



## Valeriana officinalis

### Description

Valerian is the common name for over 250 world-wide plant species of the genus *Valeriana* (Valerianaceae). Although all of the species' roots contain similar medicinal constituents and qualities, in the West *Valeriana officinalis* is almost exclusively the valerian species found in preparations.

Valerian was used in both ancient Greece and China, as noted by Dioscorides, Galen, and in early Chinese medicine texts. Valerian was acknowledged as a sleep aid and anxiolytic in the U.S. National Formulary until the 1940's, after which it fell into disuse as more potent pharmacological agents became available.<sup>1</sup>

Currently, valerian is employed as a sleep aid or sedative and as a gastrointestinal spasmolytic. Less common applications include muscular and uterine cramping, nervous headache, and as a gastrointestinal carminative.

Historically, patients that have responded best to valerian include those presenting with lack of adequate exercise and/or mental relaxation who manifest stress associated with despondency and mental depression.<sup>2,3</sup>

### Active Constituents

Valerian root contains bicyclic monoterpenes (valepotriates – notably valtrate and dihydrovaltrate), volatile oils (valeranone, valeranal, and valerenic acids), sesquiterpenes, lignans, and alkaloids. Free amino acids, such as gamma-aminobutyric acid (GABA), tyrosine, arginine, and glutamine are also present.<sup>4,5</sup> The valepotriates, discovered in 1966, were thought to be the sole active constituents, although their decomposition products, the baldrinals, and other components are understood to lend therapeutic benefit.<sup>6</sup>

Valerian's characteristic odor is generated by isovaleric acid.<sup>1,6</sup> The pungent smell can present a problem in controlled study design because of the difficulty of establishing a plausible placebo.<sup>7</sup>

### Mechanisms of Action

The essential oils in valerian appear to provide its sedative activity, while the valepotriates exert a regulatory effect on the autonomic nervous system.<sup>6</sup> Although more than 150 constituents have been identified, none appear to be solely responsible for valerian's effects, suggesting many compounds may act synergistically.<sup>8,9</sup> Valerian's mechanisms of action are not completely understood. Pharmacokinetic information, such as half-life and metabolism, is also pending.

Valerian interacts with neurotransmitters such as GABA<sup>9,10</sup> and produces a dose-dependent release of GABA.<sup>11</sup> Valerian also inhibits the enzyme-induced breakdown of GABA in the brain, with concomitant

sedation.<sup>12</sup> Valerian's inherent GABA content could directly cause sedation, although concerns exist regarding bioavailability.<sup>10,13,14</sup> The valerian lignan hydroxypinoresinol has been found to bind to benzodiazepine receptors.<sup>15</sup> The valepotriates may act as prodrugs through biotransformation into homobaldrinal by bacterial flora.<sup>8</sup> Finally, valerian's sedative effect acts more as a nervous system depressant than as a muscle relaxant.<sup>9</sup>

## Clinical Indications

### Anxiety

In a double-blind trial of 48 adults placed in an experimental situation of social stress, valerian reduced subjective sensations of anxiety and did not cause any measurable sedation.<sup>16</sup> In comparison to diazepam (2.5 mg three times daily), a valerian preparation (50 mg three times daily – standardized to 80% dihydrovaltrate) showed a similar significant reduction in Hamilton Anxiety Scale (HAM-A) after four weeks.<sup>17</sup> Valerian and *Piper methysticum* (kava kava) were compared to each other and placebo in a standardized mental stress test in 54 healthy individuals. Unlike placebo, both preparations decreased systolic blood pressure responsiveness and self-reported feelings of stress, and inhibited a stress-induced rise in heart rate.<sup>18</sup>

### Insomnia

Four placebo-controlled studies present the best evidence of the effectiveness of valerian in the treatment of insomnia. Leathwood et al in a double-blind, crossover study found valerian improved sleep latency and quality compared to placebo. The effects of the 400 mg aqueous valerian were noteworthy, with only mild increases by 900 mg administration.<sup>19</sup> In a study of 128 participants given 400 mg aqueous valerian extract or placebo, improvement was noted in sleep latency and sleep quality. Valerian was a greater benefit to self-described “poor sleepers” versus “good sleepers” over four categories including young, old, women, and men.<sup>20</sup> Vorbach treated 121 patients for four weeks with 600 mg valerian extract per day or placebo, and assessed clinical effectiveness using

four validated rating scales. After 14 days valerian was rated better than placebo on the Clinical Global Impression Scale (CGIS), and at conclusion of the study (day 28) 66 percent of patients rated valerian effective, compared to 26 percent with placebo.<sup>21</sup> Using polysomnographic recordings and questionnaires, Donath et al found sleep latency was significantly reduced in 16 insomnia patients treated with valerian, compared to placebo ( $p<0.05$ ). The percentage of slow wave sleep was also increased compared to placebo ( $p<0.05$ ).<sup>22</sup>

Other studies also support valerian in insomnia. Ziegler et al treated 202 patients with valerian (600 mg daily) or oxazepam (10 mg daily) for six weeks and found similar positive effects on sleep quality, measured by the Sleep Questionnaire, CGIS, and Global Assessment of Efficacy. Adverse events occurred in 36 percent of patients taking oxazepam, compared with 28 percent in the valerian group. All adverse effects were deemed mild or moderate.<sup>23</sup> A trial of valerian use after benzodiazepine withdrawal produced subjective improvement in sleep quality after two weeks at 100 mg three times daily.<sup>24</sup> In a study of patients complaining of insufficient sleep, significant improvement was noted after two weeks using 470-1410 mg of valerian at bedtime.<sup>25</sup>

### Muscle Spasm

Valerian has demonstrated muscle-relaxant qualities.<sup>9</sup> Valerenic acid, valtrate, and valeranone were spasmolytic in guinea pig ileum through direct effects on smooth muscle.<sup>26,27</sup> Valerian is traditionally used in the treatment of intestinal spasms, colic, and “nervous stomach,” with gastrointestinal calming noted “unless given in too large doses or too long continued.”<sup>3</sup>

### Drug-Botanical Interactions

Valerian was found to exhibit moderate-to-high (35-88%) *in vitro* inhibition of CYP3A4-mediated metabolism (similar to grapefruit). Various extracts had vastly different chemical profiles, and the authors noted it is unknown how much

CYP3A4 inhibition might occur *in vivo* when dosing with a particular commercial extract.<sup>28</sup> Valerian has been shown to prolong thiopental- and pentobarbital-induced sleep, so it may be prudent to avoid concurrent use of valerian and barbiturates.<sup>29</sup> Studies in German medical journals show valerian does not amplify the negative effects of alcohol on driving performance with combined use.<sup>30,31</sup>

A benzodiazepine-like withdrawal syndrome was noted in one case report after abrupt discontinuation of daily multi-gram intake of valerian.<sup>32</sup> Valerian might be expected to potentiate the sedative effects of drugs, notably anesthetics such as midazolam that act at the GABA receptor.<sup>33</sup> Valerian may also be useful in dampening symptoms common to tapering patients from benzodiazepines.<sup>24,34</sup>

### Side Effects and Toxicity

Valerian is on the FDA's Generally Recognized as Safe (GRAS) list. Allergic reactions are rare. Acute side effects, including nausea, headache, dizziness, and upset stomach, have been reported in fewer than 10 percent of subjects in randomized trials. There have been no case reports of problems in pediatrics or in pregnancy and lactation, although no clinical studies have been undertaken to establish safety in these areas.<sup>5,35</sup>

Residual daytime sedation has been noted with daily dosage of 900 mg valerian extract.<sup>22</sup> In a double-blind, crossover trial of 600 mg daily, there was no decline in reaction time, alertness, or concentration compared to flunitrazepam and placebo.<sup>36</sup>

In 1909, Potter noted consistent long-term use "induces a condition of low melancholy and hysterical depression."<sup>37</sup>

### Dosage

Insomnia treatment ranges from 300-600 mg before bedtime, which is equivalent to 2-3 g (~ 2 teaspoons) of dried valerian root steeped covered for 15 minutes.<sup>5</sup> When using tincture 2.5-5 mL is needed.<sup>6</sup>

Considerable variation in content and composition, as well as constituent instability, has created problems in standardization. Valepotriates rapidly hydrolyze in an aqueous solution, which speaks to the historic unreliability of some valerian preparations stored as tincture and tea.<sup>8</sup>

### References

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