

Understanding the Potential Use of Herbs in Restless Legs Syndrome

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Introduction

Restless legs syndrome (RLS) is a neurological sensorimotor disorder and has four defining criteria, as established by the International Restless Legs Syndrome Study Group: 1) an urge to move the legs, typically associated with unpleasant sensations in the legs (the arms and other body parts can sometimes be involved); 2) this urge to move and the associated sensations start or are worsened during rest; 3) the urge and sensations are ameliorated by movement; 4) these symptoms are worse or only happen in the evening or at night. Additional clinical features may include a family history of RLS, response to dopaminergic therapy, and periodic limb movements (Merlino et al 2007b).

Epidemiology

In a review of studies from various countries, it has been shown that RLS prevalence is widespread, affecting many people worldwide (Table 1) (Merlino et al.

2007b). The prevalence of RLS increases with age in both men and women up to age 79 years when it then declines, although levels are still significant (Allen et al. 2005). In one study, the age of onset was between 18.8 and 43.6 years (Winkelmann et al. 2006). There is some evidence that most cases present between ages 20-29 years, although this study did not include people under age 18 years (Allen et al. 2005). According to a population survey study conducted in the United Kingdom and the United States, RLS can occur in childhood (Picchiatti et al. 2007). The authors found that 1.9% of 8-11 year-olds and 2% of 12-17 year-olds surveyed experienced RLS symptoms, with moderate to severe symptoms (those occurring two or more times a week) present in 0.5%-1.0% of children. In the 8-11 year-old group 15% reported symptoms first appearing before age 5, 63% between the ages of 5-7, and 22% after the age of 8. Another study reported that 12%-20% of people surveyed experienced onset of symptoms before age 10, and 25% between the ages of 11-20 (Walters et al. 1996). Women are twice as likely to suffer from RLS as men (Allen et al. 2005). In studies on Swedish populations, the prevalence for women suffering from RLS was 11.4% (Ulfberg et al. 2001b), and for men was 5.8% (Ulfberg et al. 2001a).

RLS can be divided into (idiopathic) primary RLS and secondary RLS. Idiopathic RLS accounts for 70-80% of cases, and is mainly associated with a family history of the disorder. (Merlino et al. 2007b). Several loci have been identified in families with RLS. In a study of French Canadian families with RLS, an autosomal-dominant locus on chromosome 16p12.1 was found to be associated with this disorder (Levchenko et al. 2009). Other chromosomes reported to be involved are 12q13-



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Table 1: Prevalence of RLS in selected countries (Merlino et al. 2007b)

Country	Prevalence in Population Studied (%)
Chile	13
Norway, Denmark	11.5
Italy	10.6
United States	9.7-15.3
Germany	9.8-10.6
France	8.5
Turkey	3.19
South America	2
Singapore	0.1

23, 14q13-21, 9p24-22, 20p13, and 2q33 (Levchenko et al. 2006, Levchenko et al. 2009, Winkelmann et al. 2006). Symptoms of idiopathic RLS usually have an early onset (before the age of 45 years) and have a mild, slow progression (Merlino et al. 2007b). As indicated by its name, idiopathic RLS has no discernable factors contributing to its development. To date, no studies have been found in the literature that indicate any stressors or behavioral inputs such as exercise or sleep exacerbate or induce idiopathic RLS. This is an area in which more research needs to be conducted.

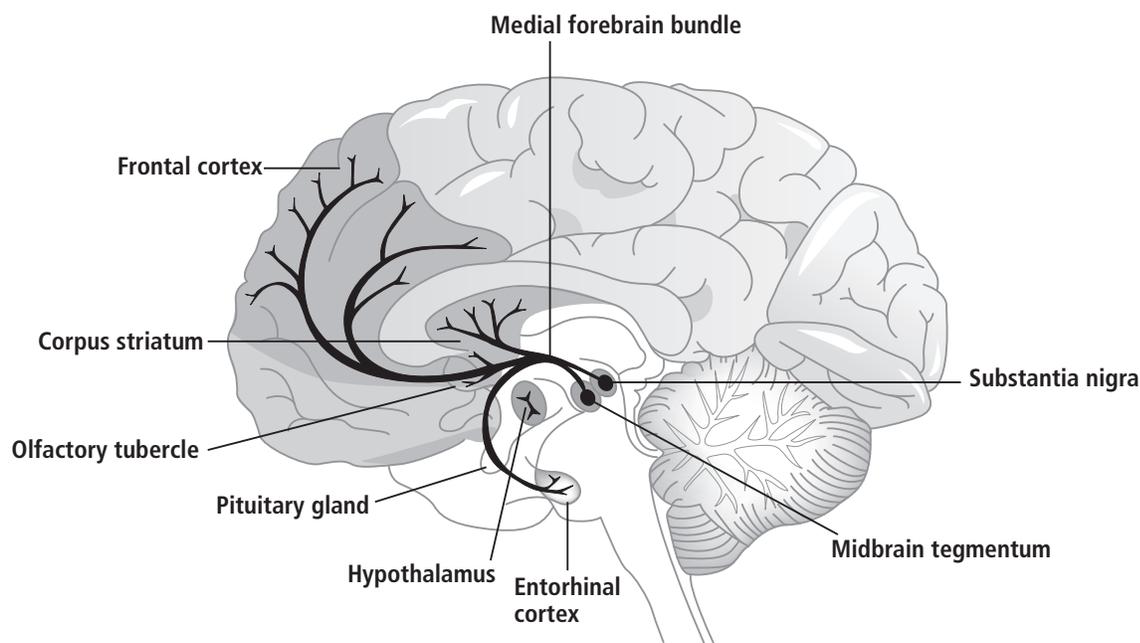
Secondary RLS accounts for about 26% of known cases, and occurs secondary to conditions such as iron deficiency, uremia, pregnancy, Parkinson's disease, type 2 diabetes mellitus, and liver disease (Franco et al. 2008, Merlino et al. 2007b). Two studies found the prevalence of RLS in dialysis patients to be between 21-32%, although they did not differentiate between pre-existing RLS and that which developed after kidney failure (Collado-Seidel et al. 1998, Gigli et al. 2004). The prevalence in pregnant women was found to be between 11 and 27% of women evaluated, depending on the study. Symptoms usually began or became worse in the third trimester and resolved after birth of the baby. Those with RLS prior to becoming pregnant reported a similar pattern of symptoms (Hensley 2009, Manconi et al. 2004a, Manconi et al. 2004b). Concerning Parkinson's disease, one study found 20.8% of these

patients also had RLS, of which only 5.3% had been diagnosed prior to the onset of Parkinson's (Ondo et al. 2002). In another study, 7.9% of patients with Parkinson's disease had RLS, the symptoms of which started after the Parkinson's diagnosis (Krishnan et al. 2003). There is a general absence of studies addressing the reasons why RLS develops in these populations.

Pathophysiology

The pathophysiology of restless legs syndrome is unclear at best (Ćervenka et al. 2006, Godau et al. 2008, Reimold et al. 2006, Stiansy et al. 2002). However, there seems to be a consensus that the dopaminergic system is involved. There are three distinct dopaminergic networks in the brain that modulate and influence different aspects of bodily function. Each network originates and targets distinct areas and accounts for dopamine's varied effects in the body. One of these pathways originates in the substantia nigra and targets the corpus striatum, and modulates voluntary movement (Rye 2004). Damage to dopaminergic neurons or their projections into these two brain regions, as well as deficient dopamine levels, have been implicated in movement disorders (Kumar et al. 2007, Sato et al. 2008, Zhao et al. 2008).

Ćervenka et al. (2006) conducted a study of 16 patients with RLS to determine whether striatal or extrastriatal dopamine 2 (D2) receptor availability was



altered in this group. Utilizing PET (positron emission tomography) technology, they found that binding of the striatum-specific radioligand [^{11}C] raclopride was significantly higher in patients with RLS versus controls. Binding of the extrastriatal radioligand [^{11}C] FLB 457 was also higher in the RLS group versus controls. The authors speculate that these results may “indicate increased D2-receptor density levels in RLS patients.” One explanation for these results is that people with RLS may have dopaminergic neurotransmission hypoactivity which is causing an up-regulation of D2 receptors, therefore increasing receptor density (Ćervenka et al. 2006). Ćervenka et al. (2006) postulate that this hypoactivity may reduce the pain threshold in RLS patients, causing the hallmark sensations in the legs. A study by Reimold and colleagues (2006) examined the relationship between spinocerebellar ataxias (SCA) and RLS by measuring the binding potential of striatal D2 receptors, also using [^{11}C] raclopride positron emission tomography. Results showed that the four patients with concurrent SCA and RLS did not exhibit “postsynaptic dopaminergic deficits”, which is in contrast to the conclusions of Ćervenka et al. (2006). These patients did not demonstrate reduced D2 receptor availability in the striatum, and the authors suggested that the issue may be extrastriatal in origin (Reimold et al. 2006).

Results from other studies further confuse the issue. Stiasny et al. (2002) discuss a study by Turjanski et al., where PET demonstrated reduced D2 receptor binding in the striatum by [^{11}C] raclopride, suggesting postsynaptic dopaminergic dysfunction in the striatum. Lending support to the idea that dopaminergic dysfunction in RLS lies in the striatum are two studies utilizing single photon emission computer tomography (SPECT). As reported by Stiasny et al. (2002), Michaud and colleagues along with Staedt and co-authors found that patients with RLS had reduced 123I-IBZM (a D2 receptor ligand) binding to striatal D2 receptors. This is supported by a different study by Michaud et al. that demonstrated the same results (cited by Wetter et al. 2004). Despite conflicting information as to the exact pathophysiology, these studies do point to dopamine dysregulation playing a role in RLS.

The endogenous opiate system has also been examined to help explain the symptoms of RLS. One group of authors studied levels of Beta-endorphin, Met-

enkephalin, and Leu-enkephalin in post-mortem brains of RLS patients (Walters et al. 2009). This team found significantly reduced levels of Beta-endorphin and Met-enkephalin in the thalamus of RLS patients versus controls. Based on these results, they hypothesize that the “urge to move” occurs because “information regarding painful stimuli from the lateral spinothalamic pathways is altered at the thalamic level because of endogenous thalamic opioid deficiency”.

Iron deficiency is another factor implicated in the pathophysiology of RLS. Godau et al. (2008) evaluated markers of iron deficiency in six patients with idiopathic RLS and found deficient brain iron levels in these patients versus controls. Results from a similar study by Godau et al. (2007) support these findings. However, the authors concede that the connection between the sensory and motor symptoms of RLS and iron deficiency is unclear (Godau et al. 2008). In another study, patients with both early- and late-onset RLS were subjected to MRI to evaluate iron content in ten regions of the brain (Earley et al. 2006). Patients with early-onset RLS were found to have a lower mean iron index in the substantia nigra region versus controls, and there was no significant difference between the early- and late-onset groups. Interestingly, the late-onset group had a higher iron index in the putamen and pons regions versus controls. As the iron index does not reflect total tissue iron, only ferritin-bound iron, these results may only point to altered iron metabolism, “the significance of which is uncertain” (Earley et al. 2006).

Clinical significance

For the person experiencing RLS the effects reach further than the consequences of dopamine dysregulation. Difficulty falling asleep or staying asleep were reported in 69.4% of children with RLS, as was daytime sleepiness (21%-33.6%) (Pacchietti et al. 2007). According to Allen et al. (2005) the most common daytime symptoms reported in adults with RLS were disturbance of normal daily activities (40.1%), lack of energy (47.6%) and negative influence on mood (50.5%). Other symptoms include inability to concentrate the day after experiencing symptoms, interrupted sleep, headaches, depressed mood, and reduced libido (Allen et al. 2005, Ulfberg et al. 2001a, Ulfberg et al. 2001b). People with RLS were also shown to score lower on quality of life

surveys than the general population (Allen et al. 2005). These results were similar to patients with type II diabetes and depression. Comprehensive care of clients with RLS to address associated symptoms is necessary.

Conventional diagnosis and treatment

RLS is a clinical diagnosis based on the four criteria described in the introduction. A polysomnogram (PSG) can be performed in uncertain cases to support the diagnosis. The PSG is evaluated for the presence of periodic limb movements (PLMs). These PLMs lend strong support to the diagnosis of RLS, as it has been estimated that 80-90% of patients with restless legs syndrome have concurrent PLMs (Hening 2004, Stiansy et al. 2002).

Levodopa (L-dopa), dopaminergic agonists, and opioids are the medications typically prescribed (Smith & Tolson 2008, Trenkwalder et al. 2008). Levodopa is transported past the blood-brain barrier and taken up into dopaminergic cells, where it is converted to

dopamine (Trenkwalder et al. 2008). Although L-dopa has been reported to improve sleep by decreasing motor and sensory disturbances in patients with RLS, an increase in symptoms has been reported several months after treatment initiation (García-Borreguero et al. 2007, Smith & Tolson 2008, Trenkwalder et al. 2008). Ergot-derived dopamine agonists such as bromocriptine, pergolide, and cabergoline typically work at D1-like, D2-like, and 5-HT_{2B} receptors. Although symptoms reportedly improve with these treatments, they are rarely used due to serious side effects including development of valvular heart disease (Smith & Tolson 2008, Trenkwalder et al. 2008). In contrast, nonergot-derived dopamine agonists such as ropinirole and pramipexole work at the D2 and D3 receptor subfamilies. They are efficacious at reducing RLS symptom severity and improving sleep, and are not associated with development of life-threatening diseases (Trenkwalder et al. 2008). Opioids are often used to treat RLS. Drugs such as oxycodone, methadone, and tramadol have limited



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Hypericum perforatum (St. John's wort)

research in regards to general and long-term efficacy in RLS and caution must be exercised when using them to prevent dependence and other side-effects. Oxycodone has been reported to decrease restlessness and sensory discomfort, and is likely the most efficacious of the opioids mentioned. Methadone and tramadol seem less effective at improving symptoms, and tramadol may actually increase symptoms (Trenkwalder et al. 2008).

Herbal therapeutics

Because the pathophysiology of RLS is unclear, pharmacology provides limited guidance in herb selection. Although there are no references to “restless legs syndrome” in traditional literature such as from the Eclectics and Physiomedicalists, herbalists can instead look at herbs for symptoms such as hypermotility, restlessness, nervousness, chorea, spasms, and insomnia to support clients with RLS. The next section, though not a full review of therapeutic options, discusses herbs that may be useful for these indications.

Categories of herbs that may demonstrate pharmacologically relevant actions include spasmolytics, nervine tonics, and sedatives. A review of the traditional literature finds that *Hypericum perforatum* (St. John’s wort), *Scutellaria lateriflora* (skullcap), *Valeriana officinalis* (valerian), *Actaea racemosa* (black cohosh), *Passiflora incarnata* (passion flower), and *Lobelia inflata* (lobelia) fall into these categories, and were all historically used to relieve symptoms similar to those of RLS.

Primary herbs of interest: *Scutellaria lateriflora*, *Hypericum perforatum*, and *Valeriana officinalis*

Some modern research exists on *Scutellaria lateriflora*, *Hypericum perforatum*, and *Valeriana officinalis* to support their historical uses for RLS-like symptoms. Traditionally, all three of these herbs have been used in nervous disorders (Cook 1869, Ellingwood 1919, Felter & Lloyd 1898). Skullcap is indicated for restlessness, nervous excitability, “general irritability with insomnia from local physical causes” (Ellingwood 1919), and nervousness manifesting as muscular excitation (Felter 1922, Felter & Lloyd 1898). These descriptions are a good fit for the clinical picture of RLS. Valerian has very similar indications, being used for irritability, restlessness, “nearly all forms of acute nervousness”



Scutellaria lateriflora (skullcap)

(Cook 1869), and “controls distress and imaginary pain and produces quiet, permitting sleep and rest” (Ellingwood 1919). Because of this, valerian may be more suitable for RLS clients who report their symptoms as pain in the legs. Although the clinical presentation of RLS does not differ significantly between people, each client has their own energetics that need to be taken into consideration when choosing herbs. Table 2 provides a brief explanation of energetic qualities to look for in a client. Valerian is warm, spicy, and bitter; because of this it is most indicated for cold, nervous constitutions. Those with hot constitutions may experience stimulating effects from valerian (Tierra 1992, Tierra 1998). In

Table 2: Clinical Presentation of the four energetic qualities (adapted from Wood 2004)

Quality	Corresponding Clinical Presentation
Hot	Red, hot tissues; increased circulation; rapid pulse; red tongue; preference for cool weather, food, etc.
Cold	Cool, pale tissues; decreased circulation; slow pulse; pale to blue/purple tongue; preference for warm weather, food, etc.
Damp	Saggy, flabby, damp tissue; body fluids phlegmy or flowing; relaxed pulse; damp, coated, swollen tongue; preference for dry weather
Dry	Dry, withered tissue; decreased energy; weak pulse; dry tongue; preference for humid weather



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Valeriana officinalis (valerian)

contrast skullcap is cool and bitter, and is more fitted to clients with excess or deficient heat (Tierra 1992). SJW is also cool and bitter (Tierra 1992), and is more suited to clients with a hot constitution (Wood 2004).

Of these three herbs, SJW is the only one that has demonstrated effects on dopamine. The constituents thought to be responsible for SJW's effects are

hyperforin and hypericin (Calapai et al. 2001, Mennini & Gobbi 2004). One study found that 2.42 mg/kg of a hyperforin-rich (30.14%) extract and 62.5 mg/kg of a 4.67% hyperforin extract (LI 160) significantly increased extraneuronal dopamine levels in the nucleus accumbens region of the rat brain (Rommelspacher et al. 2001). Another extract containing 0.3% hypericin and 4.5% hyperforin (Ph-50) was found to increase dopamine content in the diencephalon of rats, starting at a dose of 250 mg/kg. This is significant because the dopaminergic system has a role in modulating locomotor activity (Calapai et al. 2001). Braun & Cohen (2007) report that SJW inhibits the synaptic reuptake of dopamine. This is supported by research done by Roz et al. (2002). They found that a hyperforin-rich extract (% not specified) non-competitively inhibited dopamine reuptake into rat brain synaptic vesicles and synaptosomes. It must be stated, however, that they derived their extract from *H. triquetrifolium* leaves and buds. Taken together, this evidence indicates that SJW increases dopamine levels in the brain, and inhibits its reuptake. These studies may support SJW being used in RLS clients, who demonstrate dopaminergic hypoactivity. However, it is unclear whether the doses of hyperforin and hypericin used in these studies are clinically attainable. Most clinical trials on SJW focus on its use in mild to moderate depression, with little mention of its use on the nervous system. However, since many clients with RLS report symptoms of depression and anxiety (Cuellar & Ratcliffe 2009), the evidence from these trials may be useful. Since SJW works directly with the dopaminergic system, it seems reasonable to use these trials to support the use of SJW in the RLS population. Historically, the effective dose was 2-30 drops of tinctured aerial parts (Ellingwood 1919, Felter 1922), although Bone (2003) reports a much higher dose of 2-6 ml of a 1:2 extract.

In contrast to SJW, valerian has been shown to have little or no effect on dopamine. In work done by Abourashed et al. (2004), a valerian extract containing 0.388% valerenic acids did not show any binding affinity to dopamine receptors. In an animal model, a 1:10 ethanolic extract of valerian given at 1% in water, did not "prevent the reduction in dopamine uptake" induced by haloperidol, a neuroleptic drug (Fachinetto et al. 2007). However, it did demonstrate anxiolytic effects and hypolocomotion in rats after 8 weeks of

treatment. In contrast, another study found that various tested valerian extracts did not reduce locomotor activity in rats (Hattesoehl et al. 2008). These researchers did find evidence to support that valerian produces anxiolytic effects. Although valerianic acids are thought to be the active constituents in valerian (Bone 2003), an extract used in the Hattesoehl et al. (2008) study had these constituents removed. Instead of affecting dopamine, valerian may be acting primarily on GABA. It has been reported to stimulate GABA release from brain tissue, inhibit its reuptake, and possibly affect GABA receptors (Braun & Cohen 2007, Bone 2003). Bone (2003) reports that valerian's valepotriate content may be responsible for its sedative and antispasmodic effects. Despite the fact that valerian seems to have no direct effect on the dopaminergic system, the pathophysiology of RLS is still largely unclear. It may be that valerian works on a physiological level that has not yet been identified with RLS. In terms of clinical trials, valerian has been more extensively researched than SJW or skullcap. In one trial of 11,000 patients, the equivalent of 0.25 g/day dried root in an aqueous extract improved falling asleep, discontinuous sleep, and restlessness (Bone 2003). In another trial, the equivalent of 6 g valerian in a single dose and 3 g/day for 14 days was shown to "lower periods of wakefulness", and improve sleep profiles overall (Bone 2003). One clinical trial on the effects of valerian on RLS was found. RLS patients were given 800 mg valerian (1.16 mg valerianic acid) 60 minutes before bed for 8 weeks (Cuellar & Ratcliffe 2009). The group receiving treatment showed improvement over placebo in symptom severity and quality of life, but the difference was not significant. However, when the treatment group was divided into "sleepy" and "nonsleepy" subjects, a significant improvement in sleep quality and symptom severity was seen in the "sleepy" group. Historically, the therapeutic dose for valerian was 3.5-7.0 ml of tinctured root and rhizome (Felner & Lloyd 1898).

In regards to pharmacology, skullcap is again similar to valerian in that it seems to work primarily on GABA and have no direct effect on dopamine. The active constituents in skullcap have been identified as baicalin, baicalein, wogonoside, and wogonin (Zhang et al. 2008); glutamine and GABA have also been found in this herb (Awad et al. 2003). In a study by Hui et al. (2002),

wogonin at a dose of 3.75-30 mg/kg was found to have an affinity for the benzodiazepine site on the GABA_A receptor, and reduce anxiety in rats. Baicalein, baicalin, and wogonin from a 1:10 ethanolic extract and a 1:20 hot water extract were found to bind to 5-HT₇, a serotonin receptor (Gafner et al. 2003). These findings, coupled with skullcap's glutamine and GABA content, may account for its anxiolytic properties (Awad et al. 2003). Zhang et al. (2008) found that 90 mg/kg of an unspecified commercial skullcap product decreased seizures in rats, lending support to this herb's traditional use as a spasmolytic. Although the available research does not indicate that skullcap works on the known pathophysiology of RLS, it may work at a level that has yet to be researched. To date, only one clinical trial has been done on skullcap. According to the study's abstract, this herb demonstrated definite anxiolytic effects on healthy



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Actaea racemosa (black cohosh)



Passiflora incarnata (passion flower)

volunteers (Wolfson & Hoffmann 2003). Effective doses of skullcap can range from 2.0-4.5 ml of tincture (Bone 2003, Cook 1869) to 0.5-4 g fresh herb (Felter 1922).

Secondary herbs of interest: *Actaea racemosa*, *Passiflora incarnata*, and *Lobelia inflata*

Black cohosh was used as a nerve sedative and spasmolytic for nervous excitability, especially when muscles were involved (Ellingwood 1919, Felter & Lloyd 1898), and was “accepted as the best single remedy for chorea” (Felter 1922). The recommended dose is 1.5-3.5 ml a day of the tinctured root and rhizome (Bone 2003, Ellingwood 1919). Unfortunately there are no studies or clinical trials on using black cohosh in this manner. Passion flower is a spasmolytic and mild sedative, and traditionally was used for chorea, muscular twitching, convulsive movements (Ellingwood 1919, Felter 1922, Felter & Lloyd 1898), and “restlessness and irritability

with difficulty falling asleep” (Bone 2003). One study found that 0.4 mg/kg of a passion flower preparation, Pasipay, delayed seizure onset and decreased seizure duration in mice (Nassiri-Asl et al. 2007), lending support to passion flower’s historical use as a spasmolytic. The same study also found that gamma-aminobutyric acid (GABA) antagonists decreased Pasipay’s efficacy, suggesting this herb works via GABAergic activity. It is difficult to extrapolate a therapeutic dose from this study, as specifics on the Pasipay extract were not given. Felter (1922) reported doses of 0.5-7.5 g of the root and stem-base, while Bone (2003) recommends 3-6 ml of a 1:2 extract of aerial parts. Lobelia was historically used for spasmodic muscular contractions, nervous irritability, restlessness, and chorea (Ellingwood 1919, Felter 1922), and may be worth considering in a client with RLS. One study found that lobeline, a constituent of lobelia, had a dopamine-releasing effect on cells that had a dopamine

transporter, although the dose used is unclear (Wilhelm et al. 2008). Historical doses ranged from 65 mg to 4 g of the aerial parts (Felter 1922), to 12-75 drops of tincture (Ellingwood 1919). According to the American Herbal Products Association's safety handbook, lobelia can cause nausea and vomiting, and should not be taken in large doses (McGuffin et al. 1997).

Taken as a whole, there is preliminary evidence for the use valerian, skullcap, SJW, black cohosh, passion flower, and lobelia in supporting clients with restless legs syndrome based on traditional use, energetics, pharmacology, and clinical trials. SJW may be more indicated in a hot client who is also exhibiting symptoms of depression and anxiety. Valerian would be more useful for a cold, nervous, restless client with sleep disturbances resulting from RLS symptoms. Skullcap could be used similarly to valerian, however the skullcap client would present with more of a heat pattern than the valerian client. With these considerations kept in mind, the herbal clinician should be able to start formulating an effective strategy to support a client with RLS.

Key Terms

Autosomal-dominant – a pattern of inheritance where an individual has one mutant and one normal gene

Beta-endorphin – endogenous opioid peptide neurotransmitter

Chorea – neurological disease characterized by involuntary movements

Echogenicity – ability to return a signal in ultrasound exams

Lateral spinothalamic pathway – bundle of sensory axons, carries pain and temperature sensory information to the thalamus

Leu-enkephalin – endogenous opioid peptide neurotransmitter

Locus – position on a chromosome

Met-enkephalin – endogenous opioid peptide neurotransmitter

PET – nuclear medicine imaging technique, produces a 3D image of functional processes in the body

Polysomnogram – a sleep study, records biophysical changes that occur during sleep

Pons – brain region, relays information between the cerebrum and cerebellum

Putamen – brain region, regulates movement and

utilizes dopamine for its functions

Radioligand – radioactive molecule that binds to a receptor

SPECT – nuclear medicine tomographic imaging technique, provides 3D information, can be presented as cross-sectional slices through patient

Spinocerebellar ataxia – genetic disorder, symptoms include incoordination of gait and poor coordination of hands, speech, and eye movements

Striatum – referring to the corpus striatum, brain region involved in planning, modulation of movement pathways, and activated by stimuli associated with reward

Substantia nigra – brain region, plays a role in reward, addiction, and movement

Thalamus – brain region, plays a role in sleep regulation, activity, and motor control



Lobelia inflata (lobelia)

References

- Abourshed EA, Koetter U, & Brattström A 2004, *In vitro* binding experiments with a valerian, hops and their fixed combination extract (Ze91019) to selected central nervous system receptors *Phytomedicine*. 11:633-638
- Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, & Ferini-Strambi L 2005, Restless legs syndrome prevalence and impact *Archives of Internal Medicine*. 165:1286-1292
- Awad R, Arnason JT, Trudeau V, Bergeron C, Budzinski JW, Foster BC, & Merali Z 2003, Phytochemical and biological analysis of skullcap (*Scutellaria lateriflora* L.): A medicinal plant with anxiolytic properties *Phytomedicine*. 10:640-649
- Bone K 2003, *A clinical guide to blending liquid herbs*. Churchill Livingstone, St. Louis
- Braun L, & Cohen M 2007, *Herbs and natural supplements: An evidence-based guide* (2nd ed). Churchill Livingstone, Sydney
- Calapai G, Crupi A, Firezuoli F, Infrerra G, Squadrito F, Parisi A, De Sarro G, & Caputi A 2001, Serotonin, norepinephrine and dopamine involvement in the antidepressant action of Hypericum perforatum *Pharmacopsychiatry*. 34:45-49
- Červenka S, Pálhagen SE, Comley RA, Panagiotidis G, Cselényi Z, Matthews JC, Lai RY, Halldin C, & Farde L 2006, Support for dopaminergic hypoactivity in restless legs syndrome: A PET study on D2-receptor binding *Brain*. 129:2017-2028
- Chen F, Rezvani AH, & Lawrence AJ 2003, Autoradiographic quantification of neurochemical markers of serotonin, dopamine and opioid systems in rat brain mesolimbic regions following chronic St.John's wort treatment *Naunyn-Schmiedeberg's Archives of Pharmacology*. 367:126-133
- Collado-Seidel V, Kohnen R, Samtleben W, Hillebrand GF, Oertel WH, & Trenkwalder C 1998, Clinical and biochemical findings in uremic patients with and without restless legs syndrome *American Journal of Kidney Diseases*. 31:324-328
- Cook W 1869, *The Physiomedical dispensatory* Retrieved November 19, 2008, from <http://www.henriettesherbal.com/eclectic/cook/>
- Cuellar NG, & Ratcliffe SJ 2009, Does valerian improve sleepiness and symptom severity in people with restless legs syndrome? *Alternative Therapies*. 15:22-28
- Earley CJ, Barker PB, Horská A, & Allen RP 2006, MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome *Sleep Medicine*. 7:458-461
- Ellingwood F 1919, *The American materia medica, therapeutics and pharmacognosy* Retrieved November 19, 2008, from <http://www.henriettesherbal.com/eclectic/ellingwood/>
- Fachineto R, Villarinho JG, Wagner C, Pereira RP, Ávila DS, Burger ME, Calixto JB, Rocha JBT, & Ferreira J 2007, *Valeriana officinalis* does not alter the orofacial dyskinesia induced by haloperidol in rats: Role of dopamine transporter *Progress in Neuro-Psychopharmacology*. 31:1478-1486
- Felter HW 1922, *The Eclectic materia medica, pharmacology and therapeutics* Retrieved November 19, 2008, from <http://www.henriettesherbal.com/eclectic/felter/>
- Felter HW, & Lloyd JU 1898, *King's American dispensatory* Retrieved from November 19, 2008, from <http://www.henriettesherbal.com/eclectic/kings/>
- Franco RA, Ashwathnarayan R, Deshpandee A, Knox J, Daniel J, Eastwood D, Franco J, & Saeian K 2008, The high prevalence of restless legs syndrome symptoms in liver disease in an academic-based hepatology practice *Journal of Clinical Sleep Medicine*. 4:45-49
- Gafner S, Bergeron C, Batcha LL, Reich J, Arnason JT, Burdette JE, Pezzuto J, & Angerhofer CK 2003, Inhibition of [H]-LSD binding to 5-HT receptors by flavonoids from *Scutellaria lateriflora* *Journal of Natural Products*. 66:535-537
- García-Borreguero D, Allen RP, Kohnen R, Högl B, Trenkwalder C, Oertel W, Hening WA, Paulus W, Rye D, Walters A, & Winkelmann J 2007, Diagnostic standards for dopaminergic augmentation of restless legs syndrome: Report from a world association of sleep medicine – international restless legs syndrome study group consensus conference at the Max Planck Institute *Sleep Medicine*. 8:520-530
- Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, & Budai R 2004, Restless legs syndrome in end-stage renal disease *Sleep Medicine*. 5:309-315
- Godau J, Schweitzer KJ, Liepelt I, Gerloff C, & Berg D 2007, Substantia nigra hypogenicity: Definition and findings in restless legs syndrome *Movement Disorders*. 22:187-192
- Godau J, Klose U, Di Santo A, Schweitzer K, & Berg D 2008, Multiregional brain iron deficiency in restless legs syndrome *Movement Disorders*. 23:1184-1187
- Hattesoehl M, Feistel B, Sievers H, Lehnfeld R, Hegger M, & Winterhoff H 2008, Extracts of *Valeriana officinalis* L. s.l. show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties *Phytomedicine*. 15:2-15
- Hening W 2004, The clinical neurophysiology of the restless legs syndrome and periodic limb movements. Part I: Diagnosis, assessment, and characterization *Clinical Neurophysiology*. 115:1965-1974
- Hensley JG 2009, Leg cramps and restless legs syndrome during pregnancy *Journal of Midwifery and Women's Health*. 54:211-218
- Hui KM, Huen MSY, Wang HY, Zheng H, Sigel E, Baur R, Ren H, Li ZW, Wong JT, & Xue H 2002, Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi *Biochemical Pharmacology*. 64:1415-1424
- Krishnan PR, Bhatia M, & Behari M 2003, Restless legs syndrome in Parkinson's disease: A case-controlled study *Movement Disorders*. 18:181-185
- Kumar V, Abbas AK, Fausto N, & Mitchell RN 2007, *Robbins basic pathology* (8th ed). Saunders Elsevier, Philadelphia
- Levchenko A, Provost S, Montplaisir JY, Xiong L, St-Onge J, Thibodeau P, Rivière JB, Desautels A, Turecki G, Dubé MP, & Rouleau GA 2006, A novel autosomal dominant restless legs syndrome locus maps to chromosome 20p13 *Neurology*. 67:900-901
- Levchenko A, Montplaisir JY, Asselin G, Provost S, Girard SL,

- Xiong L, Lemyre E, St-Onge J, Thibodeau P, Desautels A, Turecki G, Gaspar C, Dubé MP, & Rouleau GA 2009, Autosomal-dominant locus for restless legs syndrome in French-Canadians on chromosome 16p12.1 *Movement Disorders*. 24:40-50
- Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, Mollica G, Ferini-Strambi L, & Granieri E 2004a, Restless legs syndrome and pregnancy *Neurology*. 63:1065-1069
- Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Mollica G, & Granieri E 2004b, Pregnancy as a risk factor for restless legs syndrome *Sleep Medicine*. 5:305-308
- McGuffin M, Hobbs C, Upton R, & Goldberg A (Eds) 1997, *American Herbal Products Association's botanical safety handbook*. CRC Press, Boca Raton
- Mennini T & Gobbi M 2004, The antidepressant mechanism of *Hypericum perforatum* *Life Sciences*. 75:1021-1027
- Merlino G, Fratticci L, Valente M, Del Giudice A, Noacco C, Dolso P, Cancelli I, Scalise A, & Gigli GL 2007a, Association of restless legs syndrome in type 2 diabetes: A case-control study *Sleep*. 30:866-871
- Merlino G, Valente M, Serafini A, & Gigli GL 2007b, Restless legs syndrome: diagnosis, epidemiology, classification and consequences *Neurological Sciences*. 28:S37-S46
- Nassiri-Asl M, Shariati-Rad S, & Zamansoltani F 2007, Anticonvulsant effects of aerial parts of *Passiflora incarnata* extract in mice: Involvement of benzodiazepine and opioid receptors *BMC Complementary and Alternative Medicine*. 7
- Ondo WG, Nuong KD, & Jankovic J 2002, Exploring the relationship between Parkinson disease and restless legs syndrome *Archives of Neurology*. 59:421-424
- Picchiatti D, Allen RP, Walters AS, Davidson JE, Myers A, & Ferini-Strambi L 2007, Restless legs syndrome: Prevalence and impact in children and adolescents – the peds REST study *Pediatrics*. 120:253-266
- Reimold M, Globas C, Gleichmann M, Schulze M, Gerloff C, Bares R, Machulla HJ, & Bürk K 2006, Spinocerebellar ataxia type 1, 2, and 3 and restless legs syndrome: Striatal dopamine D2 receptor status investigated by [¹¹C]raclopride positron emission tomography *Movement Disorders*. 21:1667-1673
- Rommelspacher H, Siemanowitz B, & Mannel M 2001, Acute and chronic actions of a dry methanolic extract of *Hypericum perforatum* and a hyperforin-rich extract on dopaminergic and serotonergic neurons in rat nucleus accumbens *Pharmacopsychiatry*. 34:S119-S126
- Roz N, Mazur Y, Hirshfeld A, & Rehavi M 2002, Inhibition of vesicular uptake of monoamines by hyperforin *Life Sciences*. 71:2227-2237
- Rye DB 2004, Parkinson's disease and RLS: The dopaminergic bridge *Sleep Medicine*. 5:317-328
- Sato K, Sumi-Ichinose C, Kaji R, Ikemoto K, Nomura T, Nagatsu I, Ichinose H, Ito M, Sako W, Nagahiro S, Graybiel AM, & Goto Satoshi 2008, Differential involvement of striosome and matrix dopamine systems in a transgenic model of dopa-responsive dystonia *Neuroscience*. 105:12551-12556
- Smith JE, & Tolson JM 2008, Recognition, diagnosis, and treatment of restless legs syndrome *Journal of the American Academy of Nurse Practitioners*. 20:396-401
- Stiansy K, Oertel WH, & Trenkwalder C 2002, Clinical symptomatology and treatment of restless legs syndrome and periodic limb movement disorder *Sleep Medicine Reviews*. 6:253-265
- Tierra L 1992, *The herbs of life: Health & healing using western & Chinese techniques*. The Crossing Press, Freedom, CA
- Tierra M 1998, *Planetary herbology: An integration of western herbs into the traditional Chinese and Ayurvedic systems*. Lotus Press, Twin Lakes
- Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, Costa J, Stiansny-Kolster K, & Sampaio C 2008, Treatment of restless legs syndrome: An evidence-based review and implications for clinical practice *Movement Disorders*. 23:2267-2302
- Ulfberg J, Nyström B, Carter N, & Edling C 2001a, Prevalence of restless legs syndrome among men aged 18 to 64 years: An association with somatic disease and neuropsychiatric symptoms *Movement Disorders*. 16:1159-1163
- Ulfberg J, Nyström B, Carter N, & Edling C 2001b, Restless legs syndrome among working-aged women *European Neurology*. 46:17-19
- Walters AS, Hickey K, Maltzman J, Verrico T, Joseph D, Hening W, Wilson V, & Chokroverty S 1996, A questionnaire study of 138 patients with restless legs syndrome: The "night-walkers" survey *Neurology*. 46:92-95
- Walters AS, Ondo WG, Zhu W, & Le W 2009, Does the endogenous opiate system play a role in the restless legs syndrome?: A pilot post-mortem study *Journal of the Neurological Sciences*. 279:62-65
- Wetter TC, Eisensehr H, & Trenkwalder C 2004, Functional neuroimaging studies in restless legs syndrome *Sleep Medicine*. 5:401-406
- Wilhelm CJ, Johnson RA, Eshleman AJ, & Janowsky A 2008, Lobeline effects on tonic and methamphetamine-induced dopamine release *Biochemical Pharmacology*. 75:1411-1415
- Winkelmann J, Lechtner P, Pütz B, Trenkwalder C, Hauk S, Meitinger T, Strom T, & Muller-Myhsok B 2006, Evidence for further genetic locus heterogeneity and confirmation of RLS-1 in restless legs syndrome *Movement Disorders*. 21:28-33
- Wolfson P, & Hoffmann DL 2003, An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers *Alternative Therapies in Health and Medicine*. 9:74-78 Abstract retrieved from PubMed
- Wood M 2004, *The practice of traditional western herbalism*. North Atlantic Books, Berkeley
- Zhang Z, Lian X, Li S, & Stringer JL 2008, Characterization of chemical ingredients and anticonvulsant activity of American skullcap (*Scutellaria lateriflora*) *Phytomedicine*
- Zhao Y, DeCuypere M, & LeDoux MS 2008, Abnormal motor function and dopamine neurotransmission in DYT1 delta-GAG transgenic mice *Experimental Neurology*. 210:719-730