Sleep Well, Sleep Safely

An Exploration of the Importance of Sleep and Botanical Alternatives to Conventional Hypnotics

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Introduction

An estimated 10% of U.S. adults take conventional sleep medication for poor sleep. Recent data indicates that these conventional hypnotics are associated with increased risk of mortality. At the same time, insufficient sleep alters gene expression, circadian rhythms, and immunity, leading to increased risk of obesity, cardiovascular disease, cancer and dementia. But when someone suffers from insomnia, how can they get the sleep they need, without the harsh effects of conventional sleep aids?

Herbal remedies provide a therapeutic strategy of sleep support that relies upon the restoration of circadian rhythm in concert with sedative neurological tonification. Several key botanicals provide safe and effective sleep support including scutellaria lateriflora (American skullcap), eschscholzia californica (California poppy), piper methysticum (kava kava), passiflora incarnata (passionflower), valeriana officinalis (valerian), withania somnifera (ashwagandha), and magnolia officinalis (magnolia).

What is sleep?

Sleep consists of two stages: the non-rapid eye movement phase (NREM) and the rapid eye movement phase (REM). About 80% of sleep occurs during the NREM phase, but the REM phase is the one we actually remember because that is when dreaming occurs.[1]

NREM

During NREM sleep, parasympathetic controlled activities take place; for instance, metabolism, heart rate and respiration rates decrease while blood pressure lowers. Neurotransmitter and hormonal changes occur during this phase and the body has lower than average levels of cortisol and thyrotropin. An increase in certain hormones such as growth hormones and insulin are evident in the NREM phase of sleep. A burst-pause firing pattern of neurons occurs in areas of the body including the hypothalamus and the amygdala.

REM

This stage of sleep characterized by rapid eye movements causes heart rates to be irregular and blood pressure to raise slightly. More brain activity in the cerebrum is experienced, resulting in dreams that can often be remembered upon waking.[2]

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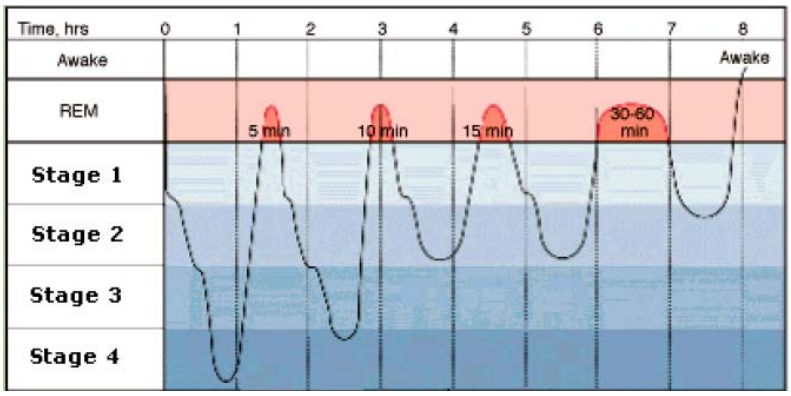
[1] A. Rechtschaffen. Perspectives in Biology and Medicine. 1998;41(3):359.

This graph shows NREM and REM patterns during an eight hour sleep cycle. Commonly, four to five cycles of REM sleep can occur within this time period.



What does “normal sleep” mean?

First, it is important to remember that optimal sleep length varies individually. Some people may need six hours of sleep while others need eight or nine. Generally speaking, most people that get consistently less than six hours of sleep start to experience problems associated with lack of sleep. Longer sleep is not necessarily associated with increased daytime alertness and well-being. Normal sleep includes some sleep latency, nighttime awakening and is consistent with mild fatigue in the afternoon.[3]

Quiet wakefulness

Defining what “normal sleep” actually means can be complex. From a historical standpoint, it might be reasonable to assume that the advent of electricity has shortened our nighttime, but in fact, our predecessors did not necessarily sleep longer than we do now. Why? Because sleeping conditions were noisier, more crowded and therefore sleep was more disrupted. In pre-industrial Europe, for instance, many accounts describe two intervals of sleep, separated by an hour or more of quiet wakefulness.

In a modern day context, this period of quiet wakefulness has been replicated in studies where subjects deprived of artificial light at night show a pattern of sleep consistent in pre-industrial Europe. In these studies, subjects have been shown to lie awake for about two hours, sleep for four hours, awake again for two to three hours of quiet rest and reflection, and sleep again for four more hours. The interval awakening is “non-anxious wakefulness” with its own altered

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[2] A. Rechtschaffen. Perspectives in Biology and Medicine. 1998;41(3):359.
[3] Harrison Y, Horne JA. Sleep. 1995;18(10):901-7

consciousness which is similar to meditation. Interestingly, this segmented sleep pattern is associated with greater dream recall.

This segmented sleep may be optimal when compared to the seamless sleep of modern society, a relatively new phenomenon. In fact, so-called "sleep disorders" may, in reality be patterns of segmental sleep breaking through into today's artificial sleep pattern.[4]

What is insomnia?

It is estimated that over half of all Americans have some form of insomnia, and at least a third of all Americans sleep less than six hours a night. In 2012 alone, there were 49 million prescriptions for sleep medications written, representing a 53% increase from 2007. With a $3.7 billion price tag, the sleep industry is clearly booming. But these numbers show that there is an obvious problem that demands a solution.

It is clear that we all need sleep, but the reasons why are still undefined. Many claim that sleep is tied to health body function and can help with immune restoration, the reduction of oxidative stress and the stabilization of blood sugar. But none of this has been proven because animal and human studies have provided inconsistent data.

Even though we don't really know why we need sleep, we do know what causes sleep issues such as insomnia. It has been proven that people with insomnia have difficulty falling and staying asleep and have short sleep duration, despite having an adequate opportunity for sleep. Insomnia can cause daytime impairment or marked distress and has been linked to increases in all-cause mortality. It can also result in an increased rate of obesity and an increased risk of developing diabetes, cardiovascular disease, and cancer.[5]

The epigenetic functions of sleep offer insight into the link between sleep and health. When people have sufficient sleep, their gene expression patterns have been shown to change in a way that is distinct from the gene expression pattern of someone who is sleep deprived. Sleep affects genetic transcription in a circadian fashion. Following sufficient sleep, the expression of only 122 genes will change in response to time awake, whereas after insufficient sleep, 856 genes change expression. The genes that are most susceptible to this change in expression are genes that are involved in cell repair, chromosomal stabilization, inflammatory, and oxidative responses.[6,7]

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[4] AR Ekirch. Am Historical Review. 2001;106(2):343-86
[5] http://www.nhlbi.nih.gov/health/prof/sleep/res_plan/section5/section5b.html
[6] Moller-Levet CS, et al. Proc Natl Acad Sci U S A. 2013;110(12):E1132-41
[7] Haghighatdoost F, et al. Nutrition. 2012;28(11-12):1146-50

Hypnotics

Achieving quality sleep can be a difficult task. But for those with insomnia, sleep can be almost impossible. In the United States, the most popular way of achieving this sleep is with sleep medications.

Benzodiazepines

There are two classes of hypnotics. The first is benzodiazepines. These drugs bind to the GABA receptor in the brain. GABA is an inhibitory neurotransmitter, so it tends to decrease the brain's overall activity. There are long-acting, medium and short-acting benzodiazepines. They are somewhat effective, but they are addictive, requiring people to increase their dosage over time in order to receive the same effects. They can also cause daytime drowsiness and somnolence later in the day. Weaning off of these hypnotics can be a difficult task, associated with numerous withdrawal symptoms.

Non-benzodiazepines

The second class of hypnotics is the non-benzodiazepines. These include such sleep aids as zolpidem (Ambien). Other hypnotics on this list include zaleplon (Sonata), eszopiclone (Lunesta), and ramelteon (Rozerem). Ambien is by far the most commonly prescribed sleep medication in the United States. This medium-acting, non-benzodiazepine sleep medication is fairly effective, but is also associated with side effects and potential hidden dangers.

The hazards of sleep medications

Approximately 6 to 10% of U.S. adults took a hypnotic for poor sleep in 2010. In a 2012 study that spanned two and a half years, researchers looked at people that had been prescribed a hypnotic. This group was compared to those who had never been prescribed a hypnotic. The study showed patients prescribed any hypnotic had approximately 4.6 times the hazard of dying over an average observation period of 2.5 years compared to non-users. At least 24 published studies have examined mortality associated with hypnotic consumption and 18 of these report significant associations with increased mortality. Receiving a sleep medication is also associated with a greater than three-fold increased risk of death, even when less than 18 pills per year are taken. Though the actual source of the higher death rates in this group is unknown, the correlations between increased mortality and sleep aids are evident.[8]

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[8] Kripke D, et al. BMJ Open. 2012;2:e000850.

Hypnotics—worth the risk?

With all of these serious and often life-threatening risks, it is important to consider if hypnotics actually work and if they are worth the risk. An eight-month randomized double blind placebo controlled trial looked at the use of Ambien in 91 adults with insomnia. The study found that overall, Ambien caused people to fall asleep about 40 minutes faster than if they were using placebo. People taking Ambien also spent 86% of their time in bed asleep, versus 79% for placebos. Therefore, there was a 7% increase in time spent in sleep due to the Ambien.[9]

An alternative explanation

Even though Ambien clearly helps with sleep duration, many botanicals can yield nearly the same effect for many individuals. Other things such as nutrition and sleep hygiene can also improve sleep.

Sleep hygiene

While there are numerous medications and botanicals that can aid sleep, one important element of healthy sleep is proper sleep hygiene. Proper sleep hygiene includes maintaining regular sleeping and waking patterns, avoidance of daytime napping, and not consuming stimulants (such as caffeine, nicotine or alcohol) in the evening. Getting vigorous exercise in the morning or afternoon, or performing relaxing exercise in the evening can also be helpful. Avoiding large meals past 7 pm, obtaining adequate exposure to daytime light, developing a relaxing bedtime routine, and using the bed only for sleep and sex can improve overall sleep satisfaction.[10]

Nutritional sleep support

When assessing sleep disorders, it's important to look at several key nutritional considerations. First, an assessment for anemia should be done, since the low iron levels associated with this disease can cause sleep disturbance. Adults typically have ferritin levels of around 25 ng/mL. If levels are lower than this, maintaining a diet of iron-rich foods and taking iron supplements can be helpful. Second, assess for sufficient energy. Interestingly, it takes some energy to sustain sleep. Those who don't have enough cellular energy will have a

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[9] Randall S. et al. Sleep. 2012;35(11):1551-7
[10] http://www.sleepfoundation.org/article/ask-the-expert/sleep-hygiene

hard time maintaining proper sleep cycles. Essential fats, B vitamins, and CoQ10 are all good options for nutritional support.

Botanical sleep support

There are several common botanicals that can be used for sleep support.

California poppy

California poppy is a member of the Papaveraceae family. This sedative is also an antidepressant and mood stabilizer. Its constituents are the alkaloids, specifically the cyptopine.

Research

In 2004, a multi-center, double blind, randomized, controlled trial looked at more than 260 adults over the age of 18 who had mild to moderate generalized anxiety disorder. Subjects were given either a placebo or a tablet which contained a water/alcohol extract of Crataegus and a dry water extract of California poppy, along with some magnesium. They took two tablets twice a day for three months. The study showed that the herbal extract outperformed the placebo. No serious side effects were noted and there were no problems with toxicity.[11]

[11] Hanus M, et al. Curr Med Res and Opinion. 2004;20(1):63-71

Dosing

California poppy can be given in extract or infusion form. As 1:2.5 hydroethanolic extract form, 30 drops can be administered three times daily. A 2.0-3.5g herb infusion can be consumed up to 4 times daily.

Cautions

California poppy should not be used during pregnancy due to possible uterine stimulation from alkaloid accumulation. This botanical may also potentiate MAO inhibitors, although no clinically relevant interactions are expected.[12]

Kava

A member of the pepper family, kava is an effective sedative and hypnotic. The roots of the plant are used and its constituents are the resinous kava lactones, also called kava alpha-pyrones (5.5%-8.3%), mainly consisting of kavain, dihydrokavain and methysticin. Kava acts as a muscle relaxant, anticonvulsant, anesthetic, analgesic, antifungal, spasmolytic and anti-depressant. The herb is rapidly absorbed within 30 minutes with a plasma half-life of 90 minutes to 3 hours.

The primary effect of kava ingestion is stimulation followed by sedation of the CNS. Small doses produce euphoric well-being, while large doses or frequently repeated small doses produce extreme relaxation, lethargy and eventually induce sleep. The effects of kava may not be noticed until after it has been used several times.[13]

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[12] McGuffin M, et al. AHPA Botanical Safety Handbook, 1997:49.
[13] Klohs M. J Med Pharm Chem. 1959 Feb;1(1):95-103.

Several studies have demonstrated that the kava lactones produce sedation and EEG changes similar to sedative drugs. Kava affects the limbic structures of the brain, especially the amygdalar complex. Acting on these centers induces sleep without sedation.[14,15]

Research

A four-week randomized, double blind placebo controlled trial looked at adults with some form of anxiety and insomnia. Subjects received either 200mg of a kava extract standardized to 70% kava lactones, or a placebo. The quality of sleep scores improved significantly in the kava group, and a sense of recuperation the next day actually improved significantly over placebo. Kava was also shown to be well-tolerated with no serious adverse events. From the study, researchers determined that in addition to its documented anxiolytic effects, kava extract is particularly effective in alleviating anxiety-related sleep disturbances.[16]

A pilot crossover trial looked at the effects of kava on 24 individuals with stress-induced insomnia. The mean duration of symptoms was 14.6 years and patients taking other psychotropic drugs were excluded. The trial lasted for six weeks followed by a two-week washout period. After this time, subjects received six weeks of valerian. The sleep disturbance parameters for the study included time to fall asleep, hours slept and mood on final waking. During the first six weeks of kava treatment, the mean total stress severity score fell from 178.1 to 126.7. The initial mean insomnia score was 138.0, falling to 107.1 after six weeks of kava intake. During the trial, no serious adverse events were reported.[17]

Safety

Human studies using kava at therapeutic dosages have failed to demonstrate any toxic effects. There are reports of possible skin irritation, but only at chronically high dosages over extended periods of time. The FDA advises that a potential risk of rare, but severe, liver injury may be associated with kava. Thus, kava should not be taken by people that have, or have had liver problems, drink alcohol, or take any medications. It is also recommended that children and pregnant and breastfeeding women not take kava.[18]

Dosing

Kava can be administered in capsule, dried rhizome, or tincture form.

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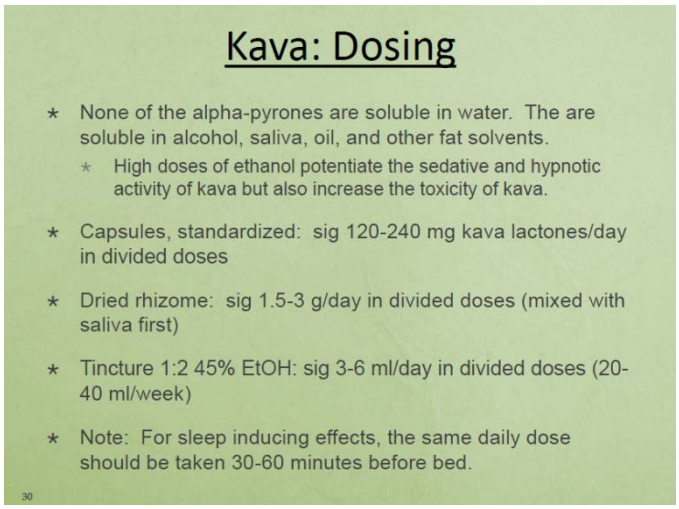
[14] Holm E. Arzneimittelforschung. 1991 Jul;41(7):673-83.
[15] Davies L. Pharmacol Toxicol. 1992 Aug;71(2):120-6.
[16] Lehrl S. J Affect Disord. 2004;78(2):101-10
[17] Wheatley D. Phytotherapy Res. 2001;15:549-551.
[18] Shimoda LM, et al. Phytother Res. 2012;26(12):1934-41



Passionflower

A member of the Passifloraceae family, the leaves of passionflower serve as anti-spasmodic, sedative, hypnotic, hypotensive, anodyne, anti-depressant, and nervine relaxants. Its constituents are the flavonoids. Passiflora has been demonstrated to cause allosteric modulation of GABA-A receptor complex via interaction at the benzodiazepine site.[19]

Indications

Passiflora is well-indicated in states of nervous tension and anxiety (nervous restlessness), overwork, and anxiety. It has anti-spasmodic effects on smooth muscles, making it beneficial for anxiety induced intestinal spasm (diarrhea), vascular constriction (hypertension), and

[19] Nassiri-Asl M. et al. Zhong Xi Yi Jie He XueBao. 2008;6:1170-3.

bronchial constriction (asthmatic wheezing). Especially useful for insomnia accompanied with or due to excessive muscular tension and spasm, passiflora acts as a spasmolytic, sedative, and anodyne. On its own, passiflora acts slowly and gently, therefore, it might be best combined with other herbs.

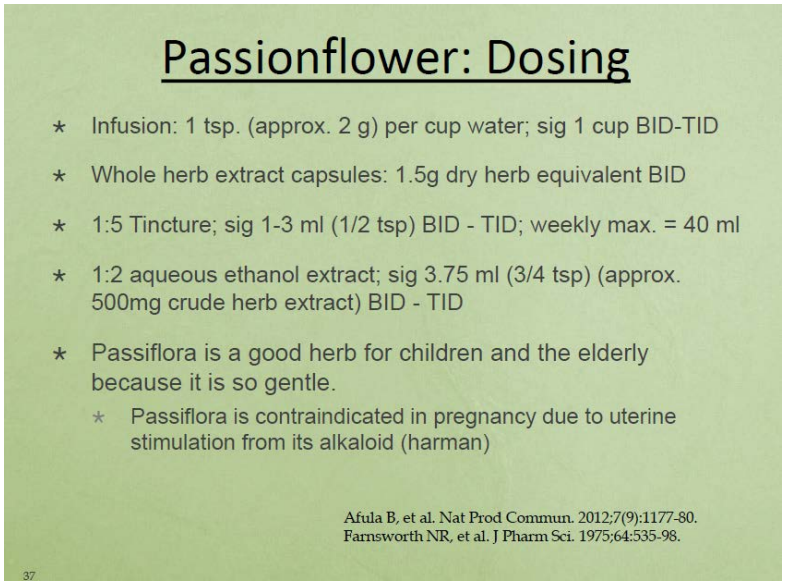
Research

Passionflower's strengths as a synergistic plant are documented by research, but the effects of passionflower can also be seen when the herb is administered on its own. A double blind randomized placebo controlled trial looked at the sleeping patterns in 41 healthy volunteers. Participants were given passionflower tea, kept a sleep diary, and measured their anxiety. In the end, sleep quality was significantly improved in the passionflower group when compared to the placebo; however, no differences in sleep duration or specific parameters of sleep quality were noted.[20]

Another study looked at the effects of passionflower when it was combined with hops and valerian. This herbal regimen was compared to Ambien. The study revealed that the combination resulted in specific and significant improvement in total sleep time for participants.[21]

Dosing

Passionflower can be administered as an infusion, in capsule form or as an extract.



[20] Ngan A. and Conduit R. Phytotherapy Res. 2011;25:1153-59
[21] Maroo N. et al. Indian J Pharmacology. 2013;45(1):34-39.

Valerian

A member of the Valerianaceae family, valerian is well-indicated in individuals with restlessness and insomnia. Valerian has sedative, hypnotic, nervine, hypotensive, and carminative effects. It helps improve quality of sleep, reduce the time it takes to fall asleep, and will not cause somnolence in the morning, nor will it affect dream recall.[22, 23]

Valerian's constituents are the volatile oils, iridoids and alkaloids. The volatile oils, particularly valerenic acid, bind to GABA-A receptors leading to the release of aminobutyric acid, which in turn inhibits the release of other neurotransmitters.

Research

A comprehensive review looked at all the randomized clinical trials published between 1950 and 2009 on valerian and/or hops and sleep. During this timeframe, 16 studies met inclusion criteria and 12 of those studies revealed that valerian, on its own, or in combination with hops, is associated with improvements in sleep latency and quality of sleep. The most commonly studied doses were 300mg, 450mg, 600mg and 900mg. However, methodological problems of studies included in this review weaken the conclusions of these findings and their application to clinical practice.[24]

A phase III randomized trial looked at 227 patients with cancer who were undergoing cancer treatment. Subjects received valerian raw root. Researchers evaluated the subjects' sleep and found that while there was no significant improvement in overall sleep quality, there were improvements in secondary fatigue outcomes as measured by both the Brief Fatigue Inventory

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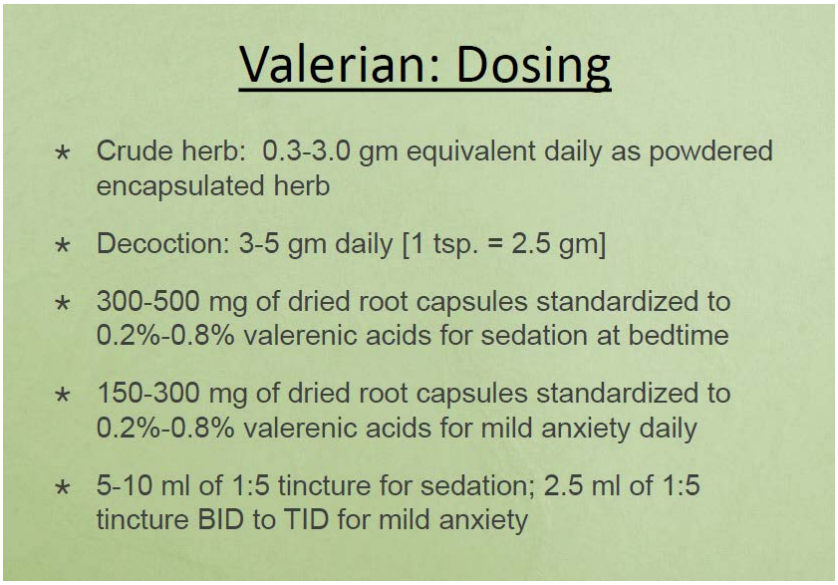
[22] Leathwood P.D., Chauffard F, J Psychiatr Res, 1983;17(2):115.
[23] Leathwood P.D., et al., Pharmacol Biochem Behav, 1982;17:65.
[24] Brownie S. Australian Fam Phys. 2010;39(6):433-437

and the Profile of Mood States fatigue-inertia subscale. No serious toxicities were reported during the study.[25]

Dosing

Valerian can be administered in a variety of ways, including tinctures and capsules.



Magnolia

A member of the Magnoliaceae family, magnolia has numerous medicinal actions. The herb allosterically modulates GABA-A, reduces cortisol secretion from adrenal glands, and enhances acetycholine release. Its constituents are the biphenolic compounds including honokiol and magnolol, other biphenolics, alkaloids, and flavonoid glycosides.

Research

A 24-week multicenter randomized controlled trial looked at 89 women with a mean age of 53.8 years who had been menopausal for 56.6 months, with sleep or mood alterations. Subjects in one group received one tablet per day of a formula containing soy isoflavones, Lactobacillus sporogenesm, magnolia bark extract, magnesium, calcium and vitamin D3. Another group was given calcium and vitamin D3. The clinical outcome of the study showed that isoflavones+ magnolia bark extract and magnesium are significantly effective in relieving

[25] Barton D. et al. J Support Oncol. 2011;9(1):24-31.

not only the typical menopausal symptoms such as hot flushing and night sweating, but also the concomitant mild psychoaffective alterations such as sleep disturbance and anxiety.[26]

Dosing

A dosage of 250mg to 1000mg of Magnolia officinalis bark can be administered to aid in sleep disorders.

Ashwagandha

Ashwagandha, or withania somnifera, is an adaptogen. A member of the Solanaceae family, ashwagandha is particularly useful when people are exhausted or debilitated. But unlike fast-acting herbs such as valerian, ashwaganda typically takes several weeks or even a month to improve sleep habits.

This herb's constituents are the alkaloids, steroidal lactones, and saponins. Ashwagandha has hypotensive, bradycardic, spasmolytic, anti-tumor, immunomodulating, anti-inflammatory, adaptogenic, and sedative effects.

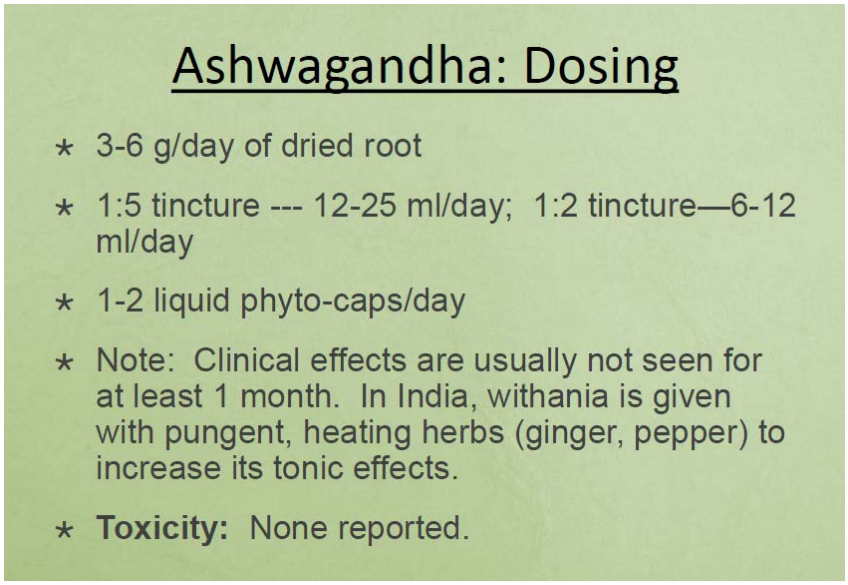
[26] Mucci M. et al. Minerva Ginecol. 2006;58:323-34

Research

A double-blind, placebo-controlled study evaluated the efficacy of an ethanolic extract of ashwagandha in 39 patients with ICD-10 anxiety disorders. At 6 weeks, significantly more patients met a priori response criteria in the drug group (88.2%) as compared with the placebo group (50%). The drug was well-tolerated and did not result in more adverse effects than did placebo.[27]

Dosing

Ashwagandha can be given as a tincture, tea or in liquid phyto-cap form.



[27] Andrade C, et al. Indian J Psychiatry. 2000;42(3):295-301.

Conclusion

Botanicals offer a well-tolerated, low toxicity option for improving sleep quality. But the effects of these herbs may not be evident until after several weeks of use. Informing patients of this will ensure that the proper treatment plan is followed through. It is also important to remember that most sedative herbs work best in combination. When used correctly, a well-designed herbal regimen can help patients achieve necessary relief from sleep issues like insomnia.

Contributor

Lise Alschuler is a naturopathic doctor with board certification in naturopathic oncology and has been a practicing since 1994. She graduated from Brown University with an undergraduate degree in Medical Anthropology and received a doctoral degree in naturopathic medicine from Bastyr University. Dr. Alschuler is past-President of the American Association of Naturopathic Physicians and a founding and current board member of the Oncology Association of Naturopathic Physicians. She also currently serves as President Emeritus on the board of the Naturopathic Post-Graduate Association. Dr. Alschuler works as an independent consultant in the area of practitioner and consumer health education. She also oversees the Quality Program for one of the largest nutritional supplement distributors in the U.S. She maintains a naturopathic oncology part-time practice out of Naturopathic Specialists, based in Scottsdale AZ. Previously, she was the department head of naturopathic medicine at Midwestern Regional Medical Center – Cancer Treatment Centers of America. She was also the clinic medical director and botanical medicine chair at Bastyr, as well she was on the faculty of Southwest College.

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