Safety and Efficacy of Herbal Sedatives in Cancer Care

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Insomnia and other sleep disturbances are common in cancer patients. Insomnia is a multifactorial health concern that currently affects at least 1 in 3 cancer patients, and yet most insomnia sufferers do not consult their physician regarding pharmaceutical options for relief. Use of hypnotic drugs (primarily benzodiazepines) is associated with increasing tolerance, dependence, and adverse effects on the central nervous system. While hypnotic drug use declined substantially in the past decade, the use of herbal sedatives appeared to increase. Mostly self-prescribed by lay people, herbal sedatives hold widespread appeal, presumably because of their lower cost and higher margin of safety when compared to pharmaceuticals. Studies of better-known herbal sedatives, notably valerian and kava, showed moderate evidence for both safety and efficacy for valerian while revealing disturbing toxicity concerns for kava. Milder sedatives or anxiolytics in need of clinical study include German chamomile, lavender, hops, lemon balm, and passionflower; St. John's wort may have anxiolytic effects with relevance to sleep. Herb-drug interactions are a possibility for some of these species, including St. John's wort. Although sufficient evidence exists to recommend some of these agents for short-term relief of mild insomnia, long-term trials and observational studies are needed to establish the safety of prolonged use as well as overall efficacy in the context of cancer treatment and management.

Keywords: *insomnia; sleep disorders; hypnotic; herbal sedatives; valerian; kava; lavender; chamomile; hops; lemon balm; passionflower*

Insomnia is among the most frequent health complaints brought to the attention of primary care providers, with a very high prevalence in the Western world. Surveys indicate that insomnia occurs in about 1 in 3 Americans (35%), with prevalence rates ranging from 20% to 38% in other affluent countries.[1-5] The prevalence of sleep-related difficulties is significantly higher in women,[6,7] the elderly (people older than 65),[8,9] hospitalized adults,[10] and psychiatric patients.[11] Insomnia and other sleep disorders are common among cancer patients, although relatively few studies have sought to measure prevalence.[12]

The prevalence of sleep disturbances among cancer patients may depend on the treatment context and on the severity of malignant disease, with more advanced cases showing high rates of sleep alterations. In a multicenter study in Baltimore, 44% of breast and lung cancer patients reported experiencing sleep disturbances during the month before the interview.[13] In a cross-sectional survey, 31% of patients (n = 982) attending clinics for breast, gastrointestinal, genitourinary, gynecologic, lung, and nonmelanoma skin cancers reported having insomnia.[14] Sleep complaints were highest at the lung and breast cancer clinics. In a study of 300 consecutive women who had been treated with radiotherapy for nonmetastatic breast cancer onset, 19% met the diagnostic criteria for an insomnia syndrome; in 95% of these cases, the insomnia was chronic, while 58% of the cases reported that cancer either caused or aggravated their sleep difficulties.[15] Up to 75% of cancer patients visiting an intensive care unit and evaluated with the Edmonton Symptom Assessment Scale reported sleep disturbances.[16]

This literature review explores the safety and efficacy of herbal agents with purported sleep-enhancing effects for people with cancer. Because long-term use of hypnotic (sleep-inducing) medications is associated with dependence and other risks, nonpharmacological strategies for the relief of sleep disturbances are needed in the context of integrative cancer care; this is especially the case when the disease has reached a chronic course.[17] Several botanicals have demonstrated some efficacy as "natural sedatives" based on both clinical and preclinical studies. Nonetheless, the efficacy of these phytomedicinal options has yet to be verified specifically in cancer patients.

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The potential gravity of insomnia in cancer has been demonstrated in studies of the circadian rhythms of cancer patients. The wrist actigraph is a device similar to a wristwatch that records all movements during times when it is worn by an experimental subject. In a study of patients receiving chrono-chemotherapy (chemotherapy administered with a specially designed pump that allows rates of infusion to be varied throughout the day and night), Mormont and colleagues found that patients who showed disturbed circadian rhythms of rest and activity, including higher levels of activity during times in bed, had a shorter survival time than did patients who had marked differences in activity between resting and active times.[18]

These differences in activity level can be viewed as one aspect of a more global circadian disruption in cancer. Endocrine, metabolic, and immunological rhythms, as well as rest-activity cycles, can be disturbed[19]; disturbances in metabolic rhythms might also fuel further disruption of rest-activity cycles. Disturbances include lower levels of contrast between rest and activity, shifts in the timing of normal daily activities such as sleep and waking, and shortening of periods of rest or activity. The impact on the progression of cancer could be significant. Hormonal levels may be altered in cancer cells, immunosuppression relevant to cancer progression could be aggravated, tolerability of cancer treatments could be decreased, and quality-of-life decrements, which could ultimately lead to reduced adherence to treatment regimens, could ensue. Insomnia could thus be either a cause or an effect of circadian disorder in cancer. In either case, it may have a negative impact on survival, as well as quality of life. Its control, whether through behavioral,[20] pharmacological, or herbal interventions, merits close attention.

A Multifactorial Risk Scenario

The risk profile for insomnia is complicated by its multifactorial etiology (Table 1). The major causes of insomnia include psychological distress, various health problems, and lifestyle factors such as smoking, alcohol, and inadequate exercise.[21] Anxiety and depression are strong predictors of insomnia, even stronger than other health indicators such as perceived health and prescribed drug use.[22,23] Depression is associated with the delayed sleep-phase syndrome, one of the most common causes of severe insomnia, characterized in part by undesirably late bedtimes and rising times.[24] In a recent study, after adjustment for an array of putative risk factors, the association between age and sleep difficulties was primarily due to depressed mood and physical health problems.[25] In Japan, sleep

disorders are the second most common reason for psychiatric evaluations among cancer patients.[26]

Lifestyle factors and substance abuse also play a powerful role in the development or exacerbation of insomnia. Regular, moderate exercise is associated with a reduced risk of insomnia and other sleep disorders.[27] In a meta-analysis of 38 exercise studies, a moderate benefit was found, and exercise duration and time of day (early morning exercise is optimal) were the most consistent moderator variables that affected sleep.[28] Habitual smoking and withdrawal from tobacco are associated with a variety of sleep disturbances.[29,30] Interestingly, nicotine increases brain serotonin secretion, while nicotine withdrawal has the opposite effect.[30] Alcohol dependence is associated with insomnia, often in conjunction with anxiety and depression.[31,32] Dietary practices may also influence insomnia.

Carbohydrate-rich diets, which are conducive to increased tryptophan entering the brain leading to high serotonin levels, may be associated with somnolent and lethargic behavior, which could be more conducive to sleep.[33] Several lines of research, including one pilot study in France,[34] indicate that high-protein, low-carbohydrate diets may adversely affect sleep quality due to an inhibitory effect on brain tryptophan metabolism.[35-38] Such dietary influence could have a profound, unrecognized impact on the outcomes of insomnia interventions.

It is clear that the etiologies of insomnia are multifactorial and difficult to neatly categorize since multiple causes may overlap. For example, patients may have difficulty sleeping in the hospital because of the sterile environment, lights, and noises but also possibly because of disease- and treatment-related stresses, medications, and hospital food.[39] Many adult patients who appear to have organically based insomnia (eg, due to sleep apnea or other health problems) have underlying psychological disturbances.[40] Against such a complex backdrop, it is easy to understand why some physicians caution vehemently against overuse and long-term use of hypnotic drug therapy for the treatment of insomnia.[41,42]

Insomnia and Sleep Quality: Definitions and Measurements

The definitions of insomnia have changed considerably over the past 2 decades to include the perceptions of patients and the effects of restless sleep on daytime functioning. In 1979, Bootzin and Nicassio defined it as the "chronic inability to obtain adequate sleep due to retarded sleep onset, frequent arousals, and/or early morning awakening."[43] A decade later, Zorick defined it as the "perception by patients that their sleep is

Table 1.   Causes of Insomnia

Physical disorders	Periodic movements during sleep, restless legs, muscle spasms, chronic muscular tension, sleep apnea, sinusitis, respiratory allergies, fibromyalgia, chronic pain, chronic headaches, migraines, cardiac disorders, digestive system disorders, poor pineal function (possibly due to toxicity)
Lifestyle factors	Inadequate or erratic exercise, high-protein diet, regular late-night activities (such as binge eating), stimulants (caffeine, nicotine, spicy food, etc), alcohol, hypnotics, tranquilizers, prescription medication, psychotropic drugs
Psychological factors	Chronic emotional distress, nightmares, mental inactivity, psychopathology (psychiatric disorders, notably anxiety and depression, but also other conditions that are known to reinforce insomnia)
Poor sleep environment	Bright light, noise, extremes in ambient temperature, overly hard or overly soft sleeping surface, uneven sleep surfaces, narrow bed space, overly mobile bed partner
Circadian rhythm factors	Poor sleep habits (eg, staying up late, extended time in bed, frequent naps, irregular schedule, bed as a cue for arousal), shift work, jet lag, delayed sleep phase syndrome, advanced sleep phase syndrome, damaged pineal gland

Adapted from Bootzin and Perlis.[54]

inadequate or abnormal."[44] In 1999, Kirkwood defined insomnia similarly as "a subjective complaint of inadequate sleep" and acknowledged the importance of the daytime consequences of insomnia (lethargy, fatigue, irritability, etc).[6] The most common types of insomnia complaints are difficulty falling asleep (initiating stage I sleep), difficulty maintaining sleep (stage II sleep), early morning awakening, and unrefreshing or unsatisfactory sleep.

Insomnia complaints can be divided into 2 categories: sleep latency problems and sleep maintenance problems. Sleep latency is the propensity to fall asleep, or the time taken to fall asleep or to reach a particular sleep stage. Younger people are more prone to sleep latency difficulties, while the elderly tend to experience problems with sleep maintenance. However, these are subjective perceptions resulting in qualitative outcomes (hence, the often-used term *sleep quality*) that could yield widely varying estimates of the prevalence of insomnia. For this reason, it is important that researchers use objective, standardized measurements for effects on insomnia and its consequences or correlates.

In sleep laboratories, sleep physiology can be measured by polysomnography, which includes the simultaneous measurement by electroencephalogram, electro-oculogram, and electromyogram. The most commonly used parameters in sleep research are sleep onset latency, slow-wave sleep, rapid eye movement (REM) sleep, REM latency, total sleep time, and wakefulness after sleep onset. Other important assessments that appear in studies of sleep include measurements of anxiety (such as the Hamilton Rating Scale for Anxiety [HAM-A]), sleep quality questionnaires, and clinical ratings of sleep by health professionals. Specific details on each of these parameters are beyond the scope of the present article.

Polysomnographic data show that those with sleep complaints tend to overreport sleep latency and underestimate the total amount of sleep time; in addition, some individuals who do not complain about their sleep show physiologic sleep parameters consistent with insomnia.[45] However, it is not known why some individuals complain about sleep disturbances while others ignore symptoms and whether these patients accurately reflect the more general insomnia population. Women are more likely than men to report insomnia at any age.[46]

The duration of complaints represents a critical measurement in the study of insomnia. Chronic insomnia comprises those complaints that persist for longer than 3 weeks duration, often extending over several months or even years. Many people suffer from chronic insomnia that can be difficult to diagnose and treat since the underlying causes are probably multiple. In contrast, transient insomnia is more treatable and often results from recent situational upsets such as changing jobs or residences or an emotional loss. Jet lag is another type of transient insomnia.

Trends in the Treatment of Insomnia

Behavioral interventions for insomnia, such as relaxation techniques and stimulus control (noise, light, bedding, etc) and pharmacologic agents such as benzodiazepines are recommended for the short-term management of this condition.[21] The benzodiazepines and zolpidem, a nonbenzodiazepine with similar effectiveness, are the hypnotics most commonly prescribed for insomnia. However, regular use of these drugs is associated with adverse effects on the central nervous system among other toxicities.[6,47,48]

Although benzodiazepines are still the most commonly prescribed hypnotic agents, and no other class of drugs has proven to be superior in terms of benefit:risk ratio,[49] they are not considered the treatment of choice for persistent insomnia. This is in part because tolerance increases over time, that is, the drugs lose their effectiveness with prolonged use.[50] Of equal concern is the established risk of dependence: benzodiazepine use has been associated with considerable abuse and addictive problems, for example, "rebound

insomnia" or increased anxiety and insomnia after withdrawal.[51] Other undesirable side effects of chronic use of hypnotic drugs include paradoxical release of anxiety and/or hostility, memory disruption, psychomotor impairment, and increased risk of accidents.[52]

Due to these shortcomings and to the lack of long-term trial data, the Food and Drug Administration (FDA) established guidelines that discourage the use of benzodiazepines and other hypnotic drugs for longer than 1 month. After this point, physicians turn to nonpharmacological methods such as stress management and behavioral modification.

Despite its high prevalence, insomnia may also be among the most undertreated disorders. The vast majority of people with insomnia, more than 85% of all cases, do not seek medical treatment for their condition, and relatively few patients with chronic insomnia are evaluated and treated in sleep disorder clinics.[2,6] Why do people with insomnia not seek allopathic treatment? Among the possible explanations are safety concerns regarding the use of hypnotic drugs (pharmaceutical sleep aids), the inherent limitations of short-term management using these drugs, and pessimism in relation to treatment outcomes shared by patients and physicians. Many lay persons intuitively link their insomnia with emotional stress and thus may assume it is temporary, malleable, and very much under their control.

In an analysis of trends in pharmacological management of insomnia from 1987 to 1996, Walsh and Schweitzer in 1999 studied data obtained from the National Disease and Therapeutic Index, which samples office-based physicians in 24 specialties.[53] In this index, "drug mentions" are office visits in which a particular type of drug therapy is recommended by a physician. These authors compiled drug mentions involving "sedative night" or "promote sleep." Total drug mentions for insomnia fell 24.4%, including a 54% drop in hypnotic drugs and a 63% drop in "other" drugs. Counteracting these trends, however, was a 146% increase in drug mentions for antidepressants. Antidepressants are increasingly used in lieu of hypnotics for the symptomatic relief of insomnia despite a definite paucity of data regarding their efficacy and the potential for side effects.[6]

Concerns regarding the safety, cost, and efficacy of conventional medications for insomnia may prompt more consumers to seek alternative over-the-counter (OTC) and non-OTC solutions for managing their insomnia. Nonpharmacologic treatments such as diet, exercise, and stress management techniques play crucial roles in managing insomnia.[54] However, many physicians recognize the need for more effective nonpharmacologic management strategies. Many people are attracted to complementary medicine and increasingly turn to herbal therapy.[55,56] Before considering the safety and efficacy of herbal sedative and hypnotic agents, it is helpful to understand the extent of public interest in their potential usefulness.

Trends in Use of Herbal Agents, Including Sleep Aids

Interest in the therapeutic and preventive potential of herbal agents is widespread, possibly due to consumer concerns about the high cost of conventional medical care and the short- and long-range side effects of synthetic medications.[57,58] Several recent national polls indicated that 1 in 3 Americans use herbal agents in any given year.[59,60] From 1990 to 1997, according to a telephone survey of 2055 adults, the proportion of US consumers who sought out a provider of herbal medicine grew from 10% to 15% and overall use of herbal medicine rose from approximately 3% to 12%.[61,62] One in 5 of the 1997 respondents reported this use was concurrent with prescription medications, and 1 in 3 shared information concerning their use of complementary therapies with their conventional health care provider.

In European countries, consumer demand for herbal agents is typically vigorous, and herbal therapy is more widely accepted by European physicians compared to their US counterparts.[63,64] More physicians in the United States, however, are becoming cognizant of the therapeutic potentials (and drawbacks) of herbal medicines, as the need to communicate with their patients on this topic becomes more critical, particularly since the US herbal market has been valued at as much as $4 billion.[65]

Herbal sleep aids such as valerian, passionflower, and kava may be among the most commonly used herbal products. The often-cited 1997 survey by Eisenberg and colleagues found that 26.4% of the respondents used herbs and other complementary therapies for insomnia; about one half of these respondents also saw a physician about their sleeping difficulties. Thus, many individuals are self-prescribing herbal sleep aids either as a substitute for or in conjunction with medical care.

Health care providers, increasingly aware of the booming consumer demand for herbal therapy and increasing interest in herbal sleep aids, have expressed the need to educate themselves and their patients in the appropriate use of these agents. Many physicians question whether sufficient research data exist for making recommendations for the relief of insomnia and restoration of normal sleep quality. In this article, we review the evidence for safety and efficacy concerning the most widely available sleep-

promoting herbs, many of which have a long history of use in Europe yet are relatively new in the United States.

Definitions and Forms of Herbal Preparations

By their strictly technical definition, herbs are "non-woody seed-producing plants that die at the end of the growing season."[66] This narrow definition would exclude many currently used botanicals (plant-derived substances), including gingko, hawthorn, and pau d'arco, which are all (woody) trees. In relation to supplements, however, herbal agents are defined more loosely to encompass all botanicals, which means all plants, plant parts, or plant-derived substances. Thus, herbal products can comprise the whole plant as well as leaves, flowers, stems, seeds, roots, fruits, bark, or other parts used for medicinal effect, fragrance, or food flavoring. The terms *herbal* and *botanical* may be used interchangeably in this context.

Excluded from this definition are single, bioactive compounds that can be extracted from plants and that are commonly sold as prescription or OTC drugs. A classic example is the cardiac drug digoxin, extracted from the foxglove *Digitalis lanata* L. (Scrophulariaceae). A more "natural" example would be the indole melatonin, which has demonstrated effectiveness against insomnia and certain sleep-wake disturbances associated with shift work and jet lag, apparently by accelerating adaptation of circadian rhythms to the imposed schedule.[67,68] A widely self-prescribed sleep aid, melatonin is an antioxidant neurohormone produced by the pineal gland in mammals but also found in the plant kingdom.[69] In fact, melatonin is derived from grains and beans for commercial purposes, which technically makes it a phytochemical supplement. Other examples of phytochemical supplements now on the market include quercetin from citrus fruits and curcumin from the East Indian herb turmeric.

There are 3 commonly used forms of herbal preparation: (1) herbal tea, the traditional herbal preparation of Europe and most Asian countries; (2) tinctures, liquid alcoholic extracts taken in the form of drops; and (3) capsules, which contain dried, powdered, or freeze-dried herb. Some herbal agents are now appearing in the form of chewable tablets, lozenges, lollipops, and creams and as a complement to vitamin-mineral supplements and food-concentrate preparations. Also growing in popularity is the essential oil or volatile oil preparation, an extract of a fragrant plant species that contains fragrance-generating compounds, such as terpenoids.

A more refined addition to the herbal preparations list is the standardized extract. Standardization is an attempt to ensure comparable and replicable doses of active compounds in each dose of an herbal preparation. This concept in phytotherapy found its first fruitful application in clinical trials, which require uniform interventions, that is, drug or supplement compositions of high reliability. Since 1980, more than 300 clinical studies have been carried out in Germany with standardized botanicals, including echinacea, garlic, gingko, kava, milk thistle, mistletoe, St. John's wort, valerian, and many others.[70] Representative samples of the same plant species can have varying compositions, including variations in the chemical compounds responsible for target biological activities. The variation in composition may be due to growing the species in different soils, to differing climatic conditions from one year to the next, to diurnal variations in phytochemical content, or to genetic variability within a single herb species. Standardization of the extracts entails a procedure of extraction and concentration of varying batches of plant material to produce an herbal product with a consistent level of the active compound (or compounds). In some herbal species, the identity of the active compound (or compounds) is unknown; in these cases, a compound unique to the species serves as a "marker" compound.

The use of standardized extracts also eliminates herbs that contain suboptimal amounts of the active compounds and moreover lowers the risk of contamination with toxic herbs due to mistaken identity. Herbal companies that use standardized extracts may be less likely to adulterate their preparations with prescription drugs or other substances, as seen, for example, in many herbal products imported from China[71] (none of the herbal sedatives reviewed in this article are Chinese herbs).

Review of the Literature on Herbal Sedatives

Evidence of therapeutic efficacy and safety concerns (adverse effects and toxicities) is summarized for this article with current data obtained in MEDLINE literature searches for each substance. The MEDLINE searches focused on controlled trials and case studies for 1990 through March 2003, under the search terms *insomnia, sleep disorders, hypnotics, valerian, kava, lavender, chamomile, hops, lemon balm,* and *passionflower.* Outcome data concerning the safety and efficacy of the herbal sedatives were extracted from all available clinical trials and abstracts. Background information regarding insomnia and herbal use was extracted from the most current literature, including review articles and textbooks.

Valerian (Valeriana officinalis L. [Valerianaceae])

Valerian is a popular European herb used since the 17th century for its mild sedative and tranquilizing properties. The genus *Valeriana* comprises about 150 species, but only *Valeriana officinalis* has emerged as an official herb of choice. Formerly listed in the United States pharmacopoeia, valerian is native to Europe and Asia and now grows in most temperate parts of the world. In most European countries, valerian still retains its official pharmacopoeial status and is a common ingredient of herbal preparations used to enhance sleep. Recent research has aimed at establishing the biochemical and pharmacological basis of the activity that has been demonstrated in a number of clinical and preclinical (in vivo and in vitro) studies.

Key constituents and mechanisms of action. Sedative properties of valerian are attributed to constituents of the essential oil, namely, monoterpenes and sesquiterpenes, which can inhibit the catabolism of gamma-aminobutyric acid (GABA), leading to sedation.[72] The sesquiterpene compound, valerenic acid, has been shown to inhibit enzyme-induced breakdown of GABA in the rodent brain.[73] Other studies found that valerian extracts had direct effects on GABA receptors but also interacted at other presynaptic components of GABAergic neurons.[74,75] High concentrations of the amino acids, GABA and glutamate, in aqueous extracts of the roots are postulated to account for much of valerian's sedative impact.[76]

Research in Germany revealed that components of valerian extracts bind to benzodiazepine receptors in vitro.[77] A lignan, hydroxypinoresinol, has been reported to have this activity.[72] A clinical example demonstrates valerian's benzodiazepine-like activity: a patient who had been taking 5 to 40 times the recommended daily herb dose for years was hospitalized and received no valerian. He displayed symptoms resembling benzodiazepine withdrawal and was then given benzodiazepines in a tapered dose, which resolved the symptoms.[72] The symptoms might also represent a specific valerian withdrawal syndrome.

A valerian extract and a hops-valerian extract exhibited partial agonist activity in an adenosine A(1) receptor assay.[78] The lignan compound from valerian, 4′-O-β-D-glucosyl-9-O-(6″-deoxysaccharosyl) olivil, was noted to be a partial agonist to adenosine receptors showing A(1) affinity, with activity at the submicromolar level. Adenosine is important in regulating sleep onset, and this olivil derivative might represent another bioactive compound in the plant species.[79] Another group of possible active compounds is the valepotriates, iridoid monoterpene-type

compounds, which are also suspected of having mutagenic, as well as cytotoxic, activity.[72]

Many formulations of valerian are currently marketed, and the herb is standardized according to the content of volatile oil and valerenic acid. There appears to be considerable variation in valerian's composition and content. This variation, along with the instability of some of the herb's constituents, poses serious problems for standardization.

Clinical studies indicating valerian efficacy. Several human trials of valerian's sedative effects have been performed, most with patients reporting sleep disorders. An early study by Vorbach et al recruited 121 patients experiencing sleep difficulties for at least 4 weeks.[80] Individuals with depression or currently using sleep aids were excluded. In this double-blind, randomized trial, patients were administered either placebo or 600 mg valerian ethanol extract daily for 4 weeks. Sleep quality was rated using a physician-rated sleep scale, von Zerrsen Mood Scale, Gortelmayer Sleep Questionnaire, and Clinical Global Impressions Scale. After 2 weeks, there were no differences, but by the end of 4 weeks, the valerian group differed significantly from the placebo group in all scales, indicating a beneficial effect on sleep quality.

Decreases in sleep latency and improved sleep quality were reported in 1982 by Leathwood and colleagues.[81,82] Their study involved 166 subjects with various sleep difficulties receiving 400 mg of an aqueous extract of valerian alone compared to either placebo or valerian as part of a proprietary mixture of herbs. Each participant received 3 of each capsule, taken in random order on nonconsecutive nights. Attrition was high, with only 128 patients completing the study; however, most of the dropouts were of an "administrative nature," such as moving, schedule conflicts, and so forth. Only 1 withdrew because of side effects. Both valerian preparations resulted in a significant decrease in subjectively evaluated sleep latency scores and improved sleep quality. The latter was most pronounced among smokers, individuals who considered themselves poor sleepers, and those who thought they normally had long sleep latencies. While valerian alone did not cause any somnolence the next morning, the proprietary preparation did result in a significant increase in reports of feeling more sleepy than usual the next morning.

As noted earlier, the sesquiterpenes in valerian root are of special pharmacological interest because of their sedative effects. Lindahl and Lindwall conducted a double-blind test on a special preparation (Valerina Natt) containing primarily sesquiterpenes.[83] The preparation showed significant reversing effect

on poor sleep ($P<.001$) when compared with placebo. Eighty-nine percent reported improved sleep from the preparation. There were no adverse side effects from taking the preparation.

One of the concerns that consumers have about taking pharmaceutical-grade sedatives is a hangover or residual fatigue and grogginess the next morning. To address this concern, Gerhard et al studied residual sedative effects of valerian, a valerian-hops combination, flunitrazepan (a common benzodiazepine), and placebo.[84] Each of the 4 groups of 20 healthy volunteers (n = 80) received single doses of 1 of the 4 materials on the morning of the study. On the afternoon of the study, and again on the following morning, subjects were tested for vigilance and reaction time. The subjective perception of sleep quality was improved in all 3 medication groups compared to placebo. However, whereas the residual effects of the benzodiazepine at both times were significant, there were no significant residual effects of the valerian-containing preparations.

A sleep laboratory study by Herrera-Arellano et al compared the effect of *Valerian officinalis* extract and that of *Valeriana edulis* ssp. *procera* (often called "valeriana mexicana" or Mexican valerian in commerce).[85] Polysomnography was used to measure sleep architecture in 20 patients given the 2 herbs in a blinded fashion. Both treatments reduced nighttime awakenings and increased REM sleep; they also increased delta sleep relative to stage 1, 2, and non-REM sleep, as well as reduced sleepiness in the morning.

A critical study of the effects of valerian on sleep structure was performed by Donath et al using polysomnography after a single valerian dose and after 14 days of administration.[86] The study was performed as a double-blind crossover trial on 16 patients with psychophysiological insomnia. The major outcome variable was sleep efficiency. The single dose of valerian had no effect on sleep structure. After 14 days dosing, latency of slow-wave sleep (associated with deeper sleep stages), percentage of time in bed in slow-wave sleep, and shorter subjective sleep latency were all significantly different in valerian and placebo, although the increase in REM percentage did not differ from placebo.

Patients recently withdrawn from benzodiazepine management of insomnia were given valerian in a blinded trial that measured sleep using an electroencephalogram (EEG) on the 1st and 15th day after benzodiazepine withdrawal.[87] Improvement was seen with the valerian group on day 15. However, this might be due in part to recovery from benzodiazepine withdrawal symptoms. Valerian also decreased wake time after sleep onset, although it did not improve sleep latency.

In a randomized, double-blind, placebo-controlled trial, Schmitz et al treated patients with temporary sleep disorders with a benzodiazepine or a hops-valerian preparation for 2 weeks.[88] Measurements of quality of life and sleep quality were equal in the 2 groups. Only the benzodiazepine-treated group had withdrawal symptoms at the end of the treatment. In addition, the patients' overall state of health improved during the treatment phase while showing a deterioration after cessation of both preparations.

A small trial in a mental health clinic in a Hispanic neighborhood used a national brand of valerian in 23 volunteers receiving mental health services who complained of insufficient sleep.[89] Subjects were instructed to take 1 capsule nightly for a week; after the first week, up to 3 capsules nightly could be taken. Sleep was evaluated on a 5-point scale at the end of weeks 1 and 2, and 20 subjects reported improved sleep after 1 week. After week 2, 16 patients still reported improved sleep, rating the helpfulness of the valerian tablets even more highly than they had the first week.

Dorn reported on a double-blind, randomized trial of valerian extract LI 156 versus oxazepam in 75 patients with nonorganic, nonpsychiatric insomnia,[90] in which 600 mg valerian extract or 10 mg oxazepam were given daily for a month. Results of the German Sleep Questionnaire B indicated that sleep quality improved for both groups and that no differences in degree of improvement between groups were seen. Similar small numbers of patients withdrew from each group due to side effects.

Ziegler et al report a double-blind, randomized trial comparing a valerian extract to oxazepam in 202 patients diagnosed with nonorganic insomnia of at least 3.5 months duration.[91] Valerian (600 mg of the LI 156 extract) and 10 mg oxazepam were given daily for 6 weeks. Valerian and oxazepam were found to have similar efficacy as measured by the German Sleep Questionnaire B, including the Sleep Quality, Refreshment After Sleep, Psychic Stability, Psychosomatic Symptoms, Dream Recall, and Sleep Duration subscales. The Clinical Global Impressions and Global Assessment of Efficacy scales, filled in by the investigators and the patients, also indicated similar efficacy. Mild to moderate adverse effects were observed in 28% of patients on valerian and 36% of patients on oxazepam; 83% of valerian patients and 73% of oxazepam patients rated their treatments as very good.

A pilot study explored the use of valerian as a sleep aid in children with intellectual deficits. Blinded administration of valerian and placebo to 5 such

children resulted in significantly better sleep latency, time awake at night, total sleep time, and sleep quality, based on sleep diaries.[92]

Kava and valerian were compared in the treatment of subjects reporting stress-induced insomnia by Wheatley.[93] Kava and valerian were given separately and in combination to a group of 24 subjects, with treatments separated by 2-week washout periods. Patient reports of stress severity, hours to fall asleep, total hours slept, and waking mood were used to assess effects of the herbs. The combined treatment was significantly better than the 2 single treatments in improvement of insomnia.

Studies reporting mixed results or no effect of valerian on nervous system/sleep parameters. In a pilot study, Balderer and Borbely followed 2 groups, one at home, the other in the sleep laboratory. In the first group, 10 normal subjects took a single dose of valerian (either 450 or 900 mg of freeze-dried aqueous extract) at home.[94] Eight other subjects took either 900 mg valerian or placebo in a sleep laboratory setting for 3 nights. Subjects in the home study reported decreased sleep latency and wake time after sleep onset, and the data suggested a dose-dependent effect. In contrast, subjects in the laboratory setting showed no changes in sleep latency, number of awakenings, and EEG spectra. In the sleep laboratory, the effects of 900 mg of valerian were not significantly different from those of placebo. The investigators speculated that the stressful sleep environment of the laboratory may have obscured the mild hypnotic action of valerian.

In another pilot study, Schulz et al studied 14 elderly women who were described as having poor sleep (defined as sleep latency longer than 30 minutes, more than 3 awakenings nightly, or total sleep less than 5 hours). Eight patients taking valerian (405 mg dried aqueous extract, daily for 1 week) were compared to 6 matched controls.[95] Based on polysomnography testing, the valerian group showed an increase in slow-wave sleep and a decrease in sleep stage 1. There was no effect of valerian on sleep latency or waking after sleep onset.

A randomized, controlled, double-blind trial was performed by Kuhlmann et al on 102 male and female volunteers to determine whether reaction time, alertness, and concentration might be altered following treatment with a valerian root extract.[96] The researchers first measured the effect the morning after a single 600-mg dose of valerian versus flunitrazepam (1 mg) and placebo (group A, n = 99). They then measured it after 2 weeks of evening administration of valerian versus placebo (group B, n = 91). The primary criterion was the median of reaction time (MRT), while secondary criteria included an alertness test, 2-handed coordination, sleep quality, and safety. The single dose of valerian did not impair the reaction abilities, MRT, concentration, or coordination. After 2 weeks of treatment, valerian and placebo recipients showed no differences for any of the criteria. Thus, neither single nor repeated evening administrations of 600 mg of valerian had a negative impact on alertness, concentration, or reaction time the morning after.

An assessment of cognitive and psychomotor effects of valerian was conducted by Hallam et al.[97] Single doses of valerian at 2 dosage levels were compared with triazolam and placebo in 9 healthy subjects. Effects on cognitive and psychomotor tests were assessed after 2, 4, and 8 hours. Valerian did not differ from placebo on any of the tests, whereas performance on the digital symbol substitution test, a standardized sedation test, and the symbol search test, a test of psychomotor speed, was significantly lower after triazolam. Specific effects on sleep were not measured in this study.

Glass et al studied effects of temazepam, diphenydramine, and valerian in 14 elderly subjects (65-89 years) since these products are frequently recommended for insomnia among the elderly.[98] They measured sedation, mood, and psychomotor performance following single doses of the 3 medications and placebo. While both temazepam and diphenhydramine resulted in sedation and temazepam resulted in deficits in psychomotor performance, valerian did not differ from placebo in any measure. The authors point out that studies of single doses of valerian frequently result in findings of no difference from placebo. In addition, studies of healthy patients, as opposed to those of patients reporting sleep difficulties, frequently report nonsignificant effects for valerian. The authors suggest that valerian may be more effective in patients with insomnia and that repeated dosing might be necessary for effectiveness. They suggest that further well-designed trials in patients with insomnia, using repeated doses of valerian, would be appropriate.

Related to the question of whether valerian is useful in sleep problems is its effect on anxiety since anxiety may interfere with sleep. Among cancer patients, insomnia, fatigue, and anxiety are highly intercorrelated,[99] so control of anxiety may aid in improving sleep. A small trial of valepotriates or diazepam in subjects with generalized anxiety disorder reported that both diazepam and valepotriates improved scores on the psychic factor of the HAM-A, while placebo did not, suggesting that valpotriates may reduce anxiety, although more studies are needed in this area.[100]

Adverse reactions and safety concerns. Valerian appears to have a wide margin of safety. In an unsuccessful suicide attempt, an 18-year-old student ingested an overdose totaling approximately 20 g of valerian root (10 times the upper limit for a normal dosage).[101] Thirty minutes after ingestion, the student experienced abdominal cramping, fatigue, chest tightness, hand tremors, and light-headedness. Vital signs were normal, and all symptoms were resolved within 24 hours following treatment with activated charcoal.

Valerian use near conception and during pregnancy and lactation is not recommended due to potential mutagenic effects of valepotriates, a group of active compounds in valerian.[80] However, because the mutagenic metabolites of valepotriates are lacking in typically used aqueous extracts and are rapidly detoxified in the liver, they probably do not pose a significant risk to humans.[102]

In rodent studies, the median lethal dose of valerian extract was 3.3 g/kg intraperitoneally, while repeated dosing with 300 and 600 mg/kg for 30 days resulted in no changes in rat body or organ weights, hematology, or blood chemistry.[103] In humans, there are no reports of severe adverse effects in the literature for dosages that would be considered normal (500 mg to 2 g taken before bedtime), although clinical trials report some minor adverse effects. A safety range of up to 12 g has been proposed.[104]

European studies suggest the absence of adverse interactions with alcohol or other drugs and that residual morning sleepiness is uncommon.[105] Valerian has been shown to prolong thiopental- and pentobarbital-induced sleep in animals, so it may be reasonable to avoid the herb when using barbiturates.[106,107] A double-blind study of alcohol combined with a mixture of valepotriates from valerian failed to detect predicted impairment of concentration.[108]

No studies have been found indicating effects of valerian on the cytochrome enzymes involved in drug metabolism. There is thus no evidence of potential effects on activation or clearance of chemotherapy drugs such as has been observed with St. John's wort. The major drug interactions of concern with valerian are those involving potentiation of effects of sedatives, hypnotics or tranquilizers, and anesthetics. Cancer patients who are anticipating surgery should be advised to cease valerian use well before the time of surgery, especially those who might be taking very large doses and thus subject to the possible withdrawal symptoms mentioned above.[109]

Kava (Piper methysticum G. Forst. [Piperaceae])

Kava (also called kava-kava), a psychoactive member of the black pepper family, has long been used both recreationally and ritualistically as a ceremonial tranquilizing beverage by cultures of the Pacific Island region.[110] Traditionally, the beverage is prepared by grinding or pounding the kava root, then mixing it with water or coconut milk to be drunk before the evening meal. As with valerian, kava has frequently been recommended by complementary medical practitioners for anxiety and sleep disorders. Various preparations of kava have become popular in Europe and the United States. In Germany, the herb is approved for "states of nervous anxiety, tension, and agitation" in doses of 60 to 120 mg of kavalactones for up to 3 months.[111] Kavain, a major chemical constituent of kava, has been prescribed for anxiety-related disorders in Europe in a pharmaceutical-type preparation. However, due to recent reports of major hepatotoxicity of kava, it has been withdrawn from sale in many markets, although some use may remain.

Key constituents and mechanisms of action. The constituents responsible for kava's sedative properties are well delineated and include 4 substituted α-pyrones, the kavalactones (also called kavapyrones): kavain, methysticin, yangonin, and dihydrokawain.[112] Kavalactones are similar in structure to myristicin, which is found in nutmeg.[113] The kavalactones account for kava's ability to act as a central nervous system depressant, including its potent analgesic and anesthetic effects via nonopiate pathways.[114,115] A dose of 120 mg/kg of either dihydrokavain or methysticin was equivalent to 2.5 mg/kg morphine.[116]

The kavalactones were shown to influence GABA binding in certain areas of the rodent brain.[117] However, in both in vivo and in vitro studies, only weak GABA-binding activity was observed.[118] While kavalactones did not efficiently block uptake of serotonin in vivo, inhibition of noradrenaline uptake was shown for 3 lactones, suggesting an additional mechanism of action.[119] Kava was also found to inhibit experimentally induced convulsions in animal models, apparently by binding to sodium ion channel receptor sites, a common target of antiepileptic drugs.[120,121] Kavalactones were found to have neuronal transmission effects similar to antiepileptic drugs that are also mood stabilizers such as valproate or lamotrigine.[122] In assays involving voltage-gated ion channels, which contribute to the clinical efficacy of these drugs, kavalactones had weak sodium and calcium antagonist properties and positively modulated potassium efflux. They also had glutamatergic and GABAergic transmission effects. The profiles of activity were especially similar to lamotrigine.

Kavain is an effective anesthetic, comparable to cocaine in strength and duration of action.[114] Subcutaneous injections of kavain can sustain anesthesia for

several hours to several days, though very high doses can induce temporary paralysis.[123] Mild numbness of the mouth is frequently experienced by users of kava teas.

Clinical studies. Numerous studies have investigated the use of kava in the treatment of anxiety disorders and, more recently, of sleep disorders. Pittler and Ernst conducted a systematic review and meta-analysis of the efficacy of kava extract for treatment of anxiety.[124] Based on their wide search of computerized databases (which included MEDLINE, EMBASE, BIOSIS, AMED, CISCOM, and the Cochrane Library), they located 11 randomized, double-blind, placebo-controlled trials involving 645 patients. A meta-analysis performed on 6 of the trials that used the HAM-A scale indicated that anxiety reduction with kava was significantly better than with placebo ($P = .01$). Adverse events reported in these studies were transient, infrequent, and mild. They concluded that kava appeared to be an efficacious treatment for anxiety on a short-term basis, although more information is required about its long-term use due to the evidence of toxicity found in other studies.

A purified kava preparation (WS 1490, Laitan), standardized to 70% kavalactones (50-70 mg of the kavalactones per 100 mg extract), was effective in 2 randomized, placebo-controlled clinical trials, with bioactivity comparable to benzodiazepines. Each trial used approximately 100 mg of the 70% standardized extract 3 times daily. In the first trial, Lehmann et al randomly assigned 58 patients with various anxiety and neurotic disorders to receive either placebo or standardized kava extract 3 times daily for 4 weeks.[125] By the end of the first week, the kava group showed a significant reduction in anxiety (assessed by HAM-A) compared to the placebo group. Also, differences between the 2 groups continued to increase throughout the course of the study. No untoward side effects were seen in these patients.

In the second randomized trial, Volz and Kieser randomly assigned 101 outpatients suffering from anxiety of nonpsychotic origin (generalized anxiety disorder, adjustment disorder with anxiety, agoraphobia, or specific phobia) to receive either placebo or the standardized kava extract (210 mg/d in divided doses) for 6 months.[126] As in the Lehmann et al study, the kava group showed significant reductions in anxiety based on HAM-A scores, although these benefits were not seen until the eighth week. The anxiolytic effects continued to increase throughout the remaining 16 weeks of the study. Changes in secondary outcome variables included reductions in Hamilton subscale scores for somatic and psychic anxiety and improvements in the Adjective Mood Scale, Self-

Report Symptom Inventory, and Clinical Global Impression Scale. Notably, 6-month treatment with kava did not lead to tolerance, in marked contrast with the prolonged use of benzodiazepines and tricyclics. In addition, no changes were observed in vital signs, clinical blood chemistry values, or hematological parameters.

Four controlled, double-blind trials on kava extracts or isolated kava compounds have been published in the German literature. Two of these trials involved kava root extract. The first trial involved 58 patients with anxiety who took 210 mg/d for 1 month.[127] In the second trial (which included a follow-up), 40 women were treated for the relief of psychoautonomic symptoms (anxiety, restlessness, and sleep disturbances) associated with menopause; they took 30 to 60 mg/d for a minimum of 56 days.[128,129] Both trials found a significantly greater reduction in HAM-A scores in the kava versus placebo groups. In a controlled treatment trial of 164 patients taking 210 mg of kavalactones (not whole kava), HAM-A scores did not differ significantly from either of the 2 conventional anxiolytic drugs, oxazepam or bromazepam.[130] Similarly, in a trial comparing oxazepam to the kava-derived compound kavain, there was no difference in anxiety reduction (based on the Anxiety Status Inventory and the Zung Self-Rating Anxiety Scale) among 38 outpatients with anxiety associated with neurotic or psychosomatic disturbances.[131]

It is likely that these consistent anxiolytic effects could translate into benefits for insomnia sufferers as well, to the extent that insomnia is being caused by anxiety, although kava's specific utility as a sleep aid has been less extensively studied. Only 2 such studies could be found, one favorable, the other null. In a study by Emser and Bartylla, kava extract resulted in improved sleep quality and specifically increased density of sleep spindles (a characteristic EEG pattern indicating deeper sleep), showing activity comparable to that of conventional tranquilizers.[132] The kava group also showed decreased sleep latency, duration of wake phase, and sleep stage 1; however, REM phase remain unchanged. The second study, by Klimke et al, failed to demonstrate any sleep-inducing effects in healthy subjects who took kavain (again, not whole kava).[133] The investigators proposed that kavain may have a greater impact on sleep quality in subjects with anxiety-related sleep disturbances than in healthy, normal populations.

Adverse reactions and safety concerns. Possible adverse effects of kava are a concern because of the herb's widespread use. The recommended dosage for kava is 60 to 120 mg, based on German Commission E guidelines, an expert advisory panel equivalent to the US

FDA. In short-term clinical studies, kava doses up to 600 mg did not interfere with cognitive performance; in fact, psychometric tests showed small increases in cognitive function, including increased vigilance and enhanced memory.[134-136] This research is supported by evidence that EEG profiles of subjects treated with kava extract (up to 600 mg) show a typical anxiolytic pattern without the sedative-hypnotic effects associated with benzodiazepines.[137]

An important safety concern with kava is that it might have effects that are additive with those of benzodiazepine drugs since both agents are thought to bind to the GABA-A receptor protein.[138] However, kava extract (3×100 mg/d) did not appear to potentiate the effects of either benzodiazepines[139] or alcohol[140] in studies by Herberg. In addition, the same concentration of kava extract did not affect driving ability or work safety.[141] There is one anecdotal report of a possible interaction between kava and the benzodiazepine drug alprazolam. This involved a 54-year-old man who suffered an acute change in mental status and was hospitalized 3 days after starting to take kava.[142] However, the patient was also taking terozosin and cimetidine, which can decrease catabolism of a number of drugs; thus, the adverse reaction may have been due to a multiple drug interaction.[103] The adverse reaction also may have been due solely to the benzodiazepine.[143]

Since chronic insomnia and anxiety disorders require prolonged treatment, long-term studies are necessary for evaluating the safety of regular kava use. In several clinical studies, patients taking high doses (3×100 mg/d) of a purified kava extract (standardized to 70% kavalactones) reported no adverse reactions when they took the extract up to 8 weeks.[129,144,145] The same standardized kava extract caused no adverse reactions when taken over a period of 25 weeks.[133,146] High doses of kava extracts have been studied in rats and dogs, resulting in only mild histopathological changes in the liver and kidneys.[103] Laboratory studies did not find mutagenic, teratogenic, or genotoxic effects in standard assays.[147]

Relatively heavy use of kava can lead to an ichthyosiform (scaly), yellowish skin eruption called kava dermopathy, which is sometimes accompanied by ocular photosensitivity. Kava dermatitis resembles pellagra but appears to be unrelated to niacin deficiency.[148] The yellow color is attributed to a kava-derived pigment deposited in skin cells that degrades over time after cessation of kava intake. This severe rash is typically seen only in Pacific Island and Australian aborigines with prolonged, heavy use of kava in dosages up to 100 times those recommended clinically.[149] Chronic heavy users taking 300 to 400 g per week suffer from malnutrition, shortness of breath, and loss of body fat; these kava abusers also show a variety of metabolic abnormalities such as increased liver enzymes, decreased albumin and plasma protein, and increased cholesterol level.[150] There are a few isolated reports of cutaneous allergic reactions following kava ingestion.[151]

The most important concerns with kava toxicity, however, are the recent reports of hepatotoxicity in kava users. More than 60 reports of liver toxicity in users of kava preparations have surfaced since 1999. Some cases have been sufficiently severe that liver transplants have been required, and 3 deaths have resulted from hepatotoxicity associated with kava.[152] The 19 cases reported from Germany were recently analyzed by staff of the City Hospital Hanau, Frankfurt/Main, Germany.[153] Complicating the assessment of kava hepatotoxicity was the use by most cases of other potentially hepatotoxic substances. Thus, in only 1 of the 19 cases could a "very probable" causal association of kava and liver toxicity be established; in a second case, a "possible" association was determined. In 5 cases, no causal relationship could be established at all. For the remaining 12 cases, insufficient data were present to determine causal association.

A recent report of patients referred to a liver transplant service with fulminant hepatic failure found that 10 of 20 patients were using dietary supplements that had potential for hepatotoxicity (ephedra, chaparral, kava, Chinese herbs, and a phenylpropanolamine-containing supplement).[154] Kava was used by 3 of the patients; in 2 of these, it was used in combination with other possibly hepatotoxic herbs. Of the 10 supplement-using patients, 8 patients did not have any other clear risk factors for liver failure, whereas patients who were not using supplements but experienced liver failure were found to be taking potentially hepatoxic drugs such as acetaminophen and disulfuram. Some other cases of liver failure in patients using kava are also without any other clear risk factors. A 14-year-old girl in the United States with a 4-month history of using a kava-containing product experienced liver failure and underwent a successful liver transplant. No other risk factors were present in this individual.[155]

Mechanisms of kava hepatotoxicity are not clear. Two electrophilic metabolites of kava, 11,12-dihydroxy-7,8-dihydrokavain-*o*-quinone and 11,12-dihydroxykavain-*o*-quinone, were detected after kava extract was incubated with liver microsomes.[156] The mercapturic acid forms of these quinone compounds were not detected in the urine of a human volunteer who ingested kava, while glucuronic acid and sulfate

conjugates were found, indicating that the quinones are probably metabolized to nontoxic forms under normal circumstances. The authors of this study commented, however, that if normal drug-metabolizing enzymes were impaired because of drug interaction, genetic deficiency of CYP450 enzymes, or saturation of conjugation pathways, conjugation of these forms might not take place and hepatotoxicity could result. It has been suggested that genetic deficiency of CYP450 2D6 might be associated with susceptibility to kava toxicity in some of the observed cases.[157] It has also been pointed out that there are no reports of liver failure among users of traditional kava preparations in the South Pacific and that genetic deficiencies of this enzyme are not known from that region, while they occur in about 10% of the European population.[158] Acute hepatitis in kava users in the South Pacific area has been reported, however, with 2 cases of women presenting with icterus, elevated transaminases, and hyperbilirubinemia, which resolved when the patients ceased taking kava.[159] No CYP450 2D6 deficiency was observed in the patients, and there was a suggestion of allergic reaction. Elevated gamma glutamyl transferase was common in 27 kava users reported in the same study.

Drug interactions based on the cytochrome P450 enzymes appear to be a possibility with kava, based on in vitro assays. A kavalactone fraction was found to inhibit cytochrome P450 3A4, a drug-metabolizing enzyme that is involved in the clearance and activation of chemotherapy drugs.[160,161] Kava extract was reported to inhibit CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A9/11; specific kavalactones were also found to inhibit specific CYP450 enzymes.[162]

Based on the reports of kava-associated hepatotoxicity, the US FDA issued a consumer alert on kava in 2002, stating that "safety is a concern for users of kava. People, especially those with liver disease or liver problems, or persons who are taking drugs that can affect the liver, should talk with their health care practitioner before using kava."[163] Cancer patients who are undergoing or have recently undergone treatment, or who are taking medications of any sort, should avoid kava. This is especially true during chemotherapy because of the potential for drug interactions. While other anxiolytic drugs, such as benzodiazepines, also may rarely cause idiosyncratic hepatotoxicity,[164] the incidence of kava toxicity, while low, is not accurately known and may be higher than that of conventional benzodiazepines. If a cancer patient feels he or she has no other feasible alternative than kava, a tea, rather than a concentrated extract, should be used because no cases of actual liver failure are known to be associated with the traditional aqueous extract.

German Chamomile (Matricaria recutita L. [Asteraceae])

Tea made with the dried leaves of German chamomile, a member of the daisy plant family, has been used as a bedtime beverage for centuries. Until recently, however, the basis for the folklore had not been scientifically substantiated. Chamomile tea is still very popular in the United States and Europe. Chamomile essential oil has been thought to have a relaxing effect.

Key constituents and mechanisms of action. The very mild sedative effects of chamomile have been attributed to the flavonoid apigenin, which binds to benzodiazepine receptors.[165] Duke notes that chamomile has anxiolytic activity in animal models, although the necessary dose is approximately 10 times higher than that of diazepam (J. Duke, personal communication, November 1999). Rodent studies have demonstrated that chamomile has shown anticonvulsant activity[166] as well as central nervous system depressant activity.[167] Chamomile has immune-modulating effects in vitro[168] and improved wound healing in a double-blind trial.[169]

Clinical studies. Clinical trials on the sedative effects of chamomile are lacking. In a pilot study of hospitalized heart patients who were given a strong dose of chamomile tea, a weak hypertensive effect was observed.[170] Ten of the 12 patients immediately entered into a deep sleep lasting an average of 90 minutes. Controlled trials are needed to test this study's observations in people with insomnia and in noninsomnia populations. Inhalation of chamomile was associated with lower α-1 activity on EEG, as was lavender and eugenol inhalation, although sandalwood oil inhalation was not.[171]

Adverse reactions and safety concerns. There are several reports of skin reactivity to chamomile. This activity manifests primarily as contact dermatitis or positive results on patch tests, possibly due to the sesquiterpene lactone component, common in the daisy plant family (Compositae or Asteraceae).[172,173] Allergic conjunctivitis can result from eye washing with chamomile tea, a folk remedy used by the general public.[174] Allergic reactions on ingestion of chamomile do not appear to be a significant problem. However, individuals with hayfever or hypersensitivity to pollens from other members of Asteraceae may cross-react to chamomile tea ingested internally.[175,176] Activity of CYP450 1A2 in Wistar rats was reduced to 39% of control level when a 2% chamomile tea solution replaced drinking water[177]; the clinical relevance of this observation in humans is not known. Chamomile also showed a moderate inhibitory effect on CYP450 3A4 in vitro, with unclear clinical relevance.[178] The formation of sister

chromatid exchanges by daunorubicin was decreased in rats pretreated with chamomile essential oil (doses of 5 to 500 mg/kg) as compared to those given corn oil.[179] Because sister chromatid exchanges may be correlated with antitumor activity of this anthracycline, this finding is of potential concern for patients undergoing anthracycline therapy. Internal intake of the essential oil (not recommended in any case), or of large doses of chamomile extracts, may be inappropriate in this circumstance.

Lavender (Lavandula angustifolia Mill. [Lamiaceae])

Lavender is used in aromatherapy as a holistic relaxant and, when inhaled, has been reported to have sedative effects in both animals and humans.[180] In some European hospitals, lavender oil is administered either in a warm bath or sprinkled onto bedclothes to help patients sleep at night. Another tradition is the placement of linen bags filled with lavender flowers under one's sleeping pillow. There is suggestive evidence that lavender oil may help relieve or prevent insomnia, according to the German Commission E monographs. Under indications for internal use, the German Commission E includes "states of unrest and difficulty falling asleep."[105] Lavender oil is administered therapeutically by inhalation, an aspect of alternative medicine known as aromatherapy.

Key constituents and mechanisms of action. Pharmacological studies have reported the constituents of lavender oil, which contains the active compounds. The main chemical constituents of lavender oil are camphor, eucalyptol, linalool, linalyl acetate, and ocimene. Lavender may contain up to 12% tannins, water-soluble polyphenols that are present in many plant foods.[181]

Laboratory studies indicate that the herb's essential oil has a depressive effect on the central nervous system. In animal studies, lavender showed strong sedative, anxiolytic, anticonvulsive, motor inhibitory, and spasmolytic effects.[182-184] In mice, caffeine-induced hyperstimulation of locomotor activity was reduced to near-normal levels by lavender inhalation but not by injection.[185]

Clinical studies. In a case series report (n = 4), lavender oil inhalation provided relief of insomnia in British psychogeriatric patients.[186] Each patient showed increased sleep time and a reduction in restlessness during sleep; sleep time decreased again after cessation of aromatherapy, then increased on restarting lavender treatment. A multiple crossover study of 23 female insomnia sufferers showed significant central nervous system depressant activity (via EEG

recordings) after inhalation of lavender oil.[187] After 3 minutes of lavender inhalation (n = 40), subjects were more relaxed and showed increased β power, suggesting drowsiness. They were also less depressed (based on the Profile of Mood Status) and performed math computations faster and more accurately compared to controls.[188] Agitated behavior of patients with severe dementia on a psychogeriatric ward was reportedly reduced on treatment days in which 2% lavender oil aromatherapy mist was diffused in the ward for 2 hours, compared to days in which water was diffused,[189] although the effect was modest.

Anxiety and depression are sleep-related variables for which the efficacy of lavender has been investigated. Patients undergoing radiation therapy were given lavender, unscented carrier oil, or other essential oils for inhalation.[190] Anxiety scores on the Hospital Anxiety and Depression Scale and the Somatic and Psychological Health Report indicated that the carrier oil group experienced less anxiety than the essential oil groups did. Lavender may have positive effects on depression, sometimes related to sleep. A study of lavender tincture and imipramine in 45 adults with mild to moderate depression revealed that a lavender-imipramine combination resulted in better control of depression than did imipramine alone.[191] The comparison of lavender versus placebo was not attempted in this study. Aromatherapy with lavender did not differ from a control treatment with water or a no-treatment control in verbal analog assessment of blood pressure, pulse rate, pain, anxiety, depression, or sense of well-being.[192] Subjects were cancer hospice patients given the study treatments for 60 minutes on 3 different days.

Adverse reactions and safety concerns. No toxicity has been reported for lavender; however, the herb does potentiate the sleep-inducing activity of several agents, including alcohol, chloral hydrate, and hexobarbital in laboratory studies.[193]

Other Herbal Agents With Potential Sedative Effects

Relatively few clinical trials have explored the sleep-enhancing properties of other herbal agents with putative potential to relieve or prevent insomnia and improve overall sleep quality. These herbs include hops, lemon balm, passionflower, and St. John's wort. The last of these boasts a substantial body of clinical trial data, but most of it deals with depression, not insomnia. Many active compounds in these herbs have been identified and studied, and animal research has indicated potential sedative effects.[103,111]

There are anecdotal and historical accounts of sleep-enhancing benefits from hops (*Humulus lupulus*

L. [Cannabaceae]) and lemon balm (*Melissa officinalis* L. [Lamiaceae]).[194] Both herbs are purported to have sedative and hypnotic effects, but clinical evidence from MEDLINE is scarce. In a double-blind crossover study of 27 subjects with sleep difficulties, participants were given valerian, hops, or lemon balm. Neither hops nor lemon balm resulted in improved sleep quality. However, 89% of subjects receiving valerian reported improved sleep quality.[195] Lemon balm was found to increase "calmness" in a randomized, double-blind, placebo-controlled trial using single doses of 600 to 1600 mg dried leaf.[196] This study used a leaf sample that had been assayed for human acetylcholinesterase inhibition and cholinergic receptor-binding properties. Another study by this group of investigators found that cognitive assessments of subjects given single doses of lemon balm indicated a lower degree of alertness in addition to calmer mood.[197] Dementia patients who showed clinically significant agitation participated in a randomized, placebo-controlled study in which lemon balm essential oil or sunflower oil was applied to their faces and arms twice daily by caregiving staff.[198] Significant reduction in agitation was noted for the lemon balm oil group.

Passionflower (*Passiflora incarnata* L. [Passifloraceae]), another purportedly mild sedative, is often combined with valerian in the herbal sleep aids found in health food stores. A double-blind trial examined the combined effects of passionflower as part of a preparation containing valerian and 4 other extracts (*Crataegus, Ballota, Cola*, and *Paullinia*) or placebo.[199] HAM-A scores were improved in subjects who took the herbal preparation compared with those who received a placebo. Given the sedative effects of valerian, however, it is impossible to say to what extent (if any) passionflower may have contributed any benefit. The effect of passionflower on anxiety was compared with that of oxazepam in 36 patients with generalized anxiety disorder in a double-blind, randomized, placebo-controlled study.[200] The anxiolytic effect of the passionflower extract did not differ from that of oxazepam in this study.

St. John's wort (*Hypericum perforatum* L. [Hypericaceae]) is a common herb that has gained explosive attention in recent years as an antidepressant, which in theory might provide relief for insomnia.[201] Only one clinical study has specifically measured the effects of St. John's wort on insomnia.[202] In an uncontrolled study of individuals with seasonal affective disorder (seasonal depression that peaks in midwinter), subjects received either St. John's wort alone or the herb plus light therapy. In both groups, there was significant reduction in insomnia and

anxiety, as well as an improvement in libido. In a comparative study of fluoxetine and St. John's wort, both treatments reduced sleep disorders, in addition to showing antidepressant effects.[203] The authors commented that the herbal medicine appeared to be particularly effective in depressed patients with symptoms of anxiety.

In a placebo-controlled crossover design, Sharpley et al found that St. John's wort significantly increased the latency to REM sleep (using polysomnography) without producing any other effect on sleep architecture, which is consistent with the herb's antidepressant effects.[204] However, the investigators did not determine whether the healthy subjects were suffering from insomnia, nor did they measure changes in sleep quality. It is biologically plausible that St. John's wort relieves depression because of its potent effect on GABA-A receptors (similar to kava and valerian).[205]

There are few reports of toxicity of the minor sedative herbs. Animal studies have indicated potentiation of barbiturate effects. Two studies of species related to passionflower found adverse effects, but neither study involved *Passiflora incarnata*. In one study of *Passiflora edulis*, which is not used in herbal medicine, there were hepatobiliary and pancreatic toxicities for both animals and humans.[206] The second study involved 5 anecdotal reports of individuals who took a product called Relaxir (*Passiflora incarnata*), resulting in altered consciousness (intoxication).[207] A further case of toxicity was reported in a 34-year-old woman taking a preparation of *Passiflora incarnata*, who presented with nausea, vomiting, drowsiness, prolonged QTc, and tachycardia.[208] As with all other herbal preparations, these herbs should not be taken during pregnancy and lactation. Flavonoids from hops were reported to inhibit CYP450 1A1 and 1A2, although not 2E1 or 3A4 in in vitro studies.[209] St. John's wort generally has a better toxicity profile than conventional antidepressant drugs[203]; its strong potential for drug interactions based on inhibition of CYP450 3A3/4 has been discussed elsewhere in the context of medical treatment of cancer.[175]

Discussion and Conclusion

Considerable research has been done in the area of herbal sedatives, particularly with valerian and kava (Table 2). In considering the epidemiology and pharmacology of these and the minor herbal sedatives, several summary points are evident. First, much work remains to be done to understand their long-range efficacy and safety, including herb-drug interactions and the effects of long-term usage. This may be especially relevant in elderly patients, who typically take multiple prescription drugs and may be at higher risk for in-

Table 2.   Herbal Agents With Purported Sedative Properties

Herbal Agent	Nature of the Evidence
Valerian	Multiple randomized, controlled clinical trials showing relief of insomnia with longer dosing, although not with single doses. Several uncontrolled clinical trials suggesting sleep-quality improvement.
Kava	Several randomized, controlled clinical trials showing relief of anxiety as well as insomnia. Several uncontrolled studies suggesting benefit. Numerous reports of hepatotoxicity.
German chamomile	One uncontrolled observation in a clinical study suggesting a beneficial effect on insomnia. Electroencephalogram data associated with relaxation.
Lavender	One uncontrolled trial and 1 case series report suggesting benefit. Mixed results in studies on agitation, depression, and anxiety.
St. John's wort	Multiple randomized controlled trials showing relief of depression. One uncontrolled study suggesting a beneficial effect on insomnia, an observation of benefit in sleep disorders in a clinical trial, and a polysomnography study indicating increased latency to rapid eye movement sleep.
Hops	One uncontrolled trial (no effect) and preclinical (laboratory) studies suggesting potential benefit on sleep.
Lemon balm	One uncontrolled trial on sleep (no effect). Double-blind studies indicate increased calm and decreased agitation.
Passionflower	One controlled clinical trial of a combined formula indicating benefit. Small controlled trial indicating similar anxiolytic effect as oxazepam.

somnia. It is equally true for patients with cancer and other chronic illnesses.

Second, the activity of herbal sedatives in sleep initiation versus sleep maintenance warrants investigation in clinical trials. The apparent dearth of side effects and morning-after effects of herbal sedatives (at least with short-term use) may make them useful adjuncts to the conventional nonpharmacological management of insomnia. Given the ever-expanding popularity of herbal medicines, unbiased questions concerning their use by patients should become standard in medical histories. This would seem especially important in the case of patients with insomnia and related disorders (anxiety and depression).

Third, future research should further the cause of herbal product standardization by focusing on such fundamental issues as the identity of active compounds and their stability in different herbal preparations. The prevalence of adulteration and contamination in herbs requires examination, especially those imported from areas where manufacturers are not tightly regulated. However, increasing reliance on standardized preparations should help minimize such problems.

As noted above, the herbs with the strongest support from clinical research are valerian and kava. Widely used in Europe, valerian has been shown to decrease sleep latency and to increase slow-wave sleep and decrease stage 1 sleep. This herb could be recommended, on an experimental basis, in patients who have responded poorly or reacted adversely to hypnotic drugs. Issues of drug interaction and adverse effects do not appear to be a problem with valerian. Kava has shown an ability to decrease sleep latency and stage 1 sleep and has shown anxiolytic potential. However, the dozens of cases of hepatotoxicity reported for

kava preparations make the use of this herb inadvisable, especially with cancer patients who may have been exposed to multiple medications that might have compromised liver function. Other herbal sedatives discussed are in need of experimental validation, although promising preliminary data exist for some (eg, passionflower).

Validation of the sedative effects of herbs can come only from well-designed studies. A number of the studies reviewed in this article were uncontrolled, either not randomized or lacking a placebo or treatment group for comparison. These studies fail to differentiate between specific therapeutic effects and nonspecific (confounding) effects. Moreover, nonrandomized studies may lead to a substantial overestimation of effect size.[210] On the other hand, controlled trials can also be seriously flawed. For example, the randomization process may be a source of bias. Some of the German reports did not detail their randomization procedures; inadequate sequence generation in randomized studies may yield larger estimates of treatment effects.[211] Also, if the herbal intervention used in such studies is inadequate (either the dose is too low or the specific preparation is not standardized and thus lacking in the active agents), then there will be no difference between the experimental and placebo groups.

Further problems exist with randomized trials on herbal medicines for sleep disorders. Despite the temptation to move quickly to obtain the high-quality data based on randomized controlled trials, preliminary phase I and II studies of specific herbal preparations should precede phase III–type trials to minimize the chances of performing complicated and expensive randomized studies using inappropriate agents, patient populations, or dosages. Finally, the study

populations in some of the trials on herbal medicines have been defined in ways that might actually include patients with sleep problems arising from quite different underlying causes, for example, a population with "sleep difficulties." More precise definition of study populations in sleep trials is required for clear and valid results to emerge on sedative or hypnotic herbs.

In a number of controlled clinical trials, both valerian and kava have compared favorably to benzodiazepines and tricyclic antidepressants often used to treat anxiety- and sleep-related disorders. However, because many herbal agents have significant pharmacological activity and thus potential adverse effects and drug interactions, health care professionals must be familiar with the potential for adverse reactions and other safety concerns. The potential of drug interactions between herbs and cancer chemotherapy drugs has now been demonstrated with the observation that St. John's wort decreases the blood levels of irinotecan, a drug metabolized by CYP450 3A4.[212] Chamomile and hops have preliminary evidence of CYP450 effects that could lead to drug interaction, but their clinical significance is not known.

In summary, the following clinical recommendations regarding herbal sedatives and cancer patients are supported by this review:

1. Sleep problems are common in cancer patients, and aggressive interventions, preferably nonpharmacologic in nature, are merited to improve the quality of life of cancer patients suffering from sleep disorders.
2. For patients for whom nonpharmacological interventions do not appear to work or who are experiencing short-term sleep problems due to stress associated with cancer treatment or progression, certain herbal medicines may represent a useful alternative to conventional sedative treatment.
3. Valerian is the herbal medicine with the best evidence for improving sleep and the lowest potential for adverse effects or drug interactions.
4. Due to its potential hepatotoxicity, kava is not recommended for cancer patients.
5. St. John's wort may improve sleep in patients who are depressed, having sleep difficulties, and in need of an antidepressant. Use of St. John's wort in patients taking other medications for cancer (or other conditions) should proceed only after an evaluation of the potential pharmacokinetic interaction.
6. Other herbal medicines, such as chamomile, hops, passionflower, lavender, and lemon balm, may be useful, although the evidence of their effectiveness is preliminary. Because of laboratory evidence on potential interactions involving CYP450, chamomile and hops should be used in lower dosage formulations such as teas, rather than concentrated extracts, in patients who are undergoing chemotherapy or treatment with other medications.

An ever-expanding variety of herbal substances from different cultures has now entered the global marketplace. Many of these are in widespread use by Americans and Europeans who tend to assume a large margin of safety as well as, in most cases, a substantial degree of therapeutic efficacy. This emerging reality poses a unique set of research and educational challenges for public health and medical professionals alike. With the ongoing advancement of our understanding of herbal medicines, our ability to integrate meaningful findings on herbal sedatives into clinical protocols and guidelines for usage by the general public will increase. We have yet to discern the potentially substantial role these agents may already play in reducing the very large prevalence of anxiety, insomnia, and other sleep disorders among cancer patients today.

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