Herbal Medicine for Insomnia

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Abstract

Insomnia is a common problem, and herbs can be quite helpful and are much safer than most drugs for insomnia. Moderately potent herbs that primarily work by enhancing sleep architecture or quality are reviewed in detail. These include *Valeriana officinalis* (valerian), *Valeriana sitchensis* (Pacific valerian) and related species, *Humulus lupulus* (hops), and *Piscidia piscipula* (Jamaica dogwood). Much milder nervines, requiring long-term use for full benefits—including *Passiflora incarnata* (passionflower), *Melissa officinalis* (lemonbalm), *Nepeta cataria* (catnip), *Scutellaria lateriflora* (skullcap), and *Centella asiatica* (gotu kola)—are discussed, and their place in improving insomnia is clarified. The much stronger and less often used sedative herbs *Gelsemium sempervirens* (gelsemium), *Pulsatilla vulgaris* (common pasque flower), *P. patens* (Eastern pasque flower), *Anemone* (*Pulsatilla*) *occidentalis* (western pasque flower), and *A. tuberosa* (desert anemone) are considered next. Finally, the delayed-onset sleep-maintaining herb *Myristica fragrans* (nutmeg) is put into clinical context.

Introduction

Insomnia is technically defined as difficulty falling asleep, staying asleep, or nonrestorative sleep causing daytime impairment or distress despite adequate opportunity and circumstance to sleep occurring at least three times per week for at least 1 month.[1] This is important because there are distinct herbs for patients with different types of insomnia. Note that circadian rhythm disorders that often affect sleep, such as jetlag, are not considered in this article.

Though there is much focus on reducing sleep latency (speeding the time to fall asleep) among people affected by insomnia and among makers of drugs for this problem, herbs actually perform well primarily at enhancing the quality of sleep (improving how restorative sleep is, in other words). The growing support for this fact is critically important in advising patients about what to expect from herbal treatment of insomnia, and because of how different this makes herbs from sedative-hypnotic drugs.

The most common classes of drugs used to treat insomnia are listed in Table 1. There is an urgent need for alternatives to these drugs given their relatively poor efficacy, significant safety concerns, and/or addictiveness, depending on the class of drug under discussion.

Some classes of sleep medications, particularly the still widely prescribed benzodiazepines, actually degrade the quality of sleep.[2] People do fall asleep faster when taking these drugs, but they do not go into deep, restorative sleep and end up groggy and impaired in the daytime. For this reason, it is well documented that benzodiazepines actually impair people's ability to drive and operate heavy machinery safely, and ultimately do not improve sleep for most people.[3] This also increases traffic accidents.[4] The opposite is true when it comes to most herbs, as discussed below.

The addictiveness of benzodiazepines is also often overlooked, particularly as longer acting agents are now in more common use (shorter acting agents are more addictive).[5] Benzodiazepines are not first-line agents and should only be used short-term (6 months or less) according to all major guidelines on their use.[6] The patients have to wean slowly off these drugs to prevent withdrawal symptoms.

Newer nonbenzodiazepine sedative drugs such as zolpidem have less tendency to reduce time spent in deep sleep, but mostly increase time spent in light sleep, which contributes to their fairly minimal clinical benefit according to meta-analyses.[7,8] Some but not all studies also implicate zolpidem-type drugs in increasing risk of traffic accidents and major injuries.[9,10] Misuse (overdose, taking them at times other than before bed, and in combination with alcohol or other sedatives) of zolpidem-type drugs is rampant and has led to the rise of so-called sleep driving, which is now a significant cause of impaired driving.[11] Though sleep driving is probably a rare adverse effect, the sheer number of people taking these drugs means that there is a significant problem with sleep driving. The problems with benzodiazepines and zolpidem-type drugs are so significant that some European countries have begun widespread public campaigns against their use.[12]

Table 1. Classes of Major Anti-Insomnia Drugs

Drug category	Major examples	Effects on sleep latency	Effects on sleep quality	Addictiveness
Benzodiazepines	Temazepam, clonazepam, lorazepam	Decrease it	Degrade it (inhibit stage 3, stage 4, and REM sleep)	High (schedule IV drugs)
Nonbenzodiazepine hypnotics (Z-drugs)	Zolpidem, zopiclone, eszopiclone	Decrease it slightly	Minimal effects on deep and REM sleep, lengthen stage 2 sleep	Low (schedule IV drugs)
H1-antagonists	Diphenhydramine	Decrease it	Minimal effects	None
Tricyclic antidepressants, general (low dose)	Amitriptyline, doxepin	Decrease it	Suppress REM sleep[a]	None
Tricyclic antidepressants, special	Trazodone (low dose), mirtazapine (low dose)	Decrease it	No effect on REM	None (mirtazapine) to moderate (trazodone)
Orexin antagonists	Suvorexant	Decrease it	Minimal effects	Low (schedule IV drug)

[a]Rebound excessive dreaming with sudden discontinuation has been observed.

Moderate Potency Hypnotic Herbs

The roots of *Valeriana officinalis* (valerian), *Valeriana sitchensis* (Pacific valerian), and possibly other species are well-known mainstays in the herbal materia medica for treating people with insomnia. Valerian is native to Europe, while Pacific valerian is from northeastern Russia and northwestern North America. A meta-analysis of clinical trials on various extracts of valerian found that it has minimal to no effect on reducing sleep latency, but it consistently and significantly improves sleep quality.[13] In head-to-head comparisons with benzodiazepines, it is just as effective and significantly safer.[14] Studies going back to the 1990s and after show that valerian reduces light (stage 1) sleep and lengthens deep (stage 3) or slow-wave sleep in humans.[15,16] One small trial in older women did not find an effect of valerian on sleep architecture compared to placebo.[17] Valerian is safe and effective in children.[18]

Some classes of sleep medications, particularly the still widely prescribed benzodiazepines, actually degrade the quality of sleep.

The mechanisms of action of valerian are complex. It has been stated, "The sedative and sleep inducing effect [of valerian] cannot be attributed to one single substance and probably not to one single mode of action."[19] There is evidence of multiple interactions between valerian's compounds, γ-amino butyric acid (GABA), and the $GABA_A$ receptor (see Fig. 1).[20] Recall that $GABA_A$ receptors are predominantly found in the central nervous system, while $GABA_B$ receptors are predominantly found in skeletal muscle. Direct activation of $GABA_A$ receptors by valerian has been shown *in vitro* and *in vivo*, particularly by the compound valerenic acid (see Fig. 2).[21] The binding sites of various valerian compounds have not been definitively determined; however, most, but not all, appear to bind to sites distinct from those of GABA, benzodiazepines, barbiturates, or ethanol.[22] Valerenic acid specifically appears to bind to the loreclezole binding site.[23] Valerenic acid and related sesquiterpenoids in valerian appear to cross the blood–brain barrier to access $GABA_A$ receptors through a nontranscellular transport system.[24] *V. edulis* spp. *procera* (Mexican valerian) root extract, which did not contain valerenic acid, was nonetheless shown to improve sleep architecture in patients with insomnia, though *V. officinalis* was somewhat superior.[25] In rats, valerian also reduces the activity of the catabolic enzyme GABA transaminase. Note that *Glycyrrhiza glabra* (licorice)

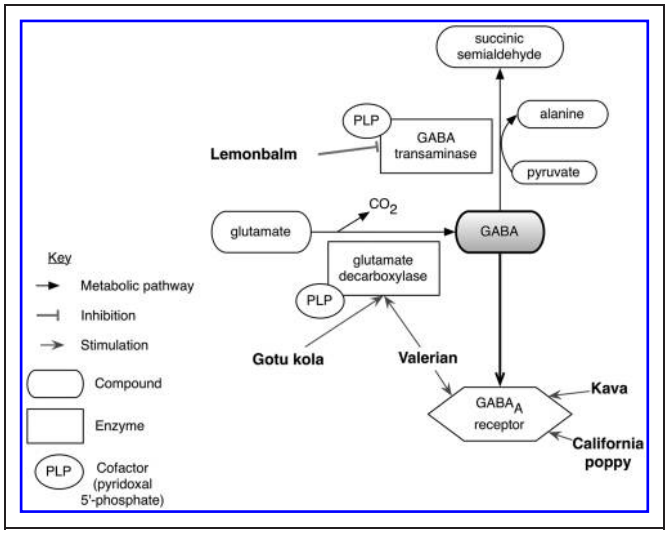

Figure 1. GABAergic effects of herbs.

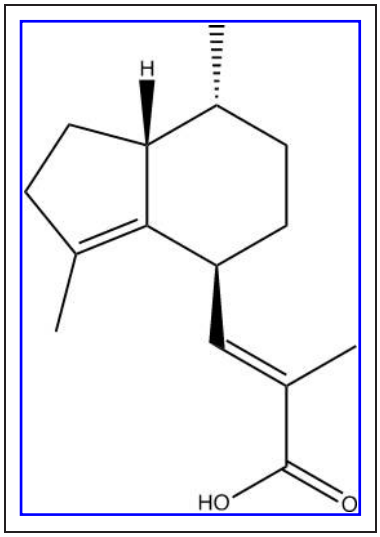

Figure 2. Valerenic acid.

has been shown to enhance the anxiolytic effects of valerian by unknown but presumably pharmacokinetic mechanisms.[26]

Valerian's constituents have been shown to have activity unrelated to GABA. For instance, multiple compounds activate the $5HT_{5a}$ serotonin receptor.[27] This receptor is concentrated in the suprachiasmatic nucleus of the hypothalamus area that plays a role in regulating the sleep–wake cycle. Lignans in the root are partial agonists of the adenosine A1 receptor, which is associated with reductions in anxiety and wakefulness.[28]

Valerian is generally very safe. Unlike benzodiazepines, valerian actually improves people's daytime alertness and driving ability.[29] It is not habit-forming. Clinically, it is noted that it, like most other herbs for sleep improvement, can very occasionally cause stimulation instead of relaxation. It is not clear in whom this occurs or why, but it is not common and not a reason to avoid this herb compared to any other. A typical dose of tincture is 2–3 ml at bedtime. A typical dose of capsules is 500–1,000 mg at bedtime. There is at least epidemiologic research showing valerian is safe in pregnancy.[30,31]

There is no evidence of any negative pharmacokinetic interactions between valerian and any drug.[32] Valerian specifically does not interact with alcohol at doses that definitively interact with benzodiazepines.[33]

Humulus lupulus (hops) strobiles (female flowers) are another midpotency herbal medicine for improving sleep quality. This vine is a circumboreal plant (native all around the Northern Hemisphere) and has separate male and female plants. Most clinical trials showing hops helpful for insomnia patients have used it in combination with valerian, with at least one of these studies suggesting a definite synergistic effect from their combination.[34,35] One study of an extract with soy and *Juniperus oxycedrus* (cade) oils and just 100 mg of hops did not find it superior to placebo for insomnia.[36] Ingestion of 333 ml nonalcoholic beer (containing around 1 g of hops) at dinnertime, compared to no beer, reduced sleep latency and improved sleep quality in healthy nurses doing shift work in one small trial.[37]

The compounds responsible for hops effects on sleep have not been determined. One study in mice suggested that hops acted in part by activating melatonin receptors.[38] A study in quail supported this idea somewhat, showing that low doses of hops (similar to concentrations found in nonalcoholic beer) seemed to enhance circadian rhythms, including reduced activity at night.[39] Binding of hops extract compounds to $5\text{-}HT_6$, $5\text{-}HT_7$, melatonin-1, and melatonin-2 receptors was seen in another *in vitro* study.[40] Various hops constituents may also activate the $GABA_A$ receptor.[41] Hops is also well-known as a phytoestrogen and inflammation modulator, but this will not be discussed in any depth here except to point out that this herb is most ideal in perimenopausal patients with chronic inflammatory conditions and insomnia.

Hops is generally very safe. Overdose may lead to unwanted estrogenic adverse effects, but this takes work to achieve. It is intensely bitter, which tends to limit dosing. Alcoholic beer intake by lactating women decreases the amount of milk their babies drink, possibly due to the hops content, though this is unknown.[42] Nonalcoholic beer increased the antioxidant content of breast milk.[43]

Piscidia piscipula (Jamaica dogwood) bark has a similar level of potency as a sleep aid as valerian, or perhaps moderately stronger. There is little research on this helpful medicine, and so its use is largely based on history and experience. Limited animal research supports its effectiveness as a moderate hypnotic.[44] This tree is also not that widespread and the use of its bark limits the sustainability of the medicine. Luckily, only small doses are used, but it should be considered a second-line therapy when other treatments fail. Jamaica dogwood should be avoided in pregnancy and lactation due to lack of information about its safety in these settings. It is otherwise safe at doses of tincture of 1–2 ml at bedtime.

A combination of valerian 300 mg, hops 30 mg, and *Passiflora incarnata* 80 mg was compared to zolpidem 10 mg at bedtime in 78 patients with chronic insomnia in a randomized, double-blind trial.[45] In this brief two-week trial, the two treatments were equally effective at reducing sleep latency and improving sleep quality. Daytime drowsiness was not different between the groups and there were no serious adverse events. This strongly suggests that herbal sleep aides are a legitimate alternative to zolpidem and related drugs, though more robust research is necessary to be certain. Another larger trial involving 184 adults with insomnia found a combination of valerian 187 mg and hops 42 mg as effective as diphenhydramine 50 mg compared to placebo for relieving insomnia over 1 month's time.[46]

Mild Potency Nervine Herbs

There are many herbs with a mild effect on sleep that are generally called nervines. We have previously written in depth about these herbs as a treatment for anxiety, but they are also highly relevant for people with insomnia.[47] Only the effects of these herbs on sleep will be reviewed here, as well as basics of

Table 2. Preclinical Studies of Inhibition of GABA Transaminase by Herbs

Herb	Part used	Model	Reference
Piper tuerckheimii (cordoncillo)	Root	*In vitro*	a
Adiantum wilsonii (Wilson's maidenhair fern)	Rhizome	*In vitro*	a
Erigeron breviscapus (dēng zhǎn cǎo, shortscape fleabane)	Whole plant	*In vitro*	b
Gastrodia elata (tiān má, gastrodia)*	Rhizome	*In vitro*	c, d
Acorus gramineus (Japanese sweet root)	Rhizome	Mice	e
Angelica dahurica (Chinese angelica)	Root	*In vitro*	f

*Endangered species, do not use.
[a]Awad R, Ahmed F, Bourbonnais-Spear N, et al. Ethnopharmacology of Q'eqchi' Maya antiepileptic and anxiolytic plants: Effects on the GABAergic system. J Ethnopharmacol 2009;125:257–264; [b]Tao YH, Jiang DY, Xu HB, Yang XL. Inhibitory effect of Erigeron breviscapus extract and its flavonoid components on GABA shunt enzymes. Phytomedicine 2008;15:92–97; [c]Choi JH, Lee DU. A new citryl glycoside from Gastrodia elata and its inhibitory activity on GABA transaminase. Chem Pharm Bull (Tokyo) 2006;54:1720–1721; [d]Ha JH, Shin SM, Lee SK, et al. In vitro effects of hydroxybenzaldehydes from Gastrodia elata and their analogues on GABAergic neurotransmission, and a structure-activity correlation. Planta Med 2001;67:877–880; [e]Koo BS, Park KS, Ha JH, et al. Inhibitory effects of the fragrance inhalation of essential oil from Acorus gramineus on central nervous system. Biol Pharm Bull 2003;26:978–982; [f]Choi SY, Ahn EM, Song MC, et al. In vitro GABA-transaminase inhibitory compounds from the root of Angelica dahurica. Phytother Res 2005;19:839–845.

their use, as so much else has been written about them. Note that all of these herbs are basically extremely safe, including in pregnancy and lactation. They require long-term use for optimal efficacy and are not typically effective at shortening sleep latency. Finally, see Figure 1 for the effects of various of these herbs on the GABA system in the brain.

Passiflora incarnata (passionflower) is a vine native to the southeastern United States. Its leaves are used as medicine, though its flower is considered among one of the most beautiful in the world. A tea in relatively low doses (one cup per night) for just one week improved sleep quality in healthy adults with mild intermittent disturbed sleep.[48] It is particularly helpful in patients with mild anxiety, showing benefits similar to those of the benzodiazepine oxazepam.[49] *In vitro* it has been shown to affect $GABA_A$ and $GABA_B$ channels and to affect GABA uptake into neurons.[50] The usual dose of tincture or glycerite is 3–5 ml at bedtime, or 1,000–2,000 mg in capsules at bedtime.

In one case study, a combination of passionflower and valerian was associated with rapid onset of hand tremor, dizziness, throbbing, and muscle fatigue in a patient who was concomitantly taking lorazepam.[51] No other cases of such interactions could be found in the literature.

Melissa officinalis (lemon balm) is from the Mediterranean region, but is now widely cultivated in temperate areas. One double-blind trial in overall healthy adults with mild insomnia found a combination of valerian and lemon balm effective compared to placebo.[52] A prior trial found this combination as effective as benzodiazepines for insomnia.[53] These two herbs together appear to mainly improve sleep quality.[54] Topical application of lemon balm to the temples has also been suggested by the late, great Rudolf Fritz Weiss, MD, for insomnia.[55] *In vitro* it inhibits GABA transaminase.[56] See Table 2 for other herbs reported to inhibit GABA transaminase in preclinical studies. Typical doses are essentially the same as for passionflower. It is also commonly used as a tea at a dose of 5 g/cup, steeped for 15–30 minutes, strained, and drunk before bed. Tea should be avoided in patients having sleep difficulties due to nocturia. Note that *Nepeta cataria* (catnip) is very similar to lemon balm and has a stronger lemon taste. Clinically, it seems even more potent than lemon balm in all its aspects.

Scutellaria lateriflora (skullcap) is a common plant of wetlands across much of North America; the leaves and flowers are used as medicine. No clinical trials appear to have been conducted on skullcap in people with insomnia. It has been shown to have a mild anxiolytic effect in healthy, mildly anxious adults.[57] It is an herb with a very strong tradition as a mild improver of sleep quality however, and should be considered right alongside the other herbs discussed here. It has a bitter quality and so may be most appropriate for patients who also have atonic digestive tracts. Doses are the same as for passionflower.

Centella asiatica (gotu kola) is a tropical native in which the entire plant (roots and aerial parts) is used as medicine. It is a multifaceted, widely applicable plant useful as a calming adaptogen, immunomodulator, and antifibrotic. While again not specifically studied in modern times for insomnia, it has shown promise as an anxiolytic in preliminary clinical trials.[58] It should be considered in immunosuppressed or anxious patients with or without sclerotic conditions also struggling with insomnia. Doses are the same as for passionflower, though it loses much of its potency when dried and is not very effective in capsules.

Sedative Herbs

For patients who primarily have difficulty falling asleep, there are stronger herbs that are more sedating and can actually reduce sleep latency. These herbs are more likely to cause daytime sleepiness if taken during the daytime, but generally lessen it when taken at bedtime due to improved sleep quality. There is no evidence that these herbs interfere with deep sleep. These herbs are not recommended either for use without the

assistance of a practitioner skilled in their use, or for practitioners until they have had a chance to train with someone who has experience with them.

Gelsemium sempervirens (gelsemium, yellow jessamine) is a vine that is native to the eastern part of North America, extending as far south as Guatemala. The root is the potent medicine and should only ever be used under direct supervision of a practitioner experienced with its use. Just 10 drops of fully concentrated (1:2–1:3 weight:volume) fresh root tincture is a good starting dose for severe difficulties falling asleep. This can be increased by 5 drops per night each night that it is ineffective, up to the point that 1 ml (30 drops) is reached, mild adverse effects occur (in which case the dose should be decreased), or sleep is readily achieved. It is also a moderately potent smooth and skeletal muscle relaxant based on clinical experience with it, and so when cramping of these structures is associated with difficulty sleeping, gelsemium should be considered. In overdose it begins to cause ataxia, diplopia, prostration, dilated pupils, ptosis, and impaired speech. In severe overdose, death from respiratory depression can occur, though this is extremely rare.

Pulsatilla vulgaris (common pasque flower), *P. patens* (eastern pasque flower), *Anemone* (*Pulsatilla*) *occidentalis* (western pasque flower), and *A. tuberosa* (desert anemone) are all used as medicine. They come from Eurasia (the former two) or North America (the latter two). The flowering tops in early seed are used. Though commonly European herbalists recommend using only dried forms of these herbs for safety, clinically these are practically without activity and are not recommended. Fresh plant material is much more active and with proper doses still safe. Touching or ingesting the fresh sap can cause blistering, but this is readily avoided when harvesting and making medicine by wearing gloves and a mask and not consuming the herb before it is mixed with ethanol.

Fresh pasque flower is an even more potent sedative, with just 5 drops of fully concentrated tincture being the starting bedtime dose. Like gelsemium, it is not safe for use except under close supervision by a practitioner experienced with pasque flower. This should be increased by just one drop per night until 15 drops (0.5 ml) dose is reached, mild adverse effects (similar to those of gelsemium) occur (which again should trigger a dose reduction), or sleep is readily achieved. Sadly, given its efficacy and safety at the doses recommended, there is no research on crude pasque flower.

Myristica fragrans (Nutmeg)

Nutmeg is the seed of *Myrtistica fragrans* and other similar species of tree, which are native to the Banda Islands. These trees are dioecious, and the fruits appear only on the female trees. The outer portion of the nutmeg when harvested is covered with a red netted structure, which yields the spice mace. This is removed and the remaining hard nut is referred to as nutmeg.

Fresh grated nutmeg (which requires a specialized spice grinder to accomplish as it is so hard) is an unusual herb in that it has a very long delayed onset of action in promoting sleep, on the order of four hours in the average person. Thus, it is the most specific herb to use for patients who wake up in the middle of the night and can't fall back asleep, when taken at bedtime. It can also be taken at dinner time (provided this is roughly four hours before bed) to have a sleep-inducing affect at bedtime. This is based on its traditional use in Ayurvedic medicine and modern clinical application, but has not been rigorously tested. One trial of an Ayurvedic formula featuring nutmeg did support its effectiveness as a sleep enhancer.[59] In the traditional medicine of the Moluccas (Spice Islands), where it is native, nutmeg was used for insomnia.[60]

The usual dose of fresh nutmeg is 0.25–0.5 teaspoons. It is traditionally taken with milk, though other fatty foods (such as nut butter) can also be used, to enhance absorption. For dried powder, at least twice the dose should be used. It can be slowly increased on subsequent nights up to a maximum of 1–2 teaspoons. In overdose (probably 3–10 times the therapeutic dose), nutmeg can cause neurological damage and hallucinations.[61]

Conclusion

Herbal medicines offer many ways to improve sleep in people with insomnia. They are most prominent as ways to enhance sleep quality, which takes some time to work. Specific agents should be chosen based on their efficacy in specific situations and taking into account other issues going on with an individual patient. The moderately potent sleep quality enhancers such as valerian, hops, and Jamaica dogwood can be considered as initial agents in most cases of insomnia, even when they feature difficulty falling or staying asleep. Combining one of these with at least one of the gentler sleep quality-enhancing nervine herbs (to obtain synergistic effects) is also recommended. If there is no improvement after 2–3 months of using these agents at appropriate doses, different herbs should be tried for another couple of months. Only at that point should sedative herbs be tried. However, for more severe sleep-onset problems, sedatives may be tried immediately. Finally, for patients who have predominant early waking, nutmeg at bedtime should be tried for 1–2 months, alone or combined with sleep quality enhancers.

Herbal medicines offer many ways to improve sleep in people with insomnia.

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