The Role of Adrenal Dysregulation in Insomnia and Anxiety

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Introduction

Anxiety disorders can manifest differently in women and can worsen premenstrually, postpartum and in the perimenopausal transition. Insomnia is pandemic in midlife women, although the cause remains unexplained within the scientific community.

This report will examine both evidence-based and traditional approaches to using select botanicals with particular attention to the influence of cortisol on sleep disturbance. It will also discuss the influence of hormonal states on insomnia and anxiety.

Anxiety Disorders

Anxiety disorders can be classified in several different categories including:

- Generalized anxiety disorder
- Panic disorder
- Obsessive compulsive disorder
- Social phobia
- Specific phobias
- Anxiety during pregnancy

General anxiety disorder (GAD)

By far the most commonly found in patients, general anxiety disorder (GAD) is twice more likely to occur in women than in men. Limited data suggests that anxiety symptoms can actually worsen premenstrually and postpartum. In addition, general anxiety disorders in women are often accompanied by some type of comorbid psychiatric disorder.

GAD is a chronic disorder, with episodic exacerbations. Symptoms tend to worsen during times of stress, often leading to acute panic disorder, which tends to improve when stress abates. General anxiety disorder is also more commonly found in single women, racial or ethnic minorities and people with lower socioeconomic status.
Anxiety – Natural treatment strategy

Acute episodes

When it comes to treating anxiety, it is important to have a number of different strategies that will benefit the patient. Patients with generalized anxiety disorder often have acute flare-ups, episodes or panic attacks. These types of acute issues are best treated with prescription medication since herbs are not fast acting enough to offer immediate relief. Having a well-developed plan in place surrounding these therapies is crucial.

Chronic episodes

In treating chronic anxiety, it is important to look for any underlying cause or association and support the patient’s ability to adapt to stress so that their tipping point is higher. Daily intervention should be given to help decrease the frequency and severity of acute episodes and improve day-to-day comfort.

Insomnia

Disruptions in sleep are a common development in the aging process. Adults who are 50 years and older commonly experience disturbed sleep. Prolonged sleep latency can be found in more than half of adults aged 50 and older. These issues typically manifest in frequent nighttime awakenings and/or early morning awakenings, followed by an inability to return to sleep. And with approximately 61% of postmenopausal women reporting sleep problems, finding the correct treatment plan can be crucial.

Finding the cause

Tests and examination of patient history can help pinpoint the primary source of a patient’s chronic insomnia. Some causes or suspects of insomnia might include:

- Hormonal states
- Habits (such as caffeine or alcohol use and diet)
- Poor sleep hygiene
- Anxiety
- Depression
- Medications
- Acute or chronic pain
- Sleep apnea
- Restless leg syndrome
By determining the cause of insomnia, a more successful treatment plan can be established. For example, if a patient is suffering from restless leg syndrome, unless that problem is addressed it will be impossible to adequately treat their insomnia. Diet and other factors such as caffeine use can have an effect on insomnia since some people are hyper sensitive to the drug. Taking away even a minuscule amount of caffeine can often vastly improve a patient’s insomnia.

Often, the presence of insomnia can be the result of something simple such as nighttime hypoglycemia, a condition that occurs when the brain is starved of glucose, thus resulting in sleeplessness. These types of issues can be determined by evaluating a patient’s blood sugar during the day. For example, if a patient says she can’t go without eating more than two hours without feeling discomfort, this is likely the cause of her insomnia.

Sleep apnea can also lead to insomnia. This is primarily found in patients who are overweight. Premenstrual and perimenopausal symptoms can cause insomnia and should be treated accordingly. Simply prescribing melatonin, valerian or hops to a patient will not fully address these issues; only when the true cause for sleeplessness is addressed can insomnia be treated.

**Sleep problems specific to women**

There are a number of sleep issues that are specific to women. Some of these might include:

- Menstrual cycle
- Pregnancy
- Postpartum
- Perimenopause/menopause
- Stress/anxiety/depression
- Sleep apnea

**Adrenal dysregulation**

Adrenal dysregulation refers to a dysregulation or dysfunction in the normal circadian rhythm of cortisol secretion. This circadian rhythm has a waveform pattern, with the nadir for cortisol occurring at about midnight and rising about two to three hours after a person falls asleep. It continues to rise into the early morning and early waking hours. Peak is around 9 a.m. As the day continues, there is a gradual decline in these levels.
Throughout this cycle, there are pulsatile secretions of cortisol with various different amplitudes. The initiation of sleep occurs concurrently with a low hypothalamic-pituitary axis activation. In fact, sleep deprivation is associated with HPA activation. Nighttime awakenings are associated with pulsatile cortisol release, which is followed by a temporary inhibition of cortisol secretion.

Dysfunction of hypothalamic-pituitary axis can play a role in some sleep disorders. In other cases, HPA axis dysfunction may actually be a result of this sleep disorder, particularly with obstructive sleep apnea. HPA axis hyperactivity can lead to fragmentation of sleep, decreased slow-wave sleep and an overall shortened sleep time. In other words, sleep problems create hypothalamic-pituitary-adrenal axis problems, and HPA axis problems create sleep problems. Both insomnia and obstructive sleep apnea are particular sleep disorders associated with HPA axis dysfunction.

Interventions to normalize HPA axis abnormality, and decrease nighttime corticotropin releasing hormone hyperactivity and cortisol can be very beneficial in treating insomnia. The goal should be to treat the hypothalamic-pituitary-adrenal loop to decrease cortisol at night.

**Nutraceuticals**

When utilized correctly, nutraceuticals can help manage dysfunctional cortisol production and possibly even elevated nighttime cortisol. Some of the key nutraceuticals include:

- Vitamin B6
- Pantothenic acid
- Vitamin C
- L-tyrosine, L-theanine
• Calcium, magnesium
• Potassium, manganese, zinc

Vitamin B6, pantothenic acid and vitamin C often become depleted when the demands of the adrenal gland/cortisol production are continuous. An abnormal adrenal response, whether it is deficit or excess, can often be addressed with these key nutrients. Interestingly, during times of stress these very nutrients can be diminished, calling for an even greater need for supplementation. For example, vitamin C is excreted through the urine at a greater rate during increased stress. A deficiency of pantothenic acid results in fatigue, headaches, insomnia and other issues. Tyrosine and L-theanine can support the adrenal glands by combating fatigue and anxiety related to stress.

Cortisol feedback control mechanisms are often dependent on adequate amounts of calcium, magnesium, potassium, manganese and zinc; therefore, using these plants and nutraceuticals in conjunction can be a key factor in success. 1, 2, 3

**Anxiety botanicals**

There are numerous herbs that can be used to treat anxiety, but perhaps the most effective herbs include:

• Magnolia (Magnolia officinalis)
• Ashwagandha (Withania somnifera)
• Kava (Piper methysticum)
• Lavender
• Magnolia (Magnolia officinalis)

**Clinical studies**

**Magnolia**

A recent, randomized parallel placebo-controlled study was conducted looking at this plant. The subjects of the study were overweight, premenopausal women who had an anxiety disorder. In the end, a decrease in transitory anxiety was shown when patients took magnolia.

1 Endoc Res 2004;30:871-875
2 Adv Nurse Pract 2006;14:47-8,82
3 Metabolism 2006;55:243-251
Interestingly, this was accomplished even though salivary cortisol levels were not significantly reduced. Improvement in mood, a greater sense of relaxation and more restful sleep were also noted with magnolia users.\textsuperscript{4, 5}

**Magnolia and phellodendron**

A clinic in Ohio conducted an unpublished study using a proprietary blend of magnolia and phellodendron. Researchers found this combination helped normalize some cortisol levels related to stress-induced obesity. This combination lowered cortisol levels by 37\% and increased DHEA by 227\%.

**Adaptogens**

A category of plants known as adaptogens have been historically shown to increase the body’s ability to adapt to stress, thus diminishing symptoms that can result from chronic stress, like fatigue, immune system problems, anxiety disorders, insomnia or irregular menses. Three of the most well-known adaptogens are rhodiola rosea, schisandra chinensis and withania somnifera.\textsuperscript{6}

**Rhodiola rosea**

The rhizome of the plant is utilized in botanical medicines. This adaptogen is a member of the Crassulaceae family. It is cooling, dry and tastes spicy and bitter. It enhances resistance to

\textsuperscript{5} J Pharm Pharmacol 1998;50:819-826.
high altitude sickness and helps in the treatment of anemia. It is also a fertility enhancer and protects against the effects of stress, hypoxia, extreme temperatures and intense physical activity.

This adaptogen increases memory, endurance and productivity. It also improves mental capacity, accuracy and helps with male sexual erectile dysfunction. It can be used to help treat anemia in pregnancy, as well as insomnia and sleep disturbances.

**Schisandra chinensis**

The fruit and seed of schisandra are the most common part of the plant used. A member of the Schisandraceae family, this adaptogen is warming, dry and can taste sour, sweet, bitter, salty or pungent. It has been shown to increase mental performance, physical endurance and the overall ability of the body to adapt to and resist the effects of stress. Schisandra has been shown to induce Phase I and Phase II enzymes.

The curative effect of Schisandra preparations is pronounced in cases of asthenic and depressive syndromes. The combination of Schisandra therapy with tranquilizers or anti-
Depressants has been shown to eliminate the side effects of these drugs and allows them to be employed at optimal doses.\textsuperscript{7, 8, 9}

**Ashwagandha (Withania somnifera)**

Ashwagandha or withania somnifera makes an excellent tonic. In fact, the word somnifera actually means “sleepmaking.” It is an amphoteric, anti-inflammatory, anti-oxidant, anti-anemic, anti-tumor and hypoglycemic agent. It is also immune supportive, and regulates HPA axis. There are not many documented side effects from ashwagandha use. In general, it has an excellent safety profile and is fairly well-tolerated in most people.

**Clinical trials**

Clinical trials and animal research support the use of ashwagandha for anxiety, cognitive and neurological disorders, inflammation and Parkinson's disease. It has chemopreventive properties that make it useful for patients undergoing radiation and chemotherapy. It can be used to treat nervous exhaustion and debility due to stress, and as an immune stimulant in patients with low white blood cell counts.\textsuperscript{10}

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\textsuperscript{7} Panossian A and Wikman G, Effects of Adaptogens on the Central Nervous System and Molecular Mechanisms Associated with Their Stress—Protective

\textsuperscript{8} Activity, Pharmaceuticals 2010, 3,188-224; doi:10.3390/ph3010188

A number of clinical trials have been conducted on withania, particularly looking at the standardized extract, also referred to as WSE. One study looked at three different doses of standardized extract (125mg QD, 125mg BID, and 250mg BID), and revealed that through these different doses, cortisol levels could be reduced along with CRP (one of the inflammatory consequences of stress). An increase in DHEA was also shown. Participants reported reduced feelings of stress and anxiety, and pulse and blood rates were also reduced. 11, 12, 13

Another study showed that ashwagandha use lead to a 35% decrease in fatigue and a 75% decrease in insomnia in subjects who were given the herb versus those who were given a placebo. Improvement in appetite was also noted in the ashwagandha group.

**Kava (Piper methysticum)**

Kava has many uses. Historical uses include: analgesia, antipsychotic, anorexia, seizures, depression, PMS, PMDD, URI, jet lag, seizures, UTI, dyspepsia and pain.

Constituents of kava include pyrones, lactones, flavonoids and alkaloids. The pyrones found in kava have been noted for their anticonvulsant, spasmylytic and antimycotic effects. Hypnotic analgesic and local anesthetic effects can also be attributed to the pyrones, as can neuroprotective effects. These effects were examined in neurological deficits after cerebral infarcs in animal studies. Results of these studies can be attributed to the ability of pyrones to

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11 Biswajit Auddy, PhD1 et al; A Standardized Withania Somnifera Extract
12 Significantly Reduces Stress-Related Parameters in Chronically Stressed Humans
13 A Double-Blind, Randomized, Placebo-Controlled Study JANA Vol.11, No.1, 2008
serve as calcium channel agonists or sodium channel blockers. In these studies, monoamine oxidase was shown to be inhibited as was the uptake of norepinephrine.

Kava is believed to act selectively on limbic structures, promoting anxiolysis without sedation. When dosed high, it can have sedative effects; however, standard doses do not typically produce this type of sedating effect. Interactions with glutamate, dopamine, NE and serotonin receptors have also been noted.

Clinical trials

Kava and menopause

There have been four randomized control trials on kava in menopausal women. The first study compared kava to a placebo. The trial ran for 12 weeks. Significant improvements in the Cooperman Index (a menopause symptom rating scale) were shown in the kava group.14

The results of a second trial which compared kava to a placebo, produced significant improvement in the Cooperman Index and the Hamilton Anxiety and Depression Status Index of subjects. The trial ran for eight weeks.15

A third study looked at women who took hormones. A combination of kava and hormones was shown to produce the greatest reduction in anxiety and depression versus the hormones alone.16

A forth study compared three groups of subjects. The first group was given 1g of calcium and 100mg of kava, the second was given 1g of calcium and 200mg of kava and the last group

14 Warnecke. Zeitschrift Phytotherapie 1990;11
15 Warnecke. Fortschr Med 1991;4
16 De Leo. Minerva Ginecol 2000;52
was given only calcium. The groups with calcium and kava showed a rapid decline in anxiety within the first month of treatment.17

**Dosages**

Typical usage can range from 70-280mg kavalactones as a single dose or in divided doses. Doses of kava that exceed 280mg have been shown to cause hepatotoxicity issues. Because of this, dosages should be given in doses no greater than 280mg.

**Lavender**

Lavender has been used botanically for a long time, but this herb has gained a lot of attention in the last few years. Perhaps the most popular use of lavender is in its essential oil form. This oil is obtained from steam distillation of the flowering tops of L. angustifolia. Lavender oil contains more than 160 constituents. Of these 160, the main active constituents are linalool, linalyl acetate, terpinen-4-ol and camphor. Other constituents found in lavender include: cis-ocimene; terpinen-4-ol, β-caryophyllene; lavandulyl acetate; 1,8-cineole; and small amounts of limonene, geraniol, lavandulol, β-pinene, camphene, geranyl acetate and neryl acetate.18, 19

**Lavender oil**

There are multiple possible mechanisms of action of lavender oil that have to do with an individual constituent or a synergistic dynamic of the constituents. The oil has potentiated

17 Cagnacci et al. Maturitas 2003;44: 103-109
expression of GABA-A receptors in vitro, and it has shown some spasmolytic activity on guinea pig ileums. Linalool, a main active ingredient of lavender oil, has been shown to inhibit glutamate binding in the brain of animals. It has also been shown to inhibit acetylcholine release and influenced ionic conductance in neurons. Linalyl acetate is described as exerting a relaxing effect. Finally, lavender oil has been shown to reduce dose-dependently spontaneous motility and caffeine-induced hyperactivity in mice. 20, 21, 22, 24, 25

Aromatherapy

Aromatherapy is one of the earliest uses of this herb. The anxiolytic activity of lavender olfaction has been demonstrated in several small and medium-sized clinical trials. The efficacy of aromatherapy of lavender is thought to be due to the psychological effects of the fragrance combined with physiological effects of volatile oils in the limbic system. It has been shown to decrease anxiety, as measured by the Hamilton rating scale, and can increase mood scores. 26, 28, 29, 30, 31, 32, 33, 34, 35

Clinical studies

Lavender and anxiety

A RDBPCT looked at the effects of lavender capsules on 97 healthy individuals. Subjects were given two different doses of lavender (100mL and 200mL) and were shown film clips to induce anxiety. Ultimately, researchers concluded that lavender had anxiolytic effects under

26 Nurs Times 1993;89:32–35.
28 Lancet 1995;346:701

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low stimulations of anxiety, but they were unable to draw conclusions about high anxiety, or even actual clinical disorders.36

**Lavender oil extract in patients with Generalized Anxiety Disorder (GAD)**

A multi-center, randomized, double-blind clinical trial compared the effects of lavender oil extract (80mg daily) to lorazepam. The trial ran for six weeks and was comprised of 77 subjects. The Hamilton Anxiety Score decreased by 45% in the lavender group and by 46% in the lorazepam group. At the end the six weeks, about 40% of subjects in the lavender group were in remission versus 27% in the lorazepam group. This 10% improvement in responder rate in the lavender group demonstrated that more subjects responded to the lavender than did the lorazepam.37

**Lavender oil improves anxiety and QOL**

A randomized, double-blind, placebo-controlled, multi-center study comprised of 221 individuals ran for 10 weeks. Clear anxiolytic effects were shown after two weeks. Improvement of sleep disturbances were shown between weeks four and six.38

**Insomnia botanicals**

Botanicals can clearly have a positive effect on anxiety. Similarly, there a number of botanicals that can be used to treat insomnia. Two of the most prevalent include valerian and hops.

**Valerian**

Preliminary data from several human trials suggests that valerian improves almost all of the subjective measures of sleep, including sleep quality and latency. It has also been shown to help with anxiety, panic disorder and sedation. It has been suggested that valerian may have more cumulative and progressive effects over four weeks than an acute effect.

Mechanisms of action

Studies on valerian typically have problems with methodologies and have not been confirmed in objective sleep labs. Despite this fact, the benefits of using valerian are apparent from historical evidence. There are at least 150 compounds in valerian. The major constituents of valerian include valepotriates (valtrate, volatile oils, valerenal, valeranone and valerenic acid); lignans and alkaloids. One of the most characteristic features of valerian is a strong odor, and that strong odor is likely generated by one of the constituents called isovaleric acid. The essential oils and flavonoids of valerian root appear to provide sedative and anxiolytic properties. Valepotriates have been shown to regulate the autonomic nervous system. Some evidence suggests that some of the components of valerian can interact with GABA receptors and thereby produce calming effects. Further, some research indicates that valerian produces a type of dose-dependent GABA release, inhibiting the breakdown of GABA in the brain.  

40 Herbal Medicine. 2000;262-263.
Clinical studies

Valerian

A study compared the effects of 600mg of valerian extract to 10mg of a benzodiazepine over a six week period. Subjects had reported insomnia for at least three and a half months. Ultimately, there were no differences noted between the two groups, demonstrating equal efficacy when comparing the botanical to the pharmaceutical.47

Another study looked at the effects of valerian versus a placebo. The study was comprised of 121 patients with insomnia. At the 14 day mark, no significant effects were shown, but at 28 days statistically significant effects were shown, reinforcing that in order to be most effective, valerian must be taken for at least a month.48

A third study compared the effects of valerian versus benzodiazepine in 75 older women. For 28 days, subjects were given a valerian extract of 600mg a day or 10mg of oxazepam. Improvements in sleep quality were shown in both groups with no significant difference between the two.49

Valerian combination

A study looked at the effects of a valerian and hops combination. Despite the fact that both of these botanicals have significant effects on sleep quality, no clear results showed using a combination of the two plants had any additional impact on sleep. Sleep latency improved by 37% in the valerian only group, by 31% in the combination product, and by 23% in the placebo group. In regard to sleep quality, 43% of the patients who received valerian alone improved versus only 25% in the placebo group and no significant improvement in the combination group.50

A combination of valerian and lemon balm showed different results. The first group was given 400mg of valerian, 160mg of lemon balm and 375mg of hops. A second group (the control group) was given a combination product with insignificant amounts of valerian, 160mg of lemon balm and 375mg of hops. Sleep quality was clearly better in 78% of patients from the first group and only 11% better for those in the control group.51

Valerian and menopausal women

A recent study on valerian was conducted on postmenopausal women between the ages of 50 and 60 years. The first group of subjects were given 530mg of valerian concentrate extract twice a day. The second group was given a placebo for four weeks. Overall, 30% of the women taking the valerian and only 4% taking the placebo reported improvement in their sleep quality.52

Dosages and cautions

Valerian can be given as an extract in 300 to 500mg doses. In dried root form, valerian can be given in 2 to 3g doses. Side effects include mild GI upset and occasional drowsiness. European monographs list no contraindications to use during pregnancy or lactation; however, the World Health Organization recommends its avoidance in pregnancy. Caution should be advised regarding concomitant use with benzodiazepines.

Hops

Hops is rich in several flavonoids. The high number of prenylated derivatives might account for the bitter flavor. The flavonoids appear to be a key to the mechanism of action for hops. These flavonoids can actually bind to estrogen receptors.

52 Menopause 2011; 18(9): 951-955.
**Clinical studies**

A study looked at hops and valerian both given in 300mg dosages. This combination did not yield a sedative effect that was different from placebo. Mild slowing of complex thoughts were shown after one hour.\(^5\)

A second DBCT comprised of 12 patients looked specifically at a placebo and 4 capsules of 60mg valerian plus 100mg hops in each capsule at bedtime. The study showed a trend for the valerian/hops combination to facilitate sleep versus the placebo, but the results were not statistically significant.\(^5\)

A third RDBT looked at the effects of a combination of hops and valerian. The 46 subjects in the trial were given either 200mg of hops extract plus 45.5mg of valerian per cap at 2 caps per day, or benzodiazepines. After 2 weeks, statistical improvement occurred similarly in both groups.\(^5\)

A fourth trial containing 128 individuals compared a hops/valerian combination (100mg hops + 200mg valerian) with a 200mg valerian only capsule versus placebo. Sleep latency improved in 37% of the valerian group, 31% of the combination group, and only 23% in the placebo group. As far as sleep quality, 43% of the valerian only group reported improvement compared to only 25% for placebo.\(^5\)

**Dosages**

Hops can be given in the following dosages:

- 300mg-400mg of hops extract
- 0.5 to 1g dried extract three times a day
- 0.5 to 1mL of liquid extract (1:1) three times a day

**Conclusion**

Anxiety is an issue that affects men and women alike. But with general anxiety disorders being found twice as often in women as men, the question of how to establish the best treatment option becomes crucial. Insomnia has similar detrimental effects on the body. Pregnancy, postpartum, perimenopause or menopause, stress/anxiety/depression and sleep

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\(^5\) Schweiz Rundsch Med Prax 1996

\(^5\) Med Klin 1977;72(25)

\(^5\) Wien Med Wochenshr 1998;148(13)

\(^5\) Pharmacol Biochem Behav 1982;17(1)
apnea can severely impact sleep quality. Knowing how to treat these issues with botanical medicines can be incredibly beneficial to the patient. Often, the botanicals themselves are enough to help address the problem, but they can often be used in conjunction with more common pharmaceuticals to address immediate and long-term needs for a patient. Understanding the benefits and shortfalls of these various botanicals will allow for a better sustained and effective treatment plan for patients suffering from either anxiety or insomnia.

**Contributor**

Dr. Tori Hudson graduated from the National College of Naturopathic Medicine in 1984, and has since served at the college in several capacities. She’s been the medical director, associate academic dean, and academic dean. Dr. Hudson is currently a clinical professor at the National College, Bastyr, and Southwest College of Naturopathic Medicine.

Dr. Hudson has over 28 years of experience and expertise in women’s health. She uses nutrition, nutraceuticals, botanical medicines, bioidentical hormones, and other therapies to treat all different types of gynecological and primary care conditions seen in women. She serves as director of her own clinic, A Woman’s Time, in Portland, Oregon, and is also the program director for the Institute of Women’s Health in Integrative Medicine, as well as the director of research and development and education for Vitanica. Dr. Hudson serves on the Scientific Advisory Board of Gaia Herbs Professional Solutions.