0 and 418.3 minutes, respectively). Nonsignificant increases in wake time during the fifth hour of sleep were also noted after consumption of 0.75 g/kg ( $7.5 \pm 21.0$  minutes) and 1.00 g/kg ( $17.8 \pm 44.8$  minutes) of alcohol as compared to placebo ( $0.6 \pm 1.9$  minutes) and alcohol doses of 0.25 g/kg ( $0.6 \pm 1.9$  minutes) and 0.50 g/kg ( $0.5 \pm 1.6$  minutes).<sup>118</sup>

To appreciate more-subtle changes in sleep, Roehrs et al<sup>122</sup> used fast Fourier transform (FFT) analysis to assess changes in electroencephalogram spectra after consumption of a single dose of alcohol (0.6 g/kg). No significant changes occurred in NREM (stages 2, 3, 4) for the whole night, whereas, during REM sleep, there were significant increases ( $P < .05$ ) in the 1.25- to 1.5-

2.25- to 2.5-, and 4.75- to 8-Hz ranges. Significant changes ( $P < .05$ ) were found during NREM sleep when the first two hours were compared with the remainder of sleep. Augmentation in the 0.25- to 1-Hz range and diminution in the 13.25- to 17-Hz and 20.25- to 25-Hz range occurred. Fast Fourier transform analysis after 0.8 g/kg alcohol resulted in an increased mean power density during all REM sleep ( $P < .05$ ) in the 0.0- to 6.0-Hz region (15.3) versus baseline (12.6). During NREM sleep, power density in the 10.0-12.0 Hz band was significantly higher ( $P < .05$ ) during the test night (3.5 vs 2.4).<sup>125</sup>

It appears that alcohol leads to a dose-dependent decrease in sleep latency. Initial increases in stages 3 and 4 sleep and augmentation in slow-wave activity may be dose related, but entire-night changes are not apparent. A reduction of REM sleep in the initial hours of sleep has been found by some investigators, especially at higher doses. All of these studies were performed in healthy, young, nonalcoholic subjects and included small numbers of subjects (1-20).

### Efficacy and Safety

Alcohol use as a sleep aid is an all-too-common and dangerous occurrence. The National Sleep Foundation, using a population-based survey of adults in 1999, found 14% of respondents used alcohol as a sleep aid.<sup>126</sup> In 1996, a random-dial, computer-assisted, telephone survey of younger adults (18-45 years) in southeastern Michigan (N = 2181) found that 13.3% of respondents (n = 290) used alcohol for sleep. The majority used alcohol sporadically, with 68% reporting regular use of less than one-week duration and 84.1% reporting fewer than 30 incidences of use within the past year.<sup>127</sup> A greater number of shift workers used alcohol than did day workers and those not working. However, regular use of alcohol for longer than four weeks in duration was reported by 32.5% of those who did not work but by only 10.8% of day or shift workers ( $P < .01$ ). In an interview study of 155 women over the age of 85 years recruited from an urban area, all participants complained of poor sleep, and most (70%, n = 91) reported drinking wine or a mixed drink before bedtime to reduce insomnia symptoms.<sup>128</sup>

Since acute alcohol ingestion may adversely affect sleep architecture, especially in the latter portion of sleep, it is possible that alcohol may be associated with insomnia symptoms. Most evidence suggests a reduction in REM sleep and stages 3 and 4 NREM sleep in the latter portion of a sleep period after acute alcohol consumption. Furthermore, an increase in stage 1 sleep and wake time may also occur in the terminal portion of sleep. Conversely, insomnia symptoms may increase the risk of alcohol dependence. A population survey using personal interviews conducted one year apart in adults over 18 years of age found that subjects with insomnia uncomplicated by a psychiatric disorder were at significantly greater risk ( $P < .05$ ) for alcohol abuse one year later than were those without sleep or psychiatric disturbances (odds ratio 2.3, 95% confidence interval 1.2-4.3).<sup>129</sup> In a longitudinal population study using mailed questionnaire responses in 1984 (n = 3201) and 1994 (n=2975), insomnia prevalence was 10.3% and 12.8%, respectively.<sup>130</sup> Only the 1994 survey included lifestyle questions, including alcohol use. Subjects reporting insomnia in 1994 had significantly more ( $P < .001$ ) symptoms of alcohol dependence than did those without insomnia (18.9% vs 8.6%). Logistic regression found alcohol

dependence was a significant risk factor for insomnia (odds ratio 1.75, 95% confidence interval 1.20-2.54). In the previously mentioned study<sup>122</sup> of alcohol effects on sleep architecture in subjects with and without insomnia, subjects were allowed to select alcohol or placebo in color-coded cups on subsequent study nights based on their preference from previous nights. The insomnia group chose alcohol a significantly greater ( $P < .002$ ) number of nights (2.08 vs 0.67). Furthermore, the insomnia group chose a greater ( $P < .01$ ) total number of ethanol doses (6.69 v. 2.00), or an average of 0.45 g/kg each night.

The adverse effects of excessive alcohol use on physical and psychological function are well known. Acute and chronic alcohol use cause disruption of sleep continuity and exacerbate insomnia symptoms. Alcohol use also worsens sleep-related breathing disturbances in a dose-dependent fashion.<sup>131</sup> Modest reductions in baseline arterial oxygen saturation (3%-4%), increased incidence and duration of obstructive apneas, and development of obstructive apneas in chronic snorers has been found after alcohol consumption of the subject's maximal social intake. Other investigators have also found worsening of obstructive sleep apnea after alcohol intake.<sup>132-134</sup> As compared to a control night, inspiratory resistance significantly increased ( $P = .01$ ) during stage 2 NREM sleep after alcohol intake in 7 snoring ( $30.2 \pm 4.4$  cm H<sub>2</sub>O·L<sup>-1</sup>·min<sup>-1</sup> vs  $63.7 \pm 19.2$ ) and 9 nonsnoring ( $16.3 \pm 7.0$  cm H<sub>2</sub>O·L<sup>-1</sup>·min<sup>-1</sup> vs  $25.9 \pm 16.5$ ) nonobese men.<sup>135</sup> The increase in inspiratory resistance was significantly greater ( $P = .05$ ) in snorers than in nonsnorers. No significant changes in minute ventilation, end-tidal CO<sub>2</sub>, or ventilatory response to hypercapnia or isocapnic hypoxia were found in either group. Possible mechanisms for the adverse effect of alcohol on sleep-disordered breathing include reduced hypoglossal nerve activity, altered carotid-body receptor function, depressed arousal response, and sleep fragmentation.<sup>136</sup> Total growth hormone levels across sleep have been shown to be significantly reduced after one night (70%,  $P = .05$ ) and nine successive nights (75%,  $P < .05$ ) of alcohol consumption (0.8 g/kg).<sup>137</sup> Values returned to baseline after withdrawal of alcohol. The clinical significance of this, if any, is unknown. Alcohol given to infants (1.5-5.6 months of age) in breast milk, in concentrations similar to those that occur one hour after maternal consumption of 0.3 g/kg of alcohol, resulted in a 25% reduction in the actigraphy-based estimates of length of sleep ( $P = .04$ ).<sup>138</sup> This finding was replicated in a later study, which also found an increase in active sleep during a period of abstinence following alcohol consumption.<sup>139</sup>

## VITAMINS AND SUPPLEMENTS

### Calcium

Relative hypercalcemia has been shown to be associated with insomnia in hemodialysis patients.<sup>140</sup> In this study, a reduction of dialysate calcium concentration (1.75-2.00 mmol/L to 1.25 mmol/L) and subsequent serum calcium level from 9.9mg/dL to 9.4 mg/dL ( $P < .0001$ ) led to significant reductions in insomnia. Those patients with constant insomnia dropped from 20.5% (n = 15) to 5.9% (n = 4). Occasional insomnia dropped from 37.0% (n = 27) to 22.1% (n=15). Those without insomnia increased from 42.5% (n = 31) to 72.0% (n = 49). All improvements were statistically significant ( $P < .005$ ). Notably, of 105 patients initially assessed, only 76 remained in the study group following inter-



vention. Explanation for the dropouts was not given. We found no published data regarding the use of calcium supplements for insomnia. Similarly, we could find no studies of the incidence of calcium derangements in primary insomnia.

### Vitamin A

Acute poisoning with vitamin A (retinol) leads to drowsiness, sluggishness, irritability, and an irresistible desire to sleep.<sup>141</sup> However, we found no data to indicate that clinically used doses of vitamin A lead to drowsiness, and vitamin A is not routinely used for insomnia therapy.

### Nicotinamide

Nicotinamide (Niacin) is biosynthesized from dietary tryptophan via the kynurenine pathway and quinolinic acid. In six normal patients given escalating doses of nicotinamide for two days followed by 3 g daily for 21 days, significant ( $P = .002$ ) increases in REM sleep were measured (18.4% baseline vs 25.0% at the end of treatment).<sup>142</sup> Using the same protocol, two female patients with insomnia experienced an increase in sleep efficiency from 58.5% at baseline to 79.5% after three weeks, with a return to 41.5% after cessation of nicotinamide.<sup>142</sup>

### Magnesium

Magnesium is thought to have a role in the promotion of human sleep. The use of magnesium enhances melatonin secretion from the pineal gland by stimulating serotonin N-acetyl transferase activity, the key enzyme in melatonin synthesis. In contrast, melatonin may decrease serum magnesium by melatonin's effects on magnesium distribution.<sup>143</sup> However, magnesium may decrease melatonin production.<sup>143</sup> No studies on the efficacy of magnesium in insomnia patients were found.

### Vitamin B<sub>12</sub>

Case-report data suggest potential beneficial effects of vitamin B<sub>12</sub> in both free-running sleep-wake rhythm (hypnocytohemeral syndrome) and in delayed sleep-phase syndrome.<sup>144,145</sup> Two reported cases of hypnocytohemeral syndrome with normal B<sub>12</sub> levels included a 15-year-old female with a 25-hour sleep-wake period and a 17-year-old male with a 24.6-hour sleep-wake period. Both were entrained to a 24-hour sleep-wake rhythm after B<sub>12</sub> treatment. The 15-year-old girl was treated with 4.5 mg of vitamin B<sub>12</sub> daily and experienced symptom recurrence two months after stopping B<sub>12</sub>. Two additional patients with delayed sleep-phase syndrome were treated with B<sub>12</sub>.<sup>144,146</sup> A 15-year-old girl received 3.0 mg of B<sub>12</sub> daily, with sleep-onset advance by two hours and a gradual decrease in sleep duration from 10 to 7 hours. A 55-year-old man with delayed sleep-phase syndrome since age 18 received 4.5 mg of B<sub>12</sub> daily with symptom improvement for over six months.

An uncontrolled multicenter trial (N = 106) evaluated B<sub>12</sub> efficacy in various sleep-wake rhythm disorders. Subjects initially received B<sub>12</sub> in 1.5 or 3.0 mg divided daily doses. Non-responders also received bright light therapy or hypnotics if necessary. Improvement occurred in patients with non-24-hour sleep disorder (32%), delayed sleep-phase syndrome (42%), irregular sleep-wake pattern (45%), and long sleepers (67%).<sup>147</sup> However, a subsequent

double-blind study showed no effect on delayed sleep-phase syndrome with 3.0 mg of B<sub>12</sub> daily for four weeks.<sup>148,149</sup> An additional 51 patients, 45 with delayed sleep-phase syndrome and 6 with non-24-hour sleep-wake syndrome were studied in double-blind fashion. No clear benefit was apparent after eight weeks of therapy.

No studies were found that evaluated B<sub>12</sub> therapy for insomnia symptoms unassociated with circadian-rhythm disturbances.

### Tryptophans

#### L-Tryptophan

*Physiologic Effects.* As early as 1974, the use of L-tryptophan was suggested as a natural hypnotic.<sup>150,151</sup> Serotonin, an end product of L-tryptophan metabolism, is involved in REM sleep.<sup>150</sup> L-tryptophan produces a decrease in REM sleep and increase in NREM sleep.<sup>150</sup> Partial blockade of L-tryptophan conversion to serotonin by parachlorophenylalanine does not alter L-tryptophan effects on sleep architecture. Use of a monoamine oxidase inhibitor, which inhibits tryptamine metabolism and increases tryptamine concentrations, in conjunction with L-tryptophan resulted in sedation and an apparent drunken state in one study. The exact mechanism of action of the sedative effects of L-tryptophan is unknown.

*Efficacy and Safety.* Sedation associated with the use of L-tryptophan has been demonstrated in both normal and insomnia groups.<sup>151</sup> Previous literature reviews concluded that L-tryptophan may be efficacious in shortening sleep-onset latency in patients with insomnia symptoms, though results were not always consistent.<sup>152,153</sup> However, L-tryptophan was taken off the market in the United States following cases of eosinophilic myalgia syndrome attributed to contamination linked to bacterial fermentation methods used in processing L-tryptophan.<sup>154</sup> Consequently, L-tryptophan is only available by prescription since 1991.

#### 5-Hydroxytryptophan

5-hydroxytryptophan (5-HTP) is an intermediate metabolite of L-tryptophan in the serotonin pathway. Therapeutic doses of 5-HTP bypass the conversion of L-tryptophan to 5-HTP by the enzyme tryptophan hydroxylase, the rate-limiting step in serotonin synthesis. Factors such as stress, insulin resistance, vitamin B<sub>6</sub> deficiency, and hypomagnesemia inhibit tryptophan hydroxylase. Use of 5-HTP resulted in less REM-sleep fragmentation in alcoholics during short-term abstinence in 1 study.<sup>155</sup> In another study, the use of 5-HTP in normal subjects was found to augment REM sleep.<sup>156</sup> In a group of 3 patients, REM sleep decreased by the second week of treatment, and rebound occurred following cessation of therapy.<sup>157</sup> Despite the very limited data found suggesting changes in REM sleep, it is unknown what effect, if any, 5-HTP has on insomnia symptoms.

## DIETARY CHANGES

### Mechanism of Action

From clinical and basic science studies, there are reasons to believe that diet can be an adjunctive treatment for insomnia. Fat introduced into the gastrointestinal tract of rodents increased total sleep and REM time in 1 study.<sup>158</sup> Intracarotid delivery of nutri-

ents from digestion can cause hypersynchrony of the electroencephalogram and induce sleep.<sup>159</sup> Eating can precipitate sleep attacks in narcoleptics.<sup>160</sup> Sleep-inducing hormones released from the gut and transport of “hypnotoxins” from digested food to the central nervous system are proposed mechanisms.<sup>158,159,161</sup> Primary candidates for hypnotoxins are intermediates of serotonin metabolism such as tryptophan.

## Efficacy and Safety

Single-blinded controlled studies in normal subjects have shown modest effects on sleep after a small fat and carbohydrate meal.<sup>162,163</sup> These effects were small statistical declines in movement time in the last third of monitored sleep periods. Such studies have led to the widely accepted notion that a snack before bedtime is part of good sleep practices in the treatment of insomnia.<sup>164,165</sup> Sleep disturbances, independent of mood, are common in those with severe weight loss from anorexia nervosa, with reported decreases in total sleep time, slow-wave sleep, and REM sleep and associated increases in wake after sleep-onset time.<sup>166</sup> Refeeding diets in these patients has shown improvements in sleep with a predictable pattern of sleep-stage recovery. The magnitude of the recovery effect toward normal sleep has been shown to be a function of recovered weight.<sup>166,167</sup>

There are relationships between specific diets that directly act on the known physiology of a disease state, which then have secondary effects on sleep. Sleep-related hypoglycemic episodes in diabetics, whether induced by diet or medication, can trigger disturbed sleep.<sup>161,168</sup> Diets leading to weight gain can exacerbate sleep apnea and, therefore, the disturbing effects of apnea on sleep.<sup>169</sup> Weight loss in obesity during controlled, extreme, therapeutic diets is associated with an increased use of sedative hypnotics.<sup>170</sup> Dietary manipulations have been shown to decrease depressive symptoms, including insomnia, in premenstrual tension syndromes.<sup>171</sup> Diets that reduce the intake of substances associated with increased symptoms of attention-deficit/hyperactivity disorder improve sleep disturbances in children with attention-deficit/hyperactivity disorder.<sup>172</sup> Dietary elimination of known psychostimulants, caffeine being the most obvious, improves sleep in insomnias of different causes.<sup>173</sup> Proponents of specific diets for insomnia without supporting data on the effectiveness of such diets could make unsubstantiated claims exploiting these known pathophysiologic relationships. For example, milk elimination in milk-intolerant infants improves many sleep characteristics in such infants with milk-induced sleeplessness.<sup>174</sup> Based on the literature reviewed, there is no evidence to suggest, however, that milk-elim-

ination diets will improve sleeplessness in all infants.

For dietary treatment of specific sleep disorders associated with insomnia, the literature is sparse. A randomized prospective study examined a vegetarian diet on feelings of nonrestorative sleep, fatigue, and insomnia in 78 patients with fibromyalgia syndrome.<sup>175</sup> The diet was designed to increase brain tryptophan, which the authors felt would improve sleep symptoms of fibromyalgia syndrome. The patients were randomly assigned to diet or amitriptyline. After six weeks, there was significant improvement in the amitriptyline group and no improvement in the diet group. The Argonne diet for the treatment of jet lag alternates “feasting” days (high-protein foods early in the day and high-carbohydrate foods at night) with “fasting” days (800 calories) for 4 days prior to travel.<sup>176</sup> This diet improved symptoms of jet lag, including insomnia, in a study of 186 military troops crossing nine time zones during deployment and return.<sup>176</sup> Although this unblinded study was prospective, participation in the diet was optional, raising the possibility of a significant selection bias.

## MISCELLANEOUS

Natrum muriaticum is sodium chloride. Occasionally, it is formulated from sea salt. It is a homeopathic remedy used primarily for the treatment of various skin conditions but is also used to treat a wide range of pathologies.<sup>177,178</sup> It is stated to improve sleep by alleviating nightmares in those with depression and remorse.<sup>179,180</sup> No studies on this compound in the treatment of insomnia were found.

Yoku-kan-san-ka-chimpi-hange (YKCH) is an herbal medicine used for insomnia. A double-blind crossover study compared YKCH to Anchu-san, an herbal drug used for gastrointestinal complaints, in 20 healthy adult men.<sup>181</sup> Using polysomnography, total sleep time was significantly increased ( $P = .04$ ) with YKCH (462 minutes vs 425 minutes). YKCH resulted in nonsignificant reductions in sleep latency (4.66 minutes vs 10.4 minutes) and stages 3 and 4 sleep (39 minutes vs 52 minutes) and nonsignificant increases in stage 2 sleep (123 minutes vs 50.6 minutes) and REM sleep (64.6 minutes vs 48.6 minutes).

## CONCLUSION

As summarized in Tables 2 through 5, most over-the-counter insomnia treatments have very limited evidence supporting safety and efficacy. The literature obtained for this paper includes seven randomized placebo-controlled studies of the short-term hypnotic effects of valerian root. Six used subjects with insomnia

**Table 2**—Adverse Effects: Products with Limited Scientific Evidence of Hypnotic Efficacy

Product	Latin name (or generic name)	Adverse effects	References
Valerian root	<i>V. officinalis</i> L.	Restless sleep, gastrointestinal upset, headache, contact allergies, mydriasis, possible carcinogen, possible hepatotoxicity	17, 28, 33
First-generation histamine-1-receptor antagonists	Diphenhydramine hydrochloride, diphenhydramine citrate, doxylamine succinate	Vomiting, depression, malaise, drowsiness, impaired mentation, extrapyramidal reactions, rhabdomyolysis, dry mouth, weakness, gastrointestinal upset, headache, impotence, urinary retention, increased intraocular pressure	94, 102, 107, 108, 110, 112, 113, 114

symptoms, and four used some form of objective measurement of sleep variables. Subjects in all three studies located in the search that rely on subjectively determined sleep parameters experienced significant improvement, whereas subjects in only one of the studies using objectively determined sleep parameters had statistically significant improvement. Most of the studies found had a small number of subjects, which could have masked a positive effect. We reviewed eight randomized placebo-controlled studies of the short-term hypnotic efficacy of first-generation H<sub>1</sub>-receptor antagonists in insomnia subjects, only one of which used objective measurements of sleep quality. One subjective study and the only objective study used an antihistamine no longer approved for over-the-counter use as a sleep aid. Of the five subjective studies of diphenhydramine, four demonstrated significant efficacy as a hypnotic for less than one or two weeks of treatment. One subjective study evaluating doxylamine also showed significant improvement. Although a greater amount of literature on the hypnotic efficacy of valerian root and first-gen-

eration H<sub>1</sub>-receptor antagonists exists, the evidence is still preliminary. The studies are frequently flawed by small sample size, lack of objective outcome measurement, and variable study populations. Furthermore, studies have only assessed short-term treatment over a few days or weeks. It is unknown if long-term habitual use is either safe or effective. There was insufficient evidence found to determine the efficacy of hops, chamomile, lemon balm, St. John's wort, niacin, magnesium, B<sub>12</sub>, dietary changes, and YKCH for the treatment of primary insomnia. No scientific data were found evaluating the efficacy of passionflower, California poppy, wild lettuce, scullcap, calcium, vitamin A, 5-HTP, or Natrum muriaticum. There is potentially significant adverse risk associated with the use of Jamaican dogwood, alcohol, L-tryptophan, and kava kava. L-tryptophan is no longer available without prescription in the United States.

**Table 3**—Adverse Effects: Products with Insufficient Scientific Evidence of Hypnotic Efficacy

Product	Latin name	Adverse effects	References
Hops	<i>Humulus lupulus</i>	Unknown	
Chamomile	<i>Matricaria recutita</i>	Vomiting, allergic reactions	37
Lemon balm	<i>Melissa officinalis</i>	Unknown	
St. John's wort	<i>Hypericum perforatum</i>	Fatigue, gastrointestinal upset, dizziness, anxiety, headache, photosensitivity, phototoxicity	41, 42, 49, 56, 59, 60, 63, 64, 65, 66, 67
Patrinia root	<i>Patrinia Scabiosaefolia Fisch</i>	Nausea	92
Niacin	Niacin, niacinamide, vitamin B <sub>3</sub>	None known at recommended daily allowances	
Magnesium	Magnesium	None known at recommended daily allowances	
Vitamin B <sub>12</sub>	Vitamin B <sub>12</sub> , cyanocobalamin, hydroxocobalamin, methylcobalamin	None known at recommended daily allowances	
Dietary changes		Unknown	
Yoku-kan-san-ka	Unknown		
chimpi-hange			

**Table 4**—Adverse Effects: Products with No Scientific Evidence of Hypnotic Efficacy

Product	Latin or Scientific name	Adverse effects	References
Passionflower	<i>Passiflora incarnata</i>	Dizziness, confusion, ataxia, possible prolonged QT	15, 16
Californian poppy	<i>Eschscholzia californica</i>	Unknown	
Wild lettuce	<i>Lactuca virosa</i>	Possible hallucinogenic	91
Scullcap		Seizures, possible hepatotoxicity	33, 90
Calcium		None known at recommended daily allowances	
Vitamin A		None known at recommended daily allowances	
5-hydroxytryptophan		Unknown	
Natrum muriaticum		Unknown	

**Table 5**—Adverse Effects: Products with Significant Safety Concerns

Product	Latin name (or generic name)	Adverse effects	References
Jamaican dogwood	<i>Piscidia piscipula</i>	Toxicity to humans	34
Alcohol		Dependence, neurotoxicity, cardiotoxicity, myelosuppression, hepatotoxicity, respiratory depression, sedation, depression	132, 133, 134, 135, 137
L-tryptophan	L-2-amino-3-(indole-3-yl) propionic acid	Eosinophilia myalgia syndrome	152
Kava kava	<i>Piper methysticum</i>	Hepatotoxicity	87

## REFERENCES

- Edinger J, Wohlge-muth W, Radtke R, Marsh G, Quillian R. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA*. 2001;285:1856-64.
- Edinger J, Wohlge-muth W, Radtke R, Marsh G, Quillian R. Does cognitive-behavioral therapy alter dysfunctional beliefs about sleep? *Sleep*. 2001;24:591-9.
- Standards of Practice Committee of the American Academy of Sleep Medicine. An American Academy of Sleep Medicine Report. Practice parameters for the nonpharmacologic treatment of chronic insomnia. *Sleep*. 1999;22:1128-33.
- Morin C, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA*. 1999;281:991-9.
- Morin C, Hauri P, Espie C, Spielman A, Buysse D, Bootzin R. Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep*. 2000;22:1134-56.
- Glyllenhaal C, Merritt S, Peterson S, Block K, T. G. Efficacy and safety of herbal stimulants and sedatives in sleep disorders. *Sleep Med Rev*. 2000;4:229-51.
- Weeks J. Is alternative medicine more cost effective? *Med Econ*. 2000;77:139-42.
- White A, Ernst E. Economic analysis of complementary medicine: a systematic review. *Complement Ther Med*. 2000;8:111-8.
- De Maye-Caruth B. Complementary medicine: health care trends for the new millennium. *Hosp Mater Manage Q*. 2000;22:18-22.
- Bogaerts Y, Van Renterghem D, Vanvuchelen J, et al. Interstitial pneumonitis and pulmonary vasculitis in a patient taking an L-tryptophan preparation. *Eur Respir J*. 1991;4:1033-6.
- Carr L, Ruther E, Berg P, Lehnert H. Eosinophilic-myalgia syndrome in Germany: an epidemiologic review. *Mayo Clin Proc*. 1994;69:620-5.
- Martin RW, Duffy J, Engel AG, et al. The clinical spectrum of the eosinophilia-myalgia syndrome associated with L-tryptophan ingestion. Clinical features in 20 patients and aspects of pathophysiology. *Ann Intern Med*. Jul 15 1990;113:124-34.
- Russman S, Lauterburg B, Helbling A. Kava hepatotoxicity. *Ann Intern Med*. 2001;135:68-9.
- Soulmani R, Chafique Y, Jarmouni S, Bousta D, Misslin R, Mortier F. Behavioural effects of *Passiflora incarnata* L. and its indole alkaloid and flavonoid derivatives and maltol in the mouse. *J Ethnopharmacol*. 1997;57:11-20.
- Akhondzadeh S, Naghavi H, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther*. 2001;26:363-7.
- Fisher A, Purcell P, Le Couteur D. Toxicity of *Passiflora incarnata* L. *J Toxicol Clin Toxicol*. 2000;38:63-6.
- Houghton P. The scientific basis for the reputed activity of Valerian. *J Pharm Pharmacol*. 1999;51:505-12.
- Muller C, Schumacher B, Brattstrom A, Abourashed E, Koetter U. Interactions of valerian extracts and a fixed valerian-hop extract combination with adenosine receptors. *Life Sci*. 2002;71:1939-49.
- Balderer G, Borbély A. Effect of valerian on human sleep. *Psychopharmacology*. 1985;87:406-9.
- Leathwood P, Chauffard F. Aqueous extract of valerian reduces latency to fall asleep in man. *Planta Med*. 1985;144-8.
- Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I. Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. *Pharmacopsychiatry*. 2000;33:47-53.
- Giedke H, Breyer-Pfaff U. Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. *Pharmacopsychiatry*. 2000;33:239.
- Leathwood P, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root (*Valeriana officinalis* L.) improves sleep quality in man. *Pharmacol Biochem Behav*. 1982;17:65-71.
- Lindahl O, Lindwall L. Double blind study of a valerian preparation. *Pharmacol Biochem Behav*. 1989;32:1065-6.
- Poyares D, Guilleminault C, Ohayon M, Tufik S. Can valerian improve the sleep of insomniacs after benzodiazepine withdrawal? *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:539-45.
- Schulz H, Stolz C, Muller J. The effect of valerian extract on sleep polygraphy in poor sleepers: a pilot study. *Pharmacopsychiatry*. 1994;27:147-51.
- Francis A, Dempster R. Effect of valerian, *Valeriana edulis*, on sleep difficulties in children with intellectual deficits: randomised trial. *Phytomedicine*. 2002;9:273-9.
- PDR for Herbal Remedies. Montvale, NJ: Medical Economics; 1998.
- Kuhlmann J, Berger W, Podzuweit H, Schmidt U. The influence of valerian treatment on "reaction time, alertness and concentration" in volunteers. *Pharmacopsychiatry*. 1999;32:235-41.
- Plushner S. Valerian: *Valeriana officinalis*. *Am J Health Syst Pharm*. 2000;57:328, 333, 335.
- Garges H, Varia I, Doraiswamy P. Cardiac complications and delirium associated with valerian root withdrawal. *JAMA*. 1998;280:1566-7.
- Chan T, Tang C, Critchley J. Poisoning due to an over-the-counter hypnotic, Sleep-Qik (hyoscyne, cyproheptadine, valerian). *Postgrad Med J*. 1995;71:227-8.
- MacGregor F, Abernethy V, Dahabra S, Cobden I, Hayes P. Hepatotoxicity of herbal remedies. *Br Med J*. 1989;299:1156-7.
- Jellin J, Gregory P, Batz F, Hitchens K, Bonakdar R, Scott G. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database. 5th ed. Stockton, CA: Therapeutic Research Faculty; 2003:770-1.
- Jellin J, Gregory P, Batz F, Hitchens K, Bonakdar R, Scott G. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database. 5th ed. Stockton, CA: Therapeutic Research Faculty; 2003:718-20.
- Newall C, Anderson L, Phillipson J. A Guide for Healthcare Professionals. London, UK: The Pharmaceutical Press; 1996.
- McGuffin M, Hobbs C, Upton R, Goldberg A, eds. American Herbal Products Association's Botanical Safety Handbook. Boca Raton, FL: CRC Press; 1997.
- Brinker F. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical Publications; 1998.
- Natural Medicines Comprehensive Database. Available at: [www.naturaldatabase.com](http://www.naturaldatabase.com). Accessed Dec. 20, 2002.
- Kennedy D, Scholey A, Tildesley N, Perry E, Wesnes K. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). *Pharmacol Biochem Behav*. 2002;72:953-64.
- Barnes J, Anderson L, Phillipson J. St. John's wort (*Hypericum perforatum* L.): a review of its chemistry, pharmacology and clinical properties. *Pharm Pharmacol*. 2001;53:583-600.
- Greeson J, Sanford B, Monti D. St. John's wort (*Hypericum perforatum*): a review of the current pharmacological, toxicological, and clinical literature. *Psychopharmacology*. 2001;153:402-14.
- Wurglics M, Westerhoff K, Kaunzinger A, et al. Batch-to-batch reproducibility of St. John's wort preparations. *Pharmacopsychiatry*. 2001;Suppl 1:S152-6.
- Suzuki O, Katsumata Y, Oya M, Bladt S, Wagner H. Inhibition of monoamine oxidase by hypericin. *Planta Med*. 1984;50:272-4.
- Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of hypericum extract. *J Geriatr Psychiatry Neurol*. 1994;Suppl 1:S57-9.
- Thiede H, Walper A. Inhibition of MAO and COMT by hypericum extracts and hypericin. *J Geriatr Psychiatry Neurol*. 1994;Suppl 1:S54-6.
- Cott J. In vitro receptor binding and enzyme inhibition by

- Hypericum perforatum extract. *Pharmacopsychiatry*. 1997;Suppl 2:S108-12.
48. Muller W, Rolli M, Schafer C, Hafner U. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry*. 1997;Suppl 2:S102-7.
  49. Nathan P. The experimental and clinical pharmacology of St. John's wort (*Hypericum perforatum* L.). *Mol Psychiatry*. 1999;4:333-8.
  50. Muller W, Singer A, Wonnemann M, Hafner U, Rolli M, Schafer C. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. *Pharmacopsychiatry*. 1998;Suppl 1:S16-21.
  51. Nathan P. *Hypericum perforatum* (St. John's wort): a non-selective reuptake inhibitor? A review of the recent advances in its pharmacology. *J Psychopharmacol*. 2001;15:47-54.
  52. Chatterjee S, Bhattacharya S, Wonnemann M, Singer A, Muller W. Hyperforin as a possible antidepressant component of hypericum extracts. *Life Sci*. 1998;63:499-510.
  53. Williams J, Mulrow C, Chiquette E, Hitchcock P, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. *Ann Intern Med*. 2000;132:743-56.
  54. Linde K, Mulrow C. St. John's wort for depression. *Cochrane Database Syst Rev*. 2000;2:CD000448.
  55. Linde K, Ramirez G, Mulrow C, Pauls A, Weidenhammer W, Melchart D. St. John's wort for depression-an overview and meta-analysis of randomized clinical trials. *BMJ*. 1996;313:253-8.
  56. Whiskey E, Werneke U, Taylor D. A systematic review and meta-analysis of *Hypericum perforatum* in depression: a comprehensive clinical review. *Int Clin Psychopharmacol*. 2000;16:239-52.
  57. Kasper S. *Hypericum perforatum*-a review of clinical studies. *Pharmacopsychiatry*. 2001;34(suppl 1):S51-5.
  58. Schrader E. Equivalence of St. John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol*. 2000;15:61-8.
  59. Harrer G, Schmidt U, Kuhn U, Biller A. Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. *Arzneimittelforschung*. 1999;49:289-96.
  60. Woelk H. Comparison of St. John's wort and imipramine for treating depression: randomized controlled trial. *BMJ*. 2000;321:536-9.
  61. Sharpley A, McGavin C, Whale R, Cowen P. Antidepressant-like effect of *Hypericum perforatum* (St John's wort) on the sleep polysomnogram. *Psychopharmacology (Berl)*. 1998;139:286-7.
  62. Schulz H, Jobert M. Effects of *Hypericum* extract on the sleep EEG in older volunteers. *J Geriatr Psychiatry Neurol*. 1994;7(suppl 1):S39-43.
  63. Schulz V. Incidence and clinical relevance of the interactions and side effects of *Hypericum* preparations. *Phytomedicine*. 2001;8:152-60.
  64. Woelk H, Burkhard G, Grunwald J. Benefits and risks of the hypericum extract LI 160: drug monitoring study with 3250 patients. *J Geriatr Psychiatry Neurol*. 1994;Suppl 1:S34-8.
  65. Lane-Brown M. Photosensitivity associated with herbal preparations of St. John's wort (*Hypericum perforatum*). *Med J Aust*. 2000;172:302.
  66. Brockmoller J, Reum T, Bauer S, Kerb R, Hubner W, Roots I. Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. *Pharmacopsychiatry*. 1997;Suppl 30:94-101.
  67. Bove G. Acute neuropathy after exposure to sun in a patient treated with St. John's wort. *Lancet*. 1998;352:1121-2.
  68. Ruschitzka F, Meier P, Turina M, Luscher T, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet*. 2000;355:548-9.
  69. Roby C, Anderson G, Kantor E, Dryer D, Burstein A. St. John's wort: effect on CYP3A4 activity. *Clin Pharmacol Ther*. 2000;67:451-7.
  70. Breidenbach T, Kliem V, Burg M. Profound drop of cyclosporin A whole blood trough levels caused by St. John's wort (*Hypericum perforatum*). *Transplantation*. 2000;69:229-30.
  71. Markowitz J, DeVane C, Boulton D, Carson S, Nahas Z, Risch S. Effect of St. John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Sci*. 2000;66:PL133-9.
  72. Breidenbach T, Hoffmann M, Becker T, Schlitt H, Klempnauer J. Drug interaction of St. John's wort with cyclosporin (letter). *Lancet*. 2000;355:1912.
  73. Durr D, Stieger B, Kullack-Ublick G, et al. St. John's wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther*. 2000;68:598-604.
  74. Moore L, Goodwin B, Jones S, et al. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc Natl Acad Sci USA*. 2000;97:7500-2.
  75. Hennessy M, Kelleher D, Spiers J, et al. St. John's wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol*. 2002;53:75-82.
  76. Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther*. 1999;66:338-45.
  77. Piscitelli S, Burstein A, Chait D, Alfaro R, Falloon J. Indinavir concentrations and St. John's wort. *Lancet*. 2000;355:547-8.
  78. Cheng T. St. John's wort interaction with digoxin. *Arch Intern Med*. 2000;160:2548.
  79. Barone G, Gurley B, Ketel B, Lightfoot M, Abul-Ezz S. Drug interactions between St. John's wort and cyclosporine. *Ann Pharmacother*. 2000;34:1013-6.
  80. Turton-Weeks S, Barone G, Gurley B, Ketel B, Lightfoot M, Abul-Ezz S. St. John's wort: a hidden risk for transplant patients. *Prog Transpl*. 2001;11:116-20.
  81. Ernst E. St. John's wort supplements endanger the success of organ transplantation. *Arch Surg*. 2002;137:316-9.
  82. Karlova M, Treichel U, Malago M, Frilling A, Gerken G, Broelsch C. Interaction of *Hypericum perforatum* (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation. *J Hepatol*. 2000;33:853-5.
  83. Johne A, Schmider J, Brockmoller J, et al. Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St. John's wort (*Hypericum perforatum*). *J Clin Psychopharmacol*. 2002;22:46-54.
  84. Gordon JR. SSRIs and St. John's wort: possible toxicity? *Am Fam Physician*. 1998;57:950,953.
  85. Lantz M, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol*. 1999;12:7-10.
  86. Yue G, Bergquist C, Gerden B. Safety of St. John's wort (*Hypericum perforatum*). *Lancet*. 2000;355:576-7.
  87. From the Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products-United States, Germany, and Switzerland, 1999-2002. *JAMA*. 2003;289:36-7.
  88. FDA Center for Food Safety and Nutrition. Consumer advisory: kava-containing dietary supplements may be associated with severe liver injury. Available at: [www.cfsan.fda.gov/~dms/addskava.html](http://www.cfsan.fda.gov/~dms/addskava.html). Accessed March 25, 2002.
  89. Hepatic toxicity possibly associated with kava-containing products-United States, Germany, and Switzerland, 1999-2002. *Morb Mortal Wkly Rep*. 2002;51:1065-7.
  90. Jellin J, Gergory P, Batz F, Hitchens K, Bonakdar R, Scott G. *Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database*. 5th ed. Stockton, CA: Therapeutic Research Faculty; 2003:1174-5.
  91. Mullins M, Horowitz B. The case of the salad shooters: intravenous injection of wild lettuce extract. *Vet Human Toxicol*. 1998;40:290-1.

92. Hecun L, Yuhua C, Yucun S. Clinical observation and pharmacological investigation of the sedative and hypnotic effects of the Chinese drug rhizome and root of *Patrinia Scabiosaefolia* Fisch. *J Tradit Chin Med*. 1986;6:89-94.
93. Federal U.S. Food and Drug Administration. Available at: [http://www.fda.gov/cder/otcmonographs/Nighttime\\_Sleep-aid/nighttime\\_sleepaid\(338\).htm](http://www.fda.gov/cder/otcmonographs/Nighttime_Sleep-aid/nighttime_sleepaid(338).htm). Accessed September 9, 2004.
94. Cirillo V, Tempero K. Pharmacology and therapeutic use of antihistamines. *Am J Hosp Pharm*. 1976;33:1200-7.
95. Mignot E, Taheri S, Nishino S. Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. *Nat Neurosci*. 2002;5:1071-5.
96. Simons F. H1-receptor antagonists. Comparative tolerability and safety. *Drug Saf*. 1994;10:351-80.
97. Meltzer E. Performance effects of antihistamines. *J Allergy Clin Immunol*. 1990;86:613-9.
98. Passalacqua G, Bousquet J, Bachert C, et al. The clinical safety of H1-receptor antagonists. An EAACI position paper. *Allergy*. 1996;51:666-75.
99. Hindmarch I. Psychometric aspects of antihistamines. *Allergy*. 1995;50:48-54.
100. White J, Rumbold G. Behavioural effects of histamine and its antagonists: a review. *Psychopharmacology*. 1988;95:1-14.
101. Roth T, Roehrs T, Koshorek G, Sicklesteel J, Zorick F. Sedative effects of antihistamines. *J Allergy Clin Immunol*. 1987;80:94-98.
102. Shapiro S, Slone D, Lewis G, Jick H. Clinical effects of hypnotics. *JAMA*. 1969;209:2016-20.
103. Teutsch G, Mahler D, Brown C, Forrest W, James K, Brown B. Hypnotic efficacy of diphenhydramine, methapyrilene, and pentobarbital. *Clin Pharmacol Ther*. 1975;17:195-201.
104. Smith G, Coletta C, McBride S, McPeck B. Use of subjective responses to evaluate efficacy of mild analgesic-sedative combinations. *Clin Pharm and Ther*. 1974;15:118-29.
105. Kales J, Tan T, Swearingen C, Kales A. Are over-the-counter sleep medications effective? All-night EEG studies. *Curr Ther Res Clin Exp*. 1971;13:143-51.
106. Derbez R, Grauer H. A sleep study and investigation of a new hypnotic compound in a geriatric population. *Can Med Assoc J*. 1967;97:1389-93.
107. Rickels K, Morris R, Newman H, Rosenfeld H, Schiller H, Weinstock R. Diphenhydramine in insomniac family practice patients: a double-blind study. *J Clin Pharmacol*. 1983;23:235-42.
108. Rickels K, Ginsberg J, Morris R. Doxylamine succinate in insomniac family practice patients: a double-blind study. *Curr Ther Res Clin Exp*. 1984;35:532-40.
109. Russo R, Gururaj V, Allen A. The effectiveness of diphenhydramine HCl in pediatric sleep disorders. *J Clin Pharmacol*. 1976;16:284-8.
110. Kudo Y, Kurihara M. Clinical evaluation of diphenhydramine hydrochloride for the treatment of insomnia in psychiatric patients: a double blind study. *J Clin Pharmacol*. 1990;30:1041-8.
111. Meuleman J, Nelson R, Clark R. Evaluation of temazepam and diphenhydramine as hypnotics in a nursing-home population. *Drug Intell Clin Pharm*. 1987;21:716-20.
112. Agostini J, Leo-Summers L, Inouye S. Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. *Arch Intern Med*. 2001;161:2091-7.
113. Halpert A, Olmstead M, Beninger R. Mechanisms and abuse liability of the anti-histamine dimenhydrinate. *Neurosci Biobehav Rev*. 2002;26:61-7.
114. Tripathi R, Tripathi B, Haggerty C. Drug-induced glaucomas: mechanism and management. *Drug Saf*. 2003;26:749-67.
115. Leybushkis B, Fasseas P, Ryan K. Doxylamine overdose as a potential cause of rhabdomyolysis. *Am J Med Sci*. 2001;322:48-9.
116. Lee Y, Lee S. Acute pancreatitis and acute renal failure complicating doxylamine succinate intoxication. *Vet Hum Toxicol*. 2002;44:165-6.
117. Rundell O, Lester B, Griffiths W, Williams H. Alcohol and sleep in young adults. *Psychopharmacologia*. 1972;26:201-18.
118. MacLean A, Cairns J. Dose-response effects of ethanol on the sleep of young men. *J Stud Alcohol*. 1982;43:434-44.
119. Williams D, MacLean A, Cairns J. Dose-response effects of ethanol on the sleep of young women. *J Stud Alcohol*. 1983;44:515-23.
120. Stone B. Sleep and low doses of alcohol. *Electroencephalogr Clin Neurophysiol*. 1980;48:706-9.
121. Dijk D, Brunner D, Aeschbach D, Tobler I, Borbély A. The effects of ethanol on human sleep EEG power spectra differ from those of benzodiazepine receptor agonists. *Neuropsychopharmacology*. 1992;7:225-32.
122. Roehrs T, Papineau K, Rosenthal L, Roth T. Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. *Neuropsychopharmacology*. 1999;20:279-86.
123. Yules R, Freedman D, Chandler K. The effect of ethyl alcohol on man's electroencephalographic sleep cycle. *Electroencephalogr Clin Neurophysiol*. 1966;20:109-11.
124. Yules R, Lippman M, Freedman D. Alcohol administration prior to sleep: the effect on EEG sleep stages. *Arch Gen Psychiatry*. 1967;16:94-7.
125. Kobayashi T, Misaki K, Nakagawa H, et al. Alcohol effect on sleep electroencephalography by fast Fourier transformation. *Psychiatry Clin Neurosci*. 1998;52:154-5.
126. National Sleep Foundation. Sleep in America poll. Available at: <http://www.sleepfoundation.org/publications/1999poll.cfm>. Accessed September 9, 2004.
127. Johnson E, Roehrs T, Roth T, Breslau N. Epidemiology of alcohol and medication as aids to sleep in early adulthood. *Sleep*. 1998;21:178-86.
128. Johnson J. Insomnia, alcohol and over-the-counter drug use in old-old urban women. *J Community Health Nurs*. 1997;14:181-8.
129. Weissman M, Greenwald S, Nino-Murcia G, Dement W. The morbidity of insomnia uncomplicated by psychiatric disorders. *Gen Hosp Psychiatry*. 1997;19:245-50.
130. Janson C, Lindberg E, Gislason T, Elmasry A, Boman G. Insomnia in men—a 10-year prospective population based study. *Sleep*. 2001;24:425-30.
131. Issa F, Sullivan C. Alcohol, snoring and sleep apnoea. *J Neurol Neurosurg Psychiatry*. 1982;45:353-9.
132. Guilleminault C. Sleep apnea syndrome: impact of sleep and sleep states. *Sleep*. 1980;3:227-34.
133. Guilleminault C, Silvestri R, Mondini S, Coburn S. Aging and sleep apnea: action of benzodiazepine, acetazolamide, alcohol and sleep deprivation in healthy elderly group. *J Gerontol*. 1984;39:655-61.
134. Taasan V, Block A, Boysen P, Wynne J. Alcohol increases sleep apnea and oxygen desaturation in asymptomatic men. *Am J Med Sci*. 1981;71:240-5.
135. Dawson A, Bigby B, Poceta J, Mitler M. Effect of bedtime alcohol on inspiratory resistance and respiratory drive in snoring and non-snoring men. *Alcohol Clin Exp Res*. 1997;21:183-90.
136. Roth T, Roehrs T, Zorick F, Conway W. Pharmacological effects of sedative-hypnotics, narcotic analgesics and alcohol during sleep. *Med Clin North Am*. 1985;69:1281-8.
137. Prinz P, Roehrs T, Vitaliano P, Linnoila M, Weitzman E. Effect of alcohol on sleep and nighttime plasma growth hormone and cortisol concentrations. *J Clin Endocrinol Metab*. 1980;51:759-64.
138. Mennella J, Gerrish J. Effects of exposure to alcohol in mother's milk on infant sleep. *Pediatrics*. 1998;101:E2.
139. Mennella J, Garcia-Gomez P. Sleep disturbances after acute exposure to alcohol in mothers' milk. *Alcohol Clin Exp Res*. 2001;25:153-8.
140. Giovambattista V, Stanic L, Mastrosimone S, Gastaldon F, Da Porto A, Bonadonna A. Hypercalcemia and insomnia on hemodialysis patients. *Nephron*. 2000;85:94-5.

141. Idzikowski C, Shapiro C. Non-psychotropic drugs and sleep. *BMJ*. 1993;306:1118-21.
142. Robinson C, Pegram G, Hyde P, Beaton J, Smythies J. The effects of nicotinamide upon sleep in humans. *Biol Psychiatry*. 1977;12:139-43.
143. Durlach J, Pages N, Bac P, Bara M, Gviet-Bara A. Biorhythms and possible central regulation of magnesium status, phototherapy, darkness therapy, and chronopathologic forms of magnesium depletion. *Magnes Res*. 2002;15:49-66.
144. Ohta T, Ando K, Iwata T. Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (Vitamin B12). *Sleep*. 1991;14:414-8.
145. Okawa M, Mishima K, Hishikawa Y. Vitamin B12 treatment for sleep-wake rhythm disorders. *Jap J Psychiatry Neurol*. 1991;45:165-6.
146. Okawa M, Mishima K, Nanmai T, Shimizu T, Iijima S, Hishikawa Y. Vitamin B12 treatment for sleep-wake rhythm disorders. *Sleep*. 1990;13:15-23.
147. Yamadera H, Takahashi K, Okawa M. A multicenter study of sleep-wake rhythm disorders: therapeutic effects of vitamin B12, bright light therapy, chronotherapy and hypnotics. *Psychiatry Clin Neurosci*. 1996;50:203-9.
148. Okawa M, Takahashi K, Egashira H, Furuta H, Higashitani Y, Higucki T. Vitamin B12 treatment for delayed sleep phase syndrome: a multi-center double blind study. *Psychiatry Clin Neurosci*. 1997;51:275-9.
149. Takahashi K, Okawa M, Matsumoto M, Mishima K, Yamadera H, Sasaki M. Double-blind test on the efficacy of methylcobalamin on sleep-wake rhythm disorders. *Psychiatry Clin Neurosci*. 1999;53:211-3.
150. Hartmann E. L-Tryptophan: A possible natural hypnotic substance. *JAMA*. 1974;230:1680-1.
151. Wyatt R, Engelman K, Kupfer D, Fram D, Sjoerdsma A, Snyder F. Effects of L-tryptophan (a natural sedative) on human sleep. *Lancet*. 1970;2:842-5.
152. Schneider-Helmert D, Spinweber C. Evaluation of L-tryptophan for treatment of insomnia: a review. *Psychopharmacology*. 1986;89:1-7.
153. Hartmann E. Effects of L-tryptophan on sleepiness and on sleep. *J Psychiatr Res*. 1982;17:107-13.
154. 5-hydroxytryptophan. *Altern Med Rev*. 1998;3:224-6.
155. Zarcone V, Hoddes E. Effects of 5-hydroxytryptophan on REM sleep in alcoholics. *Am J Psychiatry*. 1975;132:74-6.
156. Zarcone V, Kales A, Scharf M, Tjiauw-Ling T, Simmons J, Dement W. Repeated ingestion of 5-hydroxytryptophan. *Arch Gen Psychiatry*. 1973;28:843-86.
157. Autrez A, Minz M, Bussel H, Cathala H, Castaigne P. Human sleep and 5-HTTP: effects of repeated high doses and of association with benserazide (RO.04.4602). *Electroencephalogr Clin Neurophysiol*. 1976;41:408-13.
158. Fara J, Rubinstein E, Sonnenschein R. Visceral and behavioral responses to intraduodenal fat. *Science*. 1969;166:110-1.
159. Koella W. Neurohumoral aspects of sleep control. *Biol Psychiatry*. 1969;1:161-77.
160. Mitler M, Hajdukovic R, Erman M, Koziol J. Narcolepsy. *J Clin Neurophysiol*. 1990;1:93-118.
161. Podell R. The "tomato effect" in clinical nutrition. *Postgrad Med J*. 1984;76:49-65.
162. Brezinová V, Oswald I. Sleep after a bedtime beverage. *Br Med J*. 1972;2:431-3.
163. Southwell P, Evans C, Hunt J. Effect of a hot mild drink on movements during sleep. *Br Med J*. 1972;2:429-31.
164. Byerley B, Gillin J. Diagnosis and management of insomnia. *Psychiatry Clin North Am*. 1984;7:773-88.
165. Nino-Murcia G. Diagnosis and treatment of insomnia and risks associated with lack of treatment. *J Clin Psychiatry*. 1992;53(Suppl 12):43-7.
166. Lacey J, Crisp A, Kalucy R, Hartmann M, Chen C. Study of EEG sleep characteristics in patient with anorexia nervosa before and after restoration of matched population mean weight consequent of ingestion of a "normal" diet. *Postgrad Med J*. 1976;52:45-9.
167. Lacey J, Crisp A, Kalucy R, Hartmann M, Chen C. Weight gain and the sleeping electroencephalogram: study of 10 patients with anorexia nervosa. *Br Med J*. 1975;4:556-8.
168. Taylor M. Insomnia and nutrition. *Aust Fam Physician*. 1994;23:498.
169. Guilleminault C. Obstructive sleep apnea. The clinical syndrome and historical perspective. *Med Clin North Am*. 1985;69:187-203.
170. Baird I, Parsons R, Howard A. Clinical and metabolic studies of chemically defined diets in the management of obesity. *Metabolism*. 1974;23:645-57.
171. Abraham G. Nutritional factors in the etiology of the premenstrual tension syndromes. *J Reprod Med*. 1983;28:446-64.
172. Kaplan B, McNicol J, Conte R, Moghadam H. Dietary replacement in preschool-aged hyperactive boys. *Pediatrics*. 1989;83:7-17.
173. Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ. Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. *Drug Alcohol Depend*. 1993;32:239-46.
174. Kahn A, Francois G, Sottiaux M, et al. Sleep characteristics in milk-intolerant infants. *Sleep*. 1988;11:291-7.
175. Azad KA, Alam MN, Haq SA, et al. Vegetarian diet in the treatment of fibromyalgia. *Bangladesh Med Res Counc Bull*. 2000;26:41-7.
176. Reynolds NJ, Montgomery R. Using the Argonne diet in jet lag prevention: deployment of troops across nine time zones. *Mil Med*. 2002;167:451-3.
177. Rajerdran E. *Molluscum contagiosum*; a case series. *Homeopathy*. 2002;91:255-93.
178. Blackstone V. An audit of prescribing natrum muriaticum. *Br Homeopath J*. 1994;83:14-9.
179. Shore J. The salt of the essence: an exploration of the relationship between totality, essence and central delusion. *JAIH*. 1998;91:173-6.
180. Guernsey H. Key-notes de notre matiere medicale: Natrum Muriaticum. Available at: <http://homeoint.org/books4/guernsey/natrmur.htm>. Accessed September 9, 2004.
181. Aizawa R, Kanbayashi T, Saito Y, et al. Effects of Yoku-kan-san-kachimpi-hange on the sleep of normal healthy adult subjects. *Psychiatry Clin Neurosci*. 2002;56:303-4.