Treatment of Insomnia: An Alternative Approach

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Abstract
Insomnia is the most common sleep disorder, and is often associated with significant medical, psychological, and social disturbances. Conventional medical treatment for insomnia includes psychological and pharmacological approaches; however, long-term use of frequently prescribed medications can lead to habituation and problematic withdrawal symptoms. Therefore, herbal and other natural sleep aids are gaining popularity, as herbs commonly used for their sedative-hypnotic effects do not have the drawbacks of conventional drugs. Whether alternative therapies possess activity similar to conventional therapies needs further evaluation.
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Introduction

Humans sleep approximately one-third of their lives. Scientists do not fully understand the necessity for sleep, nor the mechanisms for sleep's physical and mental restoration. Sleep disruption creates fatigue and suboptimal performance, causing significant medical, psychological, and social disturbances.[1,2]

Insomnia is a widespread health complaint, and the most common of all sleep disorders.[3] In the United States, the cost of insomnia, including treatment, lost productivity, and insomnia-related accidents may exceed $100 billion per year.[4,5]

Insomnia can be defined as the subjective complaint of impairment in the duration, depth, or restful quality of sleep. It is characterized by one or more of the following problems: difficulty falling asleep, difficulty maintaining sleep, early morning wakening, and unrefreshing sleep.[6] Approximately 35 percent of the adult population have insomnia during the course of a year. Up to seven percent indicate the insomnia is chronic, severe, or both.[7-9] In contrast to the occasional sleepless night experienced by most people, insomnia may be a persistent or recurrent problem with serious complications such as anxiety and depression.[7,10,11]

Sleep Physiology

Natural sleep patterns show considerable individual variability. Most adults are comfortable with 6.5-8 hours of sleep daily, taken in a single period.[12]

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Normal sleep consists of four to six behaviorally and electroencephalographically (EEG) defined cycles of two distinct types: non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. According to Rechtshaffen,[13] sleep is staged by determining the predominant pattern in 30-second "epochs" of EEG, muscle, and eye movement activity.

Stage 1 NREM sleep represents very light sleep, from which one can be easily aroused. The predominant EEG pattern is a low voltage, mixed frequency activity. Stage 2 NREM sleep is defined by the appearance of steep spindles or K-complexes on EEG. The majority of a typical night's sleep is spent in stage 2. Stages 3 and 4 of NREM sleep are often referred to collectively as delta sleep or slow wave sleep.

REM sleep consists of relatively low-voltage, mixed-frequency EEG activity, somewhat similar to stage 1 or wakefulness, with the appearance of episodic rapid eye movement. One of the prime characteristics of REM sleep is a low level of muscle tone.[13]

Etiology and Classification

Insomnia is classified as primary or secondary, as well as acute or chronic. Insomnia occurs more frequently with aging and in women.

Primary insomnia is sleeplessness that is not attributable to a medical, psychiatric, or environmental cause. The etiology of primary insomnia relates in part to psychological conditioning processes. Secondary insomnia is a symptom caused by medical, psychiatric, or environmental factors.[14] In secondary insomnia the target of treatment is the underlying disorder.

Acute insomnia is often caused by emotional or physical discomfort, such as stressful life events or medical problems of recent onset. Various substances (caffeine, nicotine, alcohol, steroids, etc.) can impair both falling asleep and staying asleep.[15] Chronic insomnia can have multiple and varying causes,[6] and can pose a significant therapeutic challenge.

Conventional Treatment and Its Limitations

Conventional treatment for insomnia can be broadly divided into psychological treatment and pharmacological treatment.

Psychological Treatment

Psychological or behavioral interventions seek to change habits and beliefs presumed to maintain insomnia. Psychological treatment includes: (1) stimulus control therapy; (2) sleep restriction therapy; and (3) sleep hygiene education. Most specialists advocate a multi-dimensional approach, although pharmacological treatment using hypnotic agents usually predominates.

Pharmacological Treatment

Benzodiazepines

Benzodiazepines are the most commonly prescribed medications for insomnia, and have demonstrated efficacy in short-term treatment.[8] The most common side-effects of these medications are anterograde amnesia and, for long-acting drugs, residual daytime drowsiness.[6]

Tricyclic antidepressants

Tricyclic antidepressants are also prescribed for insomnia in doses sub-threshold for the treatment of depression. Minimal scientific evidence supports the efficacy or safety of this approach in the treatment of most types of insomnia.[6] Side-effects include anticholinergic effects (urinary retention, dry mouth, and constipation), cardiac toxicity, orthostatic hypotension, and sexual dysfunction.[15]

Antihistamines

The active agent in many over-the-counter medications is a sedating

antihistamine, which antagonizes central histamine H_1 receptors. These nonprescription medications are only minimally effective in inducing sleep, and may reduce sleep quality.[16] While these medications are generally safe, they have anticholinergic side-effects.[17]

Drug Therapy Limitations

Traditionally, the recommended duration of hypnotic drug use for the treatment of insomnia is four weeks.[14] Long-term use increases the likelihood of habituation and problematic withdrawal symptoms. To date, minimal safety or efficacy data are available to guide hypnotic use beyond two to three months, although an estimated 10-15 percent of patients use these medications regularly for more than one year.[17] Hypnotic drugs are often prescribed long-term to relieve insomnia in psychogeriatric patients, despite recommendations for short-term use only. Serious side-effects with long-term prescriptions complicate treating insomnia effectively. The search continues for the ideal hypnotic – one that induces sleep rapidly, maintains sleep for the entire night, and is devoid of next-morning hangover effects.

Alternative Therapies

Over-the-counter sleep aids are becoming popular as an alternative to prescription hypnotics. Surveys of young adults indicate approximately 10 percent used nonprescription medications in the past year to improve sleep.[9] Patients report self-medicating with herbs, hormones, and amino acids in an effort to improve sleep and avoid the unacceptable side-effects of prescription medications. The most commonly used botanical sleep aids are valerian and hops (Table 1); physiological substances include melatonin and 5-hydroxytryptophan. In addition, acupuncture and "low energy emission therapy" may be effective.

Medicinal Herbs

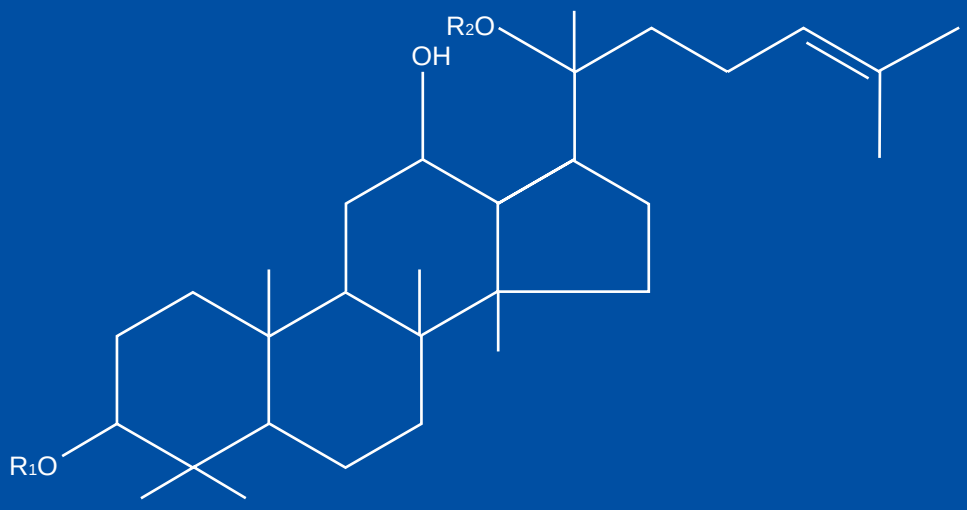
Valerian (Valeriana officinalis)

In 1996, valerian was one of the 25 best-selling herbs in the United States.[18] The use of the rhizome and roots of *V. officinalis* as an anxiolytic and sleep aid dates back 1,000 years.[32] The U.S. Food and Drug Administration (FDA) rates valerian as a GRAS (generally recognized as safe) herb.[19] It is listed in the European Pharmacopea, and is widely used as a hypnotic and daytime sedative.[20]

Valerian contains valepotriates, valerenic acid, and unidentified aqueous constituents that contribute to the sedative properties of valerian.[20] Valepotriates, a 0.5-2 percent mixture of unstable iridoid compounds, have been identified in valerian. The rhizome and root also contain 0.3-0.7 percent of a potent-smelling volatile oil containing bornyl acetate and the sesquiterpene derivatives of valerenic acid.[21] The proportion of these constituents can vary greatly between and within species.[22] The primary active ingredient of valerian has not been identified.

Valerian has been shown to have sleep-inducing, anxiolytic, and tranquilizing effects in *in vivo* animal studies and clinical trials. A placebo-controlled, crossover trial of 128 volunteers reported 400 mg of valerian extract at bedtime led to improved sleep quality, decreased sleep latency, and reduced the number of night awakenings.[23] Two other clinical studies using 400-900 mg valerian before bed also improved insomnia.[24,25] In a double-blind, cross-over, placebo-controlled trial, subjective sleep latency and wake time after sleep-onset were reduced by more than half after a 900 mg dose, with a smaller effect after 450 mg.[26] One EEG study reported 135 mg of aqueous, dried extract of valerian, taken three times daily, improved delta sleep and decreased stage 1 sleep.[27] In general, clinical studies with valerian extracts show the mild hypnotic effects of valerian decreases sleep latency and improves sleep quality.

Figure 1. Structure of Ginsenosides Rb1, Rb2, Rc.



Ginsenoside	R_1	R_2
Rb_1	-glc (2-1) glc	-glc (6-1) glc
Rb_2	-glc (2-1) glc	-glc (6-1) arap
R_c	-glc (2-1) glc	-glc (6-1) araf

Valerian extracts cause both CNS depression and muscle relaxation.[28] Sedation may result from an interaction of valerian constituents with central $GABA_A$ receptors.[29] Valerenic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain, resulting in sedation.[30] Aqueous extracts of the root contain appreciable amounts of GABA, which could directly cause sedation, but there is uncertainty about its availability.[31] Although valerian is effective in producing depression of the CNS, neither valepotriates, nor valerenic acid has any activity alone.[32] It is possible a combination of volatile oil, valepotriates, and other constituents are involved.

While valerian has been shown to be generally safe, there are concerns about its quality and efficacy.[30] Reports on the cytotoxicity of valepotriates warrant further investigation of the possible carcinogenicity of epoxide groups that act as alkylating agents.[33] Patients using large doses over several years can experience serious withdrawal symptoms following abrupt discontinuation. In 1998, a case of cardiac complications and delirium associated with withdrawal of valerian root was reported.[34]

Ginseng

Ginseng root has been used for over 2,000 years for its health-promoting properties.[35] In recent years, it has consistently been one of the top ten selling herbs in the United States.[36] Results of several studies indicate the effect of ginseng may be, at least in part, related to maintaining normal sleep and wakefulness. Of the several species of ginseng, *Panax ginseng* (Korean or Asian ginseng), *Panax quinquefolius* (American ginseng), and *Panax vietnamensis* (Vietnamese ginseng) are reported to have sleep-modulating effects.

Constituents of most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids.[37] (Figure 1) *Panax vietnamensis* contains ocotillol-type saponins, the major one being majonoside-R2 (MR2). Most pharmacological actions of ginseng are attributed to ginsenosides.[38] Except for ginsenoside Ro, the more than 20 ginsenosides that have been isolated belong to a family of plant steroids named steroidal saponins.[39] There is a wide variation (2-20%) in the ginsenoside content of different species of ginseng.[38] Moreover, within a single species cultivated in two different locations, pharmacological differences have been reported.[40]

Ginseng has an inhibitory effect on the CNS and may modulate neurotransmission. A mixture of the ginsenosides Rb_1, Rb_2, and Rc from *Panax ginseng* extracts prolonged the duration of hexobarbital-induced "sleep" in mice.[41] Rhee et al reported a *Panax ginseng* extract decreased the amount of wakefulness during a 12-hour light period and increased the amount of slow wave sleep.[42] Ginseng is known as an "adaptogen," capable of normalizing physiological disturbances. For example, Lee et al reported a *Panax ginseng* extract normalized the disturbances in sleep-waking states caused by food deprivation in rats.[43] MR2, a major ocotillol-type saponin isolated exclusively from *Panax vietnamensis* restores the hypnotic activity of pentobarbital, which was decreased by two models of psychological stress.[44,45] In a recent double-blind study investigating the influence of ginseng on the quality of life of urban dwellers, a daily dose of 40 mg ginseng extract for 12 weeks significantly improved quality of life, including sleep.[46]

There is evidence to suggest one mechanism for the CNS-depressant action of ginseng extract and ginsenosides is via regulation of GABAergic neurotransmission. Ginsenosides have been reported to compete with agonists for binding to $GABA_A$ and $GABA_B$ receptors.[47] Neuronal discharge frequency in the nucleus tractus solitarius was inhibited by *Panax quinquefolium* extract,[40] and $GABA_A$ receptor agonist muscimol.[48] The reversal effect of MR2 and diazepam on the psychological stress-induced decrease in pentobarbital sleep was antagonized by flumazenil, a selective benzodiazepine antagonist.[45]

There are few reports of severe side-effects secondary to ginseng, despite the fact that over six million people ingest it regularly in the United States.[49] The most common reported side-effects are nervousness and excitation, but these diminish with continued use or dosage reduction.[49] On the basis of its long-term usage and the relative infrequency of reported significant side-effects, it is safe to conclude that ginseng is usually not associated with serious adverse reactions.[50]

The recommended daily dosage is 1-2 g of the crude root, or 200-600 mg of extracts.[51] As the possibility of hormone-like or hormone-inducing effects cannot be ruled out, some authors suggest limiting treatment to three months.[51]

Kava Kava (Piper methysticum)

Kava kava is a large shrub cultivated in the Pacific islands. Therapeutically, the rhizome of this herb is used to treat anxiety, stress, and restlessness;[52] often the underlying causes of insomnia.

The CNS activity of kava kava is due to a group of resinous compounds known as kava lactones or kava pyrones.[21] Sedative, anticonvulsive, antispasmodic, and central muscular relaxant effects are attributed to kava.[53] Studies in animals show kava kava extracts and kava lactones induce sleep and muscle relaxation.[21] While the underlying mechanism is not entirely clear, it is possible that kava kava acts on GABA and benzodiazepine binding sites in the brain.[54] Several relatively short-term clinical studies provide favorable evidence that kava kava is effective in treating anxiety and insomnia.[55]

Table 1. Medicinal Herbs with Sleep-Inducing Effects.

Herb	Mechanism of action
Valeriana officinalis	Regulates GABAergic neurotransmission
Panax species	Regulate GABAergic neurotransmission
Piper methysticum	Central muscle relaxant
Passiflora incarnata	Regulates GABAergic neurotransmission
Humulus lupulus	Unknown

As a sleep-aid, 180-210 mg of kava lactones daily are recommended.[21] It is important to note that ethanol and other CNS depressants can potentiate the effects of kava.[52]

Passion flower (Passiflora incarnata)

The herb consists of the dried flowering and fruiting top of a perennial climbing vine (family Passifloraceae). While studies proving its effectiveness are lacking, it is usually used for insomnia.[22] Active components of passion flower may be harmala-type indole alkaloids, maltol and ethyl-maltol, and flavonoids.[52] When administered intraperitoneally to rats, passion flower extract significantly prolonged sleeping time.[56] The principal flavonoid, chrysin, was demonstrated to have benzodiazepine receptor activity.[53]

The usual daily dose is 4-8 g taken as a tea.[21] Since harmala compounds are uterine stimulants, passion flower extract is not recommended for pregnant women. Side-effects have not been reported.

Hops (Humulus lupulus)

The dried strobile of *Humulus lupulus* is a popular sleep aid. Hops has been used for centuries in the treatment of intestinal ailments, with more recent use as a sedative-hypnotic. Active ingredients in hops include a volatile oil, valerianic acid, estrogenic substances, tannins, and flavonoids.[52] The sedative effects of hops have been demonstrated to induce sleep.

The use of hops for insomnia as an infusion in tea was reported to have a calming effect within 20-40 minutes of ingestion.[57] A recommended dose is 0.5 g of the dried herb, or its equivalent in extract-based products, taken one to several times daily.[51] Side-effects are uncommon, and large doses have been ingested safely. It is not recommended for pregnant women or women with estrogen-dependent breast cancer.[19]

Physiological Agents

Melatonin

Melatonin, a hormone secreted by the pineal gland, is considered to be a remedy for insomnia caused by circadian schedule changes, such as jet lag and shift work.[58] Rapid travel across several time zones results in a desynchronization between intrinsic human circadian rhythm and the local environmental photoperiod. The severity and duration of resulting sleep disturbance varies, depending on the number of time zones crossed, direction of travel, departure time, and age. A clinical study with flight-crew members who completed a nine-day New Zealand-Los Angeles-England round trip reported that subjects who received melatonin after arrival had significantly less overall jet lag.[59]

Night shift workers, during their nights off, have problems falling asleep. Folkard et al reported that melatonin increases sleep quality compared with baseline and placebo in

night-shift workers.[60] Melatonin has also been shown to have a beneficial effect on the quality of sleep for elderly patients with insomnia.[61] Adverse effects of melatonin most commonly reported in the clinical trials include sedation, headache, depression, tachycardia, and pruritus.[60,62]

Variable melatonin dosages (0.3-5 mg) and administration timing have been studied.[58] Therefore, optimal effective dosing is unclear. The mechanisms of action of melatonin are unknown, but may involve interaction with melatonin receptors in the suprachiasmatic nucleus.[6] Melatonin may have modest efficacy in insomnia; however, long-term studies examining both efficacy and toxicity are needed.

L-Tryptophan and 5-Hydroxytryptophan

L-tryptophan is an essential amino acid that occurs in plants and animals in concentrations of 1-2 percent. A dose of 1 g of L-tryptophan has been reported to reduce sleep latency by increasing subjective "sleepiness" and also decreasing waking time.[64] Since this amino acid is a biochemical precursor to serotonin, it is thought to function by increasing serotonin in certain brain cells, thus inducing sleep.[65] L-tryptophan was widely sold as a sleep aid until 1989, when, following the deaths of 37 healthy people of eosinophilia-myalgia syndrome after consuming contaminated L-tryptophan, FDA recalled the product. It is currently available by prescription.

5-hydroxytryptophan, the immediate precursor of serotonin, is currently being used as a sleep aid, to treat depression, and as a weight loss tool. A daily dose of 100 mg was found to increase slow-wave sleep.[65] Its clinical efficacy as a sleep aid has yet to be confirmed by controlled therapeutic studies.

Other Approaches

Acupuncture

Acupuncture is best known in the United States as an alternative therapy for chronic pain. However, in traditional Chinese medicine, it is commonly employed for the treatment of insomnia. There are numerous publications in Chinese on the use of acupuncture for insomnia. The literature cited in this review, however, is restricted to articles in English.

Clinical reports on acupuncture therapy verify its efficacy in the treatment of insomnia in psychiatric patients.[66,67] Controlled, clinical trials demonstrating acupuncture's effect on insomnia are rare. A recent study of primary insomniacs treated with acupuncture showed objective as well as subjective improvements in sleep quality.[68] Many previous studies provide only subjective evaluations of sleep. Since acupuncture is an individualized treatment, controlled studies are difficult to execute.

Positive effects using scalp, body, and ear acupuncture points appeared almost immediately after treatment.[69] The mechanisms by which acupuncture treatment modulates insomnia may be understood in terms of the general mechanism by which it produces analgesia.[70] Sites in the CNS where acupuncture signals are integrated also participate in the regulation of sleep-wake cycles.[70] Additional clinical studies are necessary to elucidate how acupuncture can reharmonize a disturbed sleep-wake cycle.

Low energy emission therapy (LEET)

LEET is a method of delivering low levels of amplitude-modulated radio frequency electromagnetic fields to humans. The LEET device consists of a signal generator, microprocessor, and amplifier. The signal generator is connected to a mouthpiece that is held between the tongue and palate for the duration of the treatment.[71] Results of some

investigations suggest LEET may be a potential alternative therapy for chronic insomnia that is refractory to conventional treatment. In healthy volunteers, 15 minutes of LEET treatment induced EEG changes, and was associated with objective and subjective feelings of relaxation.[72] A double-blind, placebo-controlled study showed that 12 LEET treatments over a four-week period improved the sleep of chronic insomniacs.[73]

The mechanism underlying the effect of LEET is poorly understood. Low level electromagnetic fields, like the ones the brain is exposed to during LEET, affects *in vitro* and *in vivo* calcium release from neural cells,[74] and modifies the release of GABA[75] and the concentration of benzodiazepine receptors in the rat brain.[76] In addition, low level electromagnetic fields modify the release of melatonin in mammals.[71] So far, the administration of LEET treatment is confined to sleep disorder centers. Unlike conventional therapies, LEET may be administered on an every-other-day basis, and discontinuation does not appear to induce rebound insomnia.[73] LEET therapy-related side-effects have not been reported.

Conclusion

Insomnia is the most common sleep disorder. The inability to attain restful sleep in adequate amounts exacts a heavy toll. Conventional treatment for insomnia includes drugs that exert a depressant effect on the CNS, and psychological therapy. Most of the drugs prescribed for insomnia involve some risk of overdose, tolerance, habituation, and addiction. As alternative therapies, herbal products and other agents with sedative-hypnotic effects are being increasingly sought after by the general population. These therapies are less likely to have the drawbacks of conventional drugs. How the efficacy of alternative therapies compares to conventional therapies warrants further investigation.

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