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A COMPREHENSIVE PHARMACOGNOSTIC REPORT ON VALERIAN

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ABSTRACT

Herbalism is a traditional medicine practice based on the utilization of plants and plant extracts. In herbalism 'Valerian' is a boon medicine for several ailments. Valerian (*Valerian officinalis*) is a naturally occurring Ayurvedic medicine widely grown in the temperate zones of Europe, North America and Asia and is a safe herbal supplement indicated in various ailments, chief being for the symptoms associated with difficulty in sleeping. It improves subjective experiences of sleep when taken nightly over one- to two-week periods. Although the adverse effect profile and tolerability of this herb are excellent, long-term safety studies are lacking. Due to the this limitations and inconsistent results in currently published clinical trials, further research is needed to clarify the efficacy and side effect profile of valerian, especially in regard to long-term therapy. In present investigation, the medicinally important herbal drug Valerian is reviewed for various taxonomical aspects including botanical authenticity, historical backgrounds, description, existing common names, medicinally important species, going through cultivation, commerce, regulation to phytochemical description, pharmacodynamics, pharmacokinetics, adverse drug reactions, toxicology, contraindications and safety aspects of *Valerian.* This paper also intends to motivate and accelerate pharmaceutical research on Valerian for development of convenient, effective and Generally Regarded as Safe (GRAS) medication.

INTRODUCTION: Herbalism is a traditional medicine-practice based on the utilization of plants and plant extracts. Conventionally, it is also referred as botanical medicine, medical herbalism, herbal medicine, herbology, and phytotherapy. In written evidence, the study of herbs dates back over 5,000 years to the Sumerians, who described well-established medicinal uses for various plants. Ancient Egyptian medicine of 1000 B. C. are known to have used garlic, opium, castor oil, coriander, mint, indigo, and other herbs for medicine and the Old Testament also mentions herb use and cultivation, including mandrake, vetch, caraway, wheat, barley, and rye. Indian Ayurveda medicine has used herbs such as turmeric possibly as early as 1900 B. C. The *Sushruta Samhita* attributed to Sushruta in the 6th century B. C. also describes 700 medicinal plants, 64 preparations from mineral sources, and 57 preparations based on animal sources. In this line of herbalism 'Valerian' is a boon medicine towards treating several ailments and diseases. This manuscript provides basic information about a traditional and useful herb known as **"Valerian"** for its flavour, scent or potential therapeutic properties.

The name valerian was probably derived from the Latin word "valere" meaning to be healthy or strong. Other accounts ascribe its name to the Roman emperor Publius Licinius Valerianus, who reigned in the 3rd century. Two other ancient names are "nard" and "phu". "Nard" is derived from a Sanskrit word meaning "strong smell" and "phu" or "fu" refers to the usual exclamation of disgust that attends the experience of smelling the dried root [1-3]. More than 200 plant species belong to the genus *Valeriana,* but the one most frequently used as an herb is ***Valeriana officinalis.*** The root is used for medicinal purpose. Galen recommended valerian for insomnia in the second century AD. From the sixteenth century onward, this herb became popular as a sedative in Europe (and later in United States). Scientific studies on valerian in humans began in the 1970s, leading to its approval as a sleep aid by Germany's Commission E in 1985. However, the scientific evidence showing that valerian really works remains incomplete. As with most herbs, we are not exactly sure which ingredients in valerian are most important. Early research focused on a group of chemicals known as alepotriates, but they are no longer considered appropriate. A constituent called valerenic acid has also undergone study, but its role is far from clear. Another substance in valerian, called linarin, has also attracted research interest [4-8].

Valerian got its name from the Latin word for "well-being" Valerian was best known to ancient classical authors as a diuretic and treatment for menstrual difficulties. The Greek physician Galen used it for epilepsy in children and adults. An Italian nobleman, Fabio Colonna, born in 1567, suffered from epilepsy and found Galen's reference. He took valerian himself and claimed it completely restored his health. Colonna's experience stimulated interest in the plant as a sedative; use of valerian to relieve spasms and induce sleep evolved in the seventeenth and eighteenth centuries. Valerian was an official remedy in the United States Pharmacopoeia from 1820 to 1936 [1-2, 9]. Valerian root's popularity as a sedative herb seems to be increasing along with the stresses of modern life. For at least 500 years, Valerian root has been among the most popular remedies in the United States and Europe. In Europe, valerian root is now approved by Germany's Commission for restlessness and sleeping disorders [10-11].

Why Valerian is still used today? Valerian is commonly recommended for the mild treatment for occasional insomnia. However, evidence from the best positive study on valerian suggests that it is only useful when taken over an extended period of time for chronic sleep disorders. Like other treatments used for insomnia, valerian has also been proposed as a treatment for anxiety, but there is no reliable evidence as yet that it is effective. Finally, valerian is sometimes suggested as a treatment for a nervous stomach; however, as of yet, there is no supporting scientific evidence for this use [12-15]. Valerian has been used as a sleep aid for over 1,000 years. Its ability to help relax the central nervous system, promote feelings of calm, decrease levels of anxiety and stress, and enhance sleep are known to millions the world over. Unlike some prescription sleep aids, valerian is not known to cause morning grogginess and is non-addictive.

Use of valerian as a sedative and anti-anxiety treatment has been reported for more than 2,000 years. For example, in the 2nd Century AD, Galen recommended valerian as a treatment for insomnia. Related species have been used in traditional Chinese and Indian Ayurvedic medicine. Preparations for use on the skin have been used to treat sores and acne, and valerian by mouth has been used for other conditions such as digestive problems, flatulence (gas), congestive heart failure, urinary tract disorders, and angina (chest pain) [16-17]. As with most herbal products available in the world, valerian root extracts are not regulated for quality or consistency. Self-governing testing laboratories (such as www.consumerlab.com) generally use valeric acid content as a marker for pharmacologic activity and represent one source for reliable information to support product choice [18]. By the 18th century, valerian was widely used as a sedative and to treat nervous disorders associated with a “restless” digestive tract as well as the “vapors” in women. Other common uses included the treatment of headaches, anxiety, palpitations, high blood pressure, irritable or spastic bowel, menstrual cramps, epilepsy and childhood behavior problems and learning disabilities.

During World War I, valerian was used to prevent and treat shell shock in frontline troops, and it was used during World War II to help calm civilians subjected to air raids. Valerian was listed as a sleep aid and anxiolytic on the US national formulary until the 1940’s. It fell into disuse as more potent sedative-hypnotic pharmacologic agents became available [19-21]. Valerian is often used in combination with other sedative herbs such as chamomile, lemon balm, passion flower, St. John’s wort, hawthorn berries and hops. Some consumers combine it with melatonin. In 1998, valerian was the 10th most popular herbal remedy sold in the United States [22].

Scientific and frequently used Names: Valerian is also commonly described as Capon’s tail, cat’s love, common valerian, English valerian, fragrant valerian, garden heliotrope, German valerian, great wild valerian, heliotrope, Indian valerian, setewale, setwall, valerian, valeriana, valeriana radix, vandal root, Vermont valerian, wild valerian, Baldrianwurzel (Germam), Balderbrackenwurzel (German), Katzenwurzel (German), racine de valeriane (France) [23]. It is also known by names viz: Amantilla, All-Heal, Baldrian, Baldrianwurzel, Belgium Valerian,

Common Valerian, Fragrant Valerian, Garden Heliotrope, Garden Valerian, Indian Valerian, Mexican Valerian, Pacific Valerian, Valeriana Officinalis, Valeriana rhizome, Valerianae radix, Valeriane, American Valerian, cat's love, Cat's Valerian, St. George's herb, Setwall, Ka-no-ko-so, Katzenwurzel, kesso root, Kissokon, Vandal Root, valerian, all-heal, garden heliotrope, Setwall, phu, baldrianwurzel, Valerian edulis; Valeriana Jatamansil, synonym Valeriana Wallichii; Valeriana Officinalis; Valerian sitchensis [18-23].

Major Therapeutic Species of Valerian: The genus contains over 250 species, with many more subspecies. *Valeriana officinalis* is the species used in Europe. *V. edulis* is used in Mexico and *V. wallichii* is used in India. *V. edulis* contains substantially higher concentrations of valepotriates (up to 8%), which have mutagenic properties *in vitro* [24]. *V. fauriei* is used in Traditional Chinese Medicine and Japanese medicine. *V. capensis* is used in African traditional medicine [9]. Valeriana Jatamansil is yet another therapeutic species of Valerian [13-17, 25].

Description of Valerian Plant: The part of the plant used medicinally is the root or rhizome. The rhizome is light grayish brown, about the size of a finger joint, bearing many rootlets. The fresh root has no odor, while the dried root smells distinctly unpleasant, akin to old gym socks, due to isovaleric acid. The plant itself is 50 to 150 cm tall with pinnate leaves and white or pink hermaphroditic flowers with three stamens; the stem is upright and without branches. It is sometimes used as a border in perennial gardens [26-27].

Most Suited Habitat for Valerian: Valerian is native to Europe and Asia and has naturalized in eastern North America. This tall perennial prefers moist woodlands; it has been extensively cultivated in northern Europe. Most of the European supply is grown in Holland. It is cultivated in low lying, damp sandy humus with lime fertilizer. It is harvested in the late fall and dried. Valerian is primarily found in Europe and Northern Asian and naturally prefers damp fields, but also grow in more dry places. Valerian is an erect perennial herb. Valerian roots consist of may white coloured erect root stocks or rhizomes.

In spring, every plant forms one hollow stem. The leaves are arranged in pairs and consist of six to ten leaflets. During midsummer the valerian plant starts to bloom. The flowers are white to pink with a very unique but rather pleasant smell. The roots and other parts have a more strange and foetid smell. Cats do like this smell very much and enjoy to rub there noise against the valerian plant or dried roots.

Cultivation of Valerian: Valerian plants are available from some garden centres in the prairies and they can be transplanted into well fertilized moisture-retentive soil. Alternatively, the plants can be grown from seed or propagated by splitting established plants in spring or fall. When growing plants from seed, the beginner should be aware that germination is unpredictable and often slow. The seeds require light for germination, and must not be covered. After transplanting the seedlings, the plants require two or three years before harvesting the roots if they are to be used medicinally. Older plants will have a greater mass of root for harvest. However, most people

cultivating valerian in gardens tend to grow it for horticultural interest rather than medicinal use.

History of Valerian: Valerian has been used as a medicinal herb since at least the time of ancient Greece and Rome. Hippocrates described its properties, and Galen later prescribed it as a remedy for insomnia. In medieval Sweden, it was sometimes placed in the wedding clothes of the groom to ward off the "envy" of the elves. Sometimes people put it in a tea [28]. The Greek physician, Dioscorides, apparently recommended valerian root to treat myriad disorders including heart palpitations, digestive problems, epilepsy and urinary tract infections. Valerian was recommended by Galen during the second century as a treatment for insomnia. Valerian plants are as attractive as catnip to cats, and it is rumored that the Pied Piper's secret to clearing the streets of Hamlin was a store of valerian under his cloak [29].

By the 18th century, valerian was widely used as a sedative and to treat nervous disorders associated with a "restless" digestive tract as well as the "vapors" in women. During World War I, valerian was used to prevent and treat shell shock in frontline troops, and it was used during World War II to help calm civilians subjected to air raids. Valerian was listed as a sleep aid and anxiolytic on the US national formulary until the 1940's. It fell into disuse as more potent sedative-hypnotic pharmacologic agents became available. Related species have been used in Traditional Chinese Medicine (TCM), Ayurvedic Medicine and African herbal healing practices. *V. fauriei* is used in Traditional Chinese Medicine and Japanese medicine as a sedative, spasmolytic and antidepressant. *V. capensis* is used in African traditional medicine as a treatment for epilepsy, hysteria and nervous disorders [30]. In the 1980's valerian again assumed a place of importance as a widely used nonprescription hypnotic and daytime sedative, particularly in France, Belgium, Switzerland, Britain, Russia and Germany. Over 50 tons of valerians are sold each year in France alone. Adolescents and young adults appear to be particularly attracted to valerian and other herbs that affect the central nervous system. The German Commission E has given Valerian root a positive evaluation for use in states of restlessness. The European Scientific Cooperative on Phytotherapy cites its indications as "tenseness, restlessness and irritability with difficulty in falling asleep".

The Herbal PDR lists its primary indications as "nervousness and insomnia", as well as lack of concentration, stress headache, menstrual states of agitation, neuralgia, nervous stomach, and states of angst. It has also been included in herbal remedies for cardiovascular disorders to help reduce hypertension and reduce the effects of stress and tension on the heart. Some health resort put valerian in whirlpool baths to help reduce pain and enhance sleep for patients with fibromyalgia. Valerian is often used in combination with other sedative herbs such as chamomile, lemon balm, passion flower, St. John's wort, hawthorn berries and hops. Some consumers combine it with melatonin. In 1998, valerian was the 10th most popular herbal remedy sold in the United States [22]. For thousands of years, the Chinese, Greeks, Romans, and Indians have used valerian as a mild sedative. The origin of the word "pew" is

said to come from the foul odor of the valerian root, which a first century AD Roman physician, Dioscorides, called phu. In the mid-1800s in the United States, the Shakers began growing valerian and other herbs to market to doctors and pharmacists in America and Europe. Valerian is sometimes used to flavor foods and drinks such as root beer [31-32].

Present Regulatory Status of Valerian: In the United States, United Kingdom and other major countries of the world, valerian is sold as a dietary supplement, and dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the Food and Drug Administration are not required unless claims are made for specific disease prevention or treatment. Because dietary supplements are not always tested for manufacturing consistency, the composition may vary considerably between manufacturing lots.

Designation of Valerian: Valerian (*Valeriana officinalis*, Valerianaceae) is a hardy perennial flowering plant, with heads of sweetly scented pink or white flowers. The flowers are in bloom in the northern hemisphere from June to September. Valerian was used as a perfume in the sixteenth century. Native to Europe and parts of Asia, Valerian has been introduced into North America. It is consumed as food by the larvae of some Lepidoptera (butterfly and moth) species including Grey Pug. Other names used for this plant include garden valerian (to distinguish it from other *Valeriana* species), garden heliotrope (although not related to *Heliotropium*) and all-heal. The garden flower red valerian is also sometimes referred to as "valerian" but is a different species, from the same family but not particularly closely related. Valerian, in pharmacology and phytotherapic medicine, is the name of a herb or dietary supplement prepared from roots of the plant, which, after maceration, trituration, dehydration processes, are conveniently packaged, usually into capsules, that may be used for certain effects including sedation and anxiolytic effect. The amino acid Valine is named after this plant. Valerian is an herbal remedy derived from the dried roots of the valerian plant, *Valeriana officinalis,* which as stated earlier belongs to the Valerianaceae family. It is often cultivated for its pinkish white or lavender flowers apart for its medicinal uses.

According to one marketing research firm, valerian is the fastest-growing herbal remedy in the United States; its sales more than doubled between 2000 and 2001. The part of the plant used medicinally is the root or rhizome. The rhizome is light grayish brown, about the size of a finger joint, bearing many rootlets. The fresh root has no odor, while the dried root smells distinctly unpleasant, akin to old gym socks, due to isovaleric acid. The plant itself is 50 to 150 cm tall with pinnate leaves and white or pink hermaphroditic flowers with three stamens; the stem is upright and without branches. It is sometimes used as a border in perennial gardens [33]. The root is chiefly used for medicinal benefits. It can be found in capsule, tea, tablet or liquid extract forms in most health food stores, some drugstores and online [34-35]. Due to the limitations of small sample size, variation in formulation, and inconsistent results in currently published clinical trials, further research is needed to clarify the efficacy and side effect profile of valerian, particularly in regard to long-term therapy. Valerian is a

medicinal herb commonly used in America today. Therefore, it is likely that a clinician will be faced with managing a patient who already is taking or wants to take this herb. Valerian is approved for use as a food ingredient by the United States Food and Drug Administration (FDA) and it ranks among the 10 most widely used herbs in the world. This assignment will provide both background and practical information to assist clinicians who may encounter patients interested in the use of valerian [36].

Botany of Valerian: An understanding of valerian's botanical classification is essential because misidentification can lead to products with unexpected and potential adverse effects. The FDA's Dietary Supplement Health and Education Act (DSHEA) of 1997, effective March 1999, requires manufacturers to include the identity of all botanicals on the product's label. A botanical's common name can be used if it is listed in *Herbs of Commerce;* otherwise, the botanical Latin binomial name of the plant must appear on the label.

Valerian refers to a number of plants that are members of the family Valerianaceae of the genus Valeriana L. and includes upwards of 250 species throughout the world [31]. *Valeriana officinalis* L. is the plant most often used medicinally and is known by several names: Common valerian, All Heal, Amantilla, Balderbrackenwurzel, Capon's Tail, Great Wild valerian, Garden Heliotrope, Herba Bendicta, Setewale, Setwell, Valeriana, and Vandal root. Other species, *V. Wallichii* DC also named *V. jatamansi* Jones (Indian valerian) and *V. edulis* NUTT sp (Mexican valerian) is used when high concentrations of valepotriates are desired [37-38]. The part of the plant that is used medicinally is the root (radix) or rhizome, which is light grayish brown, about the size of a finger joint, and has a strong acrid odor (disagreeable to some) after it is long-dried. The drug or pharmacopeial name for valerian root is Valerianae radix [37-38]. Valerian is a perennial plant that is native to Europe and can grow 4 feet tall. It is cultivated to decorate gardens but also grows wild in damp grasslands. Straight, hollow stems are topped by umbrella-like heads. Its dark green leaves are pointed at the tip and hairy underneath. Small, sweet-smelling white, light purple or pink flowers bloom in June. The root is light greyish brown and has little odour when fresh [39].

The valerian plant prefers the damp lime-rich soil near streams or rivers, where it may grow as tall as 5 ft (1.5 m). It can, however, be grown in drier soil at higher elevations, where it may grow only 2 ft (0.67 m) tall. Some herbalists consider the drier-climate variety of valerian to have greater medicinal potency. The parts of the plant that are used for medicinal purposes are the roots and rhizomes (horizontal underground stems), which are typically yellowish-brown in colour. The roots and rhizomes are harvested in the autumn of the plant's second year.

They can be freeze-dried and used to prepare tablets or capsules containing the ground herb. Juice can be pressed from the fresh root, or the root may be mixed with alcohol to become a fluid extract or tincture of valerian. When valerian is used to relieve tension or induce sleep, it is frequently combined with passion flower (*Passiflora incarnata*), lemon balm (*Melissa officinalis*) or

skullcap (*Scutellaria laterifolia*). Because valerian tea has a somewhat bitter taste, flavorings are often added, including peppermint or fruit flavour, to make a more pleasant-tasting drink [40].

FIG. 1: VALERIAN PLANT

Biology of Valerian Species: *Valeriana uliginosa* starts flowering from May to July, through August [41-43]. The erect annual and perennial species of *Valeriana*, including *V. uliginosa*, normally flower and fruit in response to seasonal fluctuations of climate. As of 1951, methods of pollination were unknown, but observations on several western United States species indicate that small insects of undetermined species may be important in pollination [44].

In Great Britain, *Valeriana officinalis* is adapted to butterfly pollination and is often visited by Lepidopterans. *Valeriana dioica* is visited by Dipterans in the Tipulidae (crane fly family) and Culicidae (mosquito family) [45]. Closer observation of *V. uliginosa* in New England may show if Lepidopterans, Dipterans, or other insect groups act as pollinators. The New England Wild Flower Society (NEWFS) has 100 *Valeriana uliginosa* seeds in its seed bank [46]. Seed germinated best when it was dried warm, followed by a cold treatment, then warm again. Nine of 17 seeds germinated. No studies have been done on the underground parts of *Valeriana uliginosa*, but information from *V. sitchensis* may be applicable. *Valeriana sitchensis* has short rhizomes and very limited vegetative spread. The new rhizome tip remains at the soil surface, and the older parts of the rhizome become buried by litter, up to about 10 mm. Branching occurs when a rhizome tip turns up to form an inflorescence. New rhizomes then form from lateral buds on the upturned rhizome. The roots radiate in all directions from the rhizome, though most angles downward, and few roots remain in the litter layer. The roots are up to 1 mm in diameter and sparsely branched except at the end [47].

It is unknown if *Valeriana uliginosa* is affected by pathogenic fungi. However, *V.sambucifolia* of Sweden is a host for *Uromyces valerianae*, and this fungus also infects other *Valeriana* species. Spores develop on the lower sides of *V. sambucifolia* leaves, and heavy infections can cause early leaf withering and a strong reduction or failure of fruit set. Seedlings can also become infected. There is a significant positive correlation between population densities of *V. sambucifolia* and infection by *Uromyces*. *Valeriana officinalis* has a strong fetid and aromatic odor, and this is common in many North American species, especially those in the series Officinales (*V. uliginosa*) [44]. Valeriana is economically important as a genus, primarily for the medicinal action of *V. officinalis*, but also for an aromatic perfume and less frequently as a culinary herb (*V. edulis*).

Valeriana officinalis is used today primarily as a mild sedative, but in the past was also used as an antispasmodic, emmenagogue, carminative, diuretic, and stimulant. It was one of the six most prescribed medicines in Europe and the United States (in between 1730 to 1930). But one thing should be noted that none of the native North American species is used medicinally [48].

Phytochemical Constituents of Valerian: The roots and rhizomes (underground stems) of valerian are typically used to make supplements, including capsules, tablets, and liquid extracts, as well as teas. The root of the plant is used medicinally and is pressed into fresh juice or freeze-dried to form powder. Valerian contains over 150 chemical constituents; many are physiologically active. There is substantial variation in the chemical constituents in plants from different sources, growing conditions, processing methods and storage conditions. Even in standardized plant extracts sold in Germany, there is some variation in the amount of different chemical constituents that may account for clinical efficacy. Despite these differences, the clinical effects appear to be remarkably consistent across different preparations [49].

Although the sedative effects of the plant's root have been known for centuries, the exact chemical compounds responsible for its activities have not been identified and agreed upon. There is little correlation between the content of volatile oils and the plant's clinical effects.[50] Valerian's effects on the central nervous system have been variously attributed to valepotriates, their breakdown products (baldrinals), valerenic acid, valerenal and valeranone, and other constituents in the essential oil [32, 51-52].

Potentially Active Chemical Constituents of Valerian [53-55]:

- Iridoid valepotriates (0.5% -2.0%): valtrates, isovaltrate, didrovaltrate, valerosidate and others
- Volatile essential oil (0.2 – 02.8%): bornyl isovalerenate and bornyl acetate; valerenic, valeric, isovaleric and acetoxyvalerenic acids; valerenal, valeranone, cryptofaurinol; and other monoterpenes and sesquiterpenes
- Alkaloids (0.01 – 0.05%): valeranine, chatinine, alpha-methyl pyrrylketone, actinidine, skyanthine and naphthyridylmethylketone.
- Lignans: hydroxypinoresinol [56-57]

Other Constituents: Amino acids (e.g. arginine, γ-aminobutyric acid; GABA), glutamine, tyrosine), caffeic and chlorogenic acids (polyphenolic), methyl 2-pyrrolketone, choline, tannins (type unspecified), gum and resin. The primary compounds identified in valerian root are essential or volatile oils (monoterpenes and sesquiterpenes), iridoids or valepotriates, pyridine-type alkaloids, and other miscellaneous compounds. Research has been conducted on isolated compounds and will be discussed in the pharmacology section; however, it is unknown whether valerian's activity resides in one compound or in a combination of several. Standardization of an herb entails utilizing pharmaceutical technology to ensure a product contains specific concentrations of a targeted active compound; until it is certain which compound is responsible for the desired action,

standardization of a particular chemical may not correlate with better pharmacological activity.

Valerian contains over 150 chemical constituents; many are physiologically active. There is substantial variation in the chemical constituents in plants from different sources, growing conditions, processing methods and storage conditions. Even in standardized plant extracts sold in Germany, there is some variation in the amount of different chemical constituents that may account for clinical efficacy. Despite these differences, the clinical effects appear to be remarkably consistent across different preparations.

Isovaleric acid is responsible for the herb's unpleasant aroma. *Actinidine* is a powerful attractant to cats, who will roll in valerian; catnip contains similar chemical compounds. Valerian also seems to be one of several plant species that concentrate chromium and are sometimes used to correct deficiencies of this mineral in developing countries. The essential oil is also thought to contribute to valerian's sedative effects *Valerenic acid* has spasmolytic and muscle relaxant effects and inhibits the breakdown of GABA in the central nervous system.

Valeric acid was once considered to be responsible for the sedative effects of this herb, but studies evaluating the isolated compound failed to document any sedative effects. Roots dried at temperatures less than 40 degrees Centigrade, as the German pharmacopeia requires, contain 0.5-2.0% *valepotriates*. Although valepotriates were once thought to be the active ingredients, these compounds are chemically unstable: they degrade readily, are poorly absorbed and are not found in teas (infusions) and tinctures. Instead, their degradation products, *baldrinals*, are found in such preparations, and may account for much of valerian's sedative effect.

The lignan *hydroxypinoresinol* also binds benzodiazepine receptors in the amygdala and is thought to work synergistically with bornyl acetate, valerenic acid, and the valepotriates in terms of valerian's overall sedative effects. Valerian's alkaloids are present only in minute amounts. They have cholinesterase activity *in vitro* which has not been verified in animals or humans. Because no single chemical within valerian has been shown to account for its clinical effects, most herbalists now conclude that it is a combination of ingredients, rather than a single ingredient, that accounts for valerian's medicinal effects. Remedies prepared from related species, *V. edulis* (Mexican valerian) or *V. wallichii* (Indian valerian) contain mixtures of valepotriates, with large amounts of didrovaltrate and isovaltrate; these preparations are used to treat problems with mental concentration, stress and anxiety. The onset of action appears to be within 30 minutes; the effects are largely gone within four hours. Though, other studies note cumulative benefits from taking the herb several times daily over one month. However, additional pharmacokinetic studies are needed.

Pharmacology of Valerian: The chemical composition of valerian includes sesquiterpenes of the volatile oil (including valeric acid), iridoids (valepotriates), alkaloids, furanofuran lignans, and free amino acids such as GABA, tyrosine, arginine, and glutamine. Although the sesquiterpene components of the

volatile oil are believed to be responsible for most of valerian's biologic effects, it is likely that all of the active constituents of valerian act in a synergistic manner to produce a clinical response. Research into physiologic activity of individual components has demonstrated direct sedative effects (valepo-triates, valeric acid) and interaction with neurotransmitters such as GABA (valeric acid and unknown fractions). The most likely pharmacologically active compounds in valerian are found in the valepotriates and the essential oil components. The valepotriates are lipophilic and highly unstable when exposed to conditions of heat, moisture, or acidity. Possible cytotoxicity demonstrated by two valepotriates: valtrate and didrovaltrate, which has raised safety concerns. In vitro studies have shown that these compounds caused cell death in cultured rat hepatoma cells.

However, in vivo studies have shown no significant cytotoxic effects of valtrate on mouse bone marrow early progenitor cells. Generally, valepotriates have been described to impart spasmolytic or relaxing effects on the smooth muscle system, sedative properties, anti-convulsant activity, psychostimulant activity, and effectiveness in the treatment of behavior disorders. They have also been observed to antagonize the hypnotic effect of alcohol, and to blunt the toxicity of ethanol in animals. It has been suggested that valepotriates interact synergistically with the essential oil constituents to produce nervous system activity. The sedative properties of valerian's essential oil components may be partially due to the kessane derivatives, which comprise a major portion of the essential oil. In animal tests, alpha-kessyl alcohol, an essential oil constituent, appears to be responsible for the oil's anti-depressant action. Valerenic acid has also shown sedative, spasmolytic, and musclerelaxant action. Preliminary studies have been performed to verify the mechanism of action of valerian. Receptor binding studies (using guinea pig brains) have shown that constituents contained in the extract of *V. officinalis* do bind to benzodiazepine or GABA receptors. Another study using an extract of valerian (rhizomes and root of *V. officinalis*) on synaptosomes isolated from rat brain cortices demonstrated GABA activation and the reuptake inhibition of the neurotransmitter in nerve terminals.

In addition to sleep disorders, valerian has been used for gastrointestinal spasms and distress, epileptic seizures, and attention deficit hyperactivity disorder. However, scientific evidence is not sufficient to support the use of valerian for these conditions. Be aware that the U. S. FDA does not strictly regulate herbs and dietary supplements. There is no guarantee of strength, purity or safety of products containing or claiming to contain valerian. Decisions to use herbs or supplements should be carefully considered. Individuals using prescription drugs should discuss taking herbs or supplements with their pharmacists or health care providers before starting. Scientists have studied valerian for the following health problems:

Insomnia: Several studies suggest that taking valerian by mouth may reduce the time it takes for people to fall asleep and may improve sleep quality, especially in those who routinely suffer from insomnia or sleep difficulties. One study conducted in children with intellectual difficulties reports that valerian may be useful

in the long-term treatment of sleep disruption. Valerian does not appear to cause a "hangover" effect the morning after use. Preliminary findings suggest that effects may be better with repeat use, rather than single-dose use. One study suggests a positive effect in insomniacs who are experiencing withdrawal symptoms from benzodiazepine. Another study showed that valerian extract may be comparable to the effects of the prescription benzodiazepine drug oxazepam (Serax) for insomnia. Further research is necessary to confirm these results. Several clinical studies have shown that valerian is effective in the treatment of insomnia, most often by reducing sleep latency. A double-blind, placebo-controlled trial compared 400-mg aqueous extract of valerian and a commercial valerian/hops preparation with placebo of encapsulated brown sugar. A total of 128 volunteers completed a subjective study evaluating the effects of single doses of each test compound taken in random order on sleep latency, sleep quality, sleepiness on awakening, night awakenings, and dream recall. Valerian extracts demonstrated statistically significant improvement over placebo in sleep latency and sleep quality.

There was no difference between valerian extract and placebo in the other two parameters. The commercial valerian/hops preparation resulted in no changes in sleep latency, sleep quality, or night awakenings, and an increase in sleepiness on awakening. No information on the preparation of the commercial product was available, so the reasons for the lack of effect are unknown. Examination of the study subgroups showed that the positive effects of valerian extract on sleep were most significant in older male patients who considered them to be poor sleepers, female poor sleepers, younger poor sleepers, smokers, and those who habitually have lengthy sleep latencies. Subjects who rated themselves as habitually good sleepers were largely unaffected by the valerian extract. In a double-blind study, eight subjects who described themselves as having lengthy sleep latency wore a wrist activity meter and provided subjective sleep ratings in a study of the effects of valerian. Participants received either a 450 or 900 mg dose of an aqueous extract of valerian root or placebo.

Single-dose (450 and 900 mg) valerian extract resulted in significant decreases in measured and subjective sleep latency and more stable sleep during the first quarter of the night, with no effect on total sleep time. The 900 mg dose produced increased sleepiness on awakening compared with placebo. A randomized, placebo-controlled, double-blind, cross-over study involving 16 patients with insomnia confirmed by polysomnography demonstrated no effects on sleep efficiency after a single 600-mg dose of the valerian extract Sedonium, while multiple doses over 14 days resulted in significant improvement in parameters of slow-wave sleep measured by polysomnography.

There was a non-significant trend toward reduced subjective sleep latency after the long-term valerian treatment. Several studies have shown valerian’s efficacy in patients who do not have sleep disturbances. A small study of 10 patients at home and eight patients at a sleep laboratory who received two different dosages (450 and 900 mg) of an aqueous extract of valerian root demonstrated

that both groups experienced a greater than 50% improvement in sleep latency and wake time after sleep onset. The efficacy results were based on questionnaires, self- rating scales, and night time motor activity. Electro-encephalographic recordings in the laboratory section of the study showed no differences in efficacy between valerian and placebo, and data indicated a dose-dependent mild hypnotic effect of the valerian extract. A recent systematic analysis of randomized trials of the effect of valerian on patients with insomnia included reports in all languages. Another study demonstrated effects after days 1 and 8 in slow-wave sleep, but no effect on subjective measures of sleep. Results were contradictory in six acute-dose studies. The authors pointed out the wide variety of methodologies used in the studies, and the lack of attention to factors such as randomization, blinding, compliance, withdrawal, confounding variables, diagnostic criteria, and statistical analysis.

They concluded that evidence for valerian in the treatment of insomnia is inconclusive, and that more rigorous trials are necessary. A recent report compared a 600 mg dose of the valerian extract Sedonium with 10 mg of oxazepam over a six-week period in 202 patients who were diagnosed with non-organic insomnia. The two agents were equally effective in increasing sleep quality as measured by the Sleep Questionnaire B, and these results were confirmed by subscales of the SF-B, the Clinical Global Impression Scale, and the Global Assessment of Efficacy. Mild to moderate adverse events occurred in 28.4% of patients receiving the valerian extract and 36% of patients taking oxazepam.

Valerian is a popular alternative to commonly prescribed medications for sleep problems because it is considered to be both safe and moderate. Some studies bear this out, although not all have found valerian to be effective. One of the best designed studies found that valerian was no more effective than placebo for the first 28 days, but after that valerian greatly improved sleep for those who were taking it. That has led researchers to speculate that you may need to take valerian for a few weeks before it begins to work. Other studies have shown that valerian reduces the time it takes to fall asleep and improves the quality of sleep itself. Plus, unlike many prescription sleep aids, valerian may have fewer side effects such as morning drowsiness.

The use of valerian is supported by some evidence from clinical studies. The problem with many of the studies, however, is they've generally been small, used different amounts of valerian for varying lengths of time, or had problems with the study design, making it impossible to form a conclusion about the effectiveness of valerian. Valerian appears to be less effective than prescription sleep medication. One possible advantage of valerian, however, is that it may not have as much of a "hangover" effect on mental or physical functioning the following day. Also, people taking sleeping pills sometimes have a temporary worsening of insomnia when they are discontinued, an effect that hasn't been reported with valerian.

Sedative: A few studies suggest that valerian does not possess significant sedative properties. A small double-blind, randomized, crossover, placebo-controlled study was

performed in healthy elderly people to assess the effects of temazepam (Restoril), diphenhydramine (Benedryl) and valerian. The results confirmed that valerian was not different from placebo (sugar pill) on any measure of drowsiness (psychomotor function) or sedation.

Anxiety: Anxiety disorders are a very common mental health problem in the general population and in the primary care setting. In the US National Comorbidity Survey Kessler 1994 found one year prevalence for anxiety disorders of 17% and a lifetime prevalence of almost 25% [59]. Using the Composite International Diagnostic Interview (CIDI) in 1996-99, Bijl et al. included 7076 people in 90 municipalities in the Netherlands, and detected a prevalence rate for anxiety of 19.3% in the general population [60]. In Brazil, the prevalence of anxiety was reported at 12.1% in Brasilia, 6.9% in Sao Paulo and 5.4%in Porto Alegre [61]. One study has found a marked reduction in quality of life and psychosocial functioning in people with anxiety disorders [62].

Although anxiety is a treatable disorder, it is often not diagnosed and treated properly. The majority of patients suffering from anxiety consult their general practitioner, and often their complaint presents as a physical symptom, such as headache, palpitations, breathing difficulties or chest pain [63]. Anxiety may be associated with physical disorders such as diabetes, arthritis and cancer, or it may be the primary symptom of a specific psychiatric disorder such as generalized anxiety disorder, post-traumatic stress disorder, panic or obsessive compulsive disorder. Benzodiazepines are effective in short-term treatment but their overuse may cause dependence [81]. Psychotherapy is effective and is commonly used to treat anxiety [64-68]. A systematic review on psychological therapies for generalized anxiety disorder has been conducted and is expected to be published soon in The Cochrane Library [69]. Another systematic review has found that cognitive behavioral therapies and pharmacological treatments including buspirone, trazodone, imipramine and ritanserin significantly improved anxiety [70]. However; psychotherapy may be an unrealistic option in public health settings in many countries as it is costly and time consuming, and although pharmacological treatments are effective, they may be limited by their side effects and cost. Herbal medicines are in popular usage worldwide, and could be considered as a treatment option for anxiety disorders if shown to be effective and secure. A systematic evaluation on the effectiveness of kava kava showed its superiority as compared with placebo [71].

No systematic review on valerian for anxiety has yet been conducted. Valerian is one of the most popularly used herbal medicines for insomnia and is also used for anxiety. It is used in the form of a dried herb (0.5-2 g taken 3-4 times/day), extract (0.5-2.0 ml) or tincture (2-4 ml). Hydroalcoholic and aqueous extracts of valerian roots have shown affinity for the GABA-A receptor in the brains of rats [8]. In another experiment, valerian oil injected intraperitoneally showed central depressive and muscle relaxation activity in mice [32]. Valepotriates are the most active principle of valerian, but are very labile and unlikely to be present in the finished preparations. In rats there is evidence of inhibition of motor activity,

inhibition of aggressiveness, prolongation of anaesthesia by hexobarbital [72] but with better motor coordination [73]. In humans, valerian does not seem to potentiate the effect of alcohol, but demonstrates a positive action in tests of concentration and efficiency, [74] and has been successful in the treatment of insomnia and tension. Although valerian has been used for a long time for treating anxiety disorders its efficacy and side effects are not yet fully established. This review aimed to examine the effectiveness and safety of anxiety disorders [75-80]. Although early evidence suggests that valerian may possess some anti-anxiety properties, there are no clear answers in this area.

Some of these studies have been done using combination products containing more than one herb. More research is needed before valerian can be recommended as a treatment for anxiety and related disorders. Traditional herbalists have used valerian as an anxiolytic, frequently in combination with other herbal preparations such as passion flower and St. John's wort. There is a minimal amount of scientific data confirming this indication for valerian. One randomized, double-blind, placebo-controlled trial compared valerian (100 mg) with propranolol (20 mg), a valerianpropranolol combination, and placebo in an experimental stress situation in healthy subjects.

Unlike propranolol, valerian had no effect on physiologic arousal but significantly decreased subjective feelings of somatic arousal. In a recent preliminary, randomized, double blind, placebo-controlled trial, 1636 patients with a diagnosis of generalized anxiety disorder were treated with placebo, diazepam in a dosage of 2.5 mg three times daily, or valerian extract in a dosage of 50 mg three times daily (80% dihydrovaltrate, 15% valtrate, and 5% acevaltrate) for four weeks. Dosage was regulated at one week if an interviewing psychiatrist deemed an increase or decrease necessary. Although the study was limited by a small number of patients in each group, relatively low dosages of the active agents, and a short duration of treatment, the authors found a significant reduction in the psychic factor of the Hamilton Anxiety Scale (HAMA) with diazepam and valerian. Another RCT17 compared 120 mg of kava, 600 mg of valerian, and placebo taken daily for seven days in relieving physiologic measures of stress induced under laboratory conditions in 54 healthy volunteers. Valerian and kava, but not placebo, significantly decreased systolic blood pressure responsively, heart rate reaction, and self-reported stress.

Depression: A multicenter clinical trial was performed to assess the effectiveness of valerian extract and St. John's wort in depression with comorbid anxiety. The studied determined that symptoms of depression and anxiety improved faster with valerian than with St. John's wort alone. Valerian alone has not been proven to aid in depression or anxiety. More research is necessary before this therapy can be recommended.

Menopausal Symptoms: Valerian has been studied along with other herbs to help with sleep disturbances and hot flashes present during pre and post menopause. Further research is needed to make a recommendation.

Stress: Valerian may be beneficial to health by reducing the physical reactions during stressful situations. A clinical trial studied the effects of valerian or kava on psychological stress induced in a laboratory. The study found that valerian or kava may reduce the physical reactions of stress and may therefore be beneficial to health. More studies are needed before any conclusions can be made.

Unproven Uses: Valerian has been suggested for many other uses, based on tradition or on scientific theories. However, these uses have not been thoroughly studied in humans, and there is limited scientific evidence about safety or effectiveness. Some of these suggested uses are for conditions that are potentially very serious and even life-threatening. One should consult physician care provider before using valerian for any unproven use like absence of menstrual period, aches, acne, anorexia, arthritis, epilepsy, urinary tract disorders etc.

Mechanism of Action of Valerian: Many chemical constituents of valerian have been identified, but it is not known which may be exactly responsible for its sleep-promoting effects in animals and in *in vitro* studies. It is likely that there is no single active compound and that valerian's effects result from multiple constituents acting independently or synergistically. Two categories of constituents have been proposed as the major source of valerian's sedative effects. The first category comprises the major constituents of its volatile oil including valerenic acid and its derivatives, which have demonstrated sedative properties in animal studies. However, valerian extracts with very little of these components also have sedative properties, making it probable that other components are responsible for these effects or that multiple constituents contribute to them. The second category comprises the iridoids, which include the valepotriates. Valepotriates and their derivatives are active as sedatives *in vivo* but are unstable and break down during storage or in an aqueous environment, making their activity difficult to assess. A possible mechanism by which a valerian extract may cause sedation is by increasing the amount of GABA, an inhibitory neurotransmitter) available in the synaptic cleft. Results from an in vitro study using synaptosomes suggest that a valerian extract may cause GABA to be released from brain nerve endings and then block GABA from being taken back into nerve cells. In addition, valerenic acid inhibits an enzyme that destroys GABA.

Valerian extracts contain GABA in quantities sufficient to cause a sedative effect, but whether GABA can cross the blood-brain barrier to contribute to valerian's sedative effects is not known. Glutamine is present in aqueous but not in alcohol extracts and may cross the blood-brain barrier and be converted to GABA. Levels of these constituents vary significantly among plants depending on when the plants are harvested, resulting in marked variability in the amounts found in valerian preparations. The Valerenic acid also appears to inhibit the enzyme system responsible for the central catabolism of GABA, increasing GABA concentration and decreasing CNS activities. There is also some evidence that may suggest valerian containing other constituent such as lignan and GABA, which may be responsible for sedative effects of valerian because of valerian's historical use as a

sedative, anti-convulsant, migraine treatment and pain reliever, most basic science research has been directed at the interaction of valerian constituents with the GABA neurotransmitter receptor system. These studies remain inconclusive and all require independent replication. Valerian also contains isovaltrate, which has been shown to be an agonist for adenosine A_1 receptor sites. This action may contribute to the herb's sedative effects. Under the US Preventative Services Task Force's (USPSTF) classification system for herbs, valerian was rated as probably safe and effective as a sleep aid, based on evidence from randomized clinical trials. In respect to its spasmolytic properties, it was rated possibly effective and probably safe, based on animal studies.

While valerian appears to be safe and possibly effective, the literature available in the English language evaluating this herb is limited due to small sample size, short study duration, and some inconsistent results. Valerian's long-term safety has yet to be demonstrated, and therefore it should not be recommended for extended use for any indication. Valerian's main attribute may be that it serves as an alternative, with a low incidence of side effects, to synthetic sedative agents. When recommended, patients should be counseled about possible side effects and closely monitored during therapy [7-8].

Pharmacokinetics of Valerian: There are inadequate data on the pharmacokinetics of valerian preparations and their constituent compounds. The pharmacokinetics of valerenic acid were explored in a single-dose study involving six healthy adults who received a 70% ethanol extract of valerian root (drug to extract ratio 5: 1) 600 mg in the morning. For five participants, maximum serum concentrations of valerenic acid occurred between one and two hours after valerian administration and ranged from 0.9 to 2.3 ng/mL; valerenic acid concentrations were measurable for at least five hours after valerian administration. For one subject, maximum concentrations occurred at both one and five hours after valerian administration. The mean elimination half-life ($t_{1/2}$) for valerenic acid was 1.1 hrs and the mean area under the plasma concentration time curve was 4.80 µg/mL/hr. Further investigation of the pharmacokinetics of valerian is required, including those of different manufacturers' preparations and their constituents.

Fundamental Use of Valerian: Valerian is a versatile Ayurvedic remedy for a variety of ailments and diseases. It was given during World War I to soldiers suffering from battle shock. It has also been recommended for the relief of menstrual cramps and as a carminative, or preparation that relieves gas in the stomach and intestines. Lotions made with valerian extract are said to soothe skin rashes and swollen joints. There is some disagreement among researchers about the efficacy of valerian as a tranquilizer and aid to sleep. While a team of Swiss researchers found a valerian/lemon balm combination to be significantly more effective than a placebo in inducing sleep, another group in the United States concluded that valerian is overrated as a sedative. Further research may help to settle the question, but multiple studies that are currently available are inconclusive. Following

sections sequentially narrates basic uses of valerian:

Food Use: Valerian is not generally used as a food. Valerian is listed by the Council of Europe as a natural source of food flavouring. Previously, valerian has been listed as GRAS (Generally Recognised as Safe).

Medicinal Use: Valerian is used against sleeping disorders, restlessness and anxiety, and as a muscle relaxant and is often indicated as transition medication when discontinuing benzodiazepines. It has been recommended for epilepsy but that is not supported by research (although valproic acid-an analogue of one of Valerian's constituents, valeric acid is used as an anticonvulsant and mood-stabilizing drug). It has also been reported to cause agitation, headaches and night terrors in some individuals. This may be due to the fact that some people lack a digestive conversion property necessary to effectively break down Valerian. One study found that valerian tends to sedate the agitated person and stimulate the fatigued person, bringing about a balancing effect on the system.

Valerian is used for insomnia and other disorders and can be a useful alternative to benzodiazepine drugs. However more recent research has shown it to be ineffective in this use. A recent article states, "Most studies found no significant differences between valerian and placebo either in healthy individuals or in persons with general sleep disturbance or insomnia." In the United States Valerian is sold as a nutritional supplement. Therapeutic use has increased as dietary supplements have gained in popularity, especially after the Dietary Supplement Health and Education Act was passed in 1994. This law allowed the distribution of many agents as over-the-counter supplements, and therefore allowed them to bypass the regulatory requirements of the Food and Drug Administration (FDA). Under the US Preventative Services Task Force's (USPSTF) classification system for herbs, valerian was rated as probably safe and effective as a sleep aid, based on evidence from randomized clinical trials. In respect to its spasmolytic properties, it was rated possibly effective and probably safe, based on animal studies.

While valerian appears to be safe and possibly effective, the literature available in the English language evaluating this herb is limited due to small sample size, short study duration, and some inconsistent results. Valerian's long-term safety has yet to be demonstrated, and therefore it should not be recommended for extended use for any indication. Valerian's main attribute may be that it serves as an alternative, with a low incidence of side effects, to synthetic sedative agents. When recommended, patients should be counseled about possible side effects and closely monitored during therapy.

Other Herbal Use: Valerian is stated to possess sedative, mild anodyne, hypnotic, antispasmodic, carminative and hypotensive properties. Traditionally, it has been used for hysterical states, excitability, insomnia, hypochondriasis, migraine, cramp, intestinal colic, rheumatic pains, dysmenorrhoea, and specifically for conditions presenting nervous excitability. Modern interest in valerian is focused on its use as a sedative and hypnotic. A Community Herbal Monograph adopted by the European Medicines Agency's Committee on

Herbal Medicinal Products states the following therapeutic indications for valerian root: traditional use, for support of mental relaxation and to aid natural sleep; well-established use, for the relief of mild nervous tension and difficulty in falling asleep.

Classical Uses Based on Tradition or Scientific Theory: The below uses are based on tradition or scientific theories. They often have not been thoroughly tested in humans, and safety and effectiveness have not always been proven. Some of these conditions are potentially serious, and should be evaluated by a qualified healthcare provider.

Acne, amenorrhea (lack of menstruation), angina (chest pain), anorexia, anti-seizure, antiperspirant, antiviral, arthritis, asthma, bloating, bronchospasm, congestive heart failure, constipation, cough, cramping (abdominal, pelvic, menstrual), digestive problems, diuretic (increase urine flow), dysmenorrhea (pain with menstrual cycle), emmenagogue (stimulation of menstrual blood flow), epilepsy, fatigue, fever, flatulence (gas), hangovers, headache, heart disease, heartburn, high blood pressure, HIV, hot flashes, hypochondria, irritable bowel syndrome, liver disorders, measles, memory enhancement, migraine, mood enhancement, muscle pain/spasm/tension, nausea, nerve pain, pain relief, restlessness, stomach ulcers, premenstrual syndrome (PMS), restless leg syndrome, rheumatic pain, skin disorders, stress, urinary tract disorders, vaginal infections, vertigo, viral gastroenteritis, vision problems, withdrawal from tranquilizers.

Recommended Dosage: The doses listed below are based on scientific research, publications or traditional use. Because most herbs and supplements have not been thoroughly studied or monitored, safety and effectiveness may not be proven. Brands may be made differently, with variable ingredients even within the same brand. Appropriate dosing should be discussed with a health care provider before starting therapy; always read the recommendations on a product's label. The dosing for unproven uses should be approached cautiously, because scientific information is limited in these areas. Valerian has only been studied for four to six weeks of use. It should not be used for longer without the supervision of a health care provider. The below doses are based on scientific research, publications, traditional use, or expert opinion. Many herbs and supplements have not been thoroughly tested, and safety and effectiveness may not be proven. Brands may be made differently, with variable ingredients, even within the same brand. The below doses may not apply to all products. You should read product labels, and discuss doses with a qualified healthcare provider before starting therapy.

For Mild Insomnia:

Adults (Aged 18 or Older):

- **Capsules:** 300-1800 mg of valerian have been taken my mouth
- **Aqueous or aqueous-ethanol extract**: A dose of 1.5 to three grams of herb has been taken by mouth 30 to 60 minutes before going to bed
- **Tea:** A dose of 1.5 to three grams of valerian root steeped in 150 mL of boiling water for 5-10 minutes has been taken orally about 30 to 60 minutes before going to bed

Children (Younger than 18): The dosing and safety of valerian have not been studied thoroughly in children, and valerian is therefore not recommended.

For Sedation or Stress Reduction:

- **Aqueous or aqueous-ethanol extract:** A dose of 100 to 600 mg taken by mouth before or after stressful events has been used.
- **Tea:** A dose of 1.5 to three grams of valerian root steeped in 150 ml of boiling water has been taken by mouth five to 10 minutes before or after stressful events.

Experts in herbal preparations recommend that valerian products should be standardized to contain 0.8% valerenic or valeric acid. Adults may use the following amounts of valerian to reduce nervousness or relieve menstrual cramps:

- 2–3 g dried root in tea, up to several times daily
- 1/4–1/2 tsp (1–3 ml) valerian tincture, up to several times daily
- 1/4 tsp (1–2 ml) fluid extract
- 150–300 mg valerian extract, standardized to contain0.8% valerenic acid.

To relieve insomnia, one of the above dosages may be taken 30–45 min before bedtime. It may take one to two weeks of regular use before the herbal preparation takes effect. When giving valerian to children, recommended adult dosages should be adjusted in proportion to the child's weight. Most dosages of herbal products are calculated for an adult weighing 150 lb (70 kg). A child weighing 75 lb (35 kg) should therefore receive 1/2 the adult dose.

Quality of Plant Material and Commercial Products (Table 1): According to the British and European Pharmacopoeias, valerian consists of the dried underground parts of *V. officinalis* L., including the rhizome surrounded by the roots and stolons. It contains not less than 5 mL/kg of essential oil for the whole drug and not less than 3 mL/kg for the cut drug, both calculated with reference to the dried drug, and not less than 0.17% of sesquiterpenic acids expressed as valerenic acid, calculated with reference to the dried drug. As with other plants, there can be variation in the content of active compounds (e.g. valerenic acid derivatives and valepotriates) found in valerian rhizomes and roots.

TABLE 1: PRICE OF AVAILABLE MARKETED PRODUCTS OF VALERIAN

DRUG	MONTHLY COST (Rs)	SIDE EFFECTS	CONTRAINDICATION
Valerian 500 mg	125	Dizziness, stomach upset	Pregnant/nursing
Zolpidem Tartrate (AMBIEN ® 10 mg)	5100	Dizziness, headache	Renal, hepatic, or respiratory impairment
Diphenhydramine HCl 50 mg	155	Dry mouth, dizziness	Hypersensitivity
Temazepam 15 mg	640	Dizziness, addictive	Pregnancy complications

*Price may vary according to the location, where valerian is sold

General Preparations of Valerian: Valerian fluid extracts and tinctures are sold in alcohol or alcohol-free (glycerite) bases. Powdered valerian is available in capsule or tablet form, and also as a tea. Valerian root has a sharp odor, and to mask the scent valerian is often combined with other calming herbs, including passionflower (*Passiflora incarnata*), hops (*Humulus lupulus*), lemon balm (*Melissa officinalis*), skullcap (*Scutellaria lateriflora*), and kava (*Piper methysticum*). Kava has been associated with liver damage, so it is best avoided [59].

The chief constituent of Valerian is a yellowish-green to brownish-yellow oil which is present in the dried root varying from 0.5- 2% though an average yield rarely exceeds 0.8%. This variation in quantity is partly explained by location: a dry, stony soil, yielding a root richer in oil than one that is moist and fertile. The volatile oils that form the active ingredient are extremely pungent, somewhat reminiscent of well-matured cheese or wet dog. Valerian tea should not be prepared with boiling water, as this may drive off the lighter oils.

Preparations of valerian marketed as dietary supplements are made from its roots, rhizomes (underground stems), and stolons (horizontal stems). Dried roots are prepared as teas or tinctures, and dried plant materials and extracts are put into capsules or incorporated into tablets. There is no scientific agreement as to the active constituents of valerian, and its activity may result from interactions among multiple constituents rather than any one compound or class of compounds. The content of volatile oils, including valerenic acids; the less volatile sesquiterpenes; or the valepotriates (esters of short-chain fatty acids) is sometimes used to standardize valerian extracts. As with most herbal preparations, many other compounds are also present. Valerian is sometimes combined with other botanicals. Because this fact sheet focuses on valerian as a single ingredient, only clinical studies evaluating valerian as a single agent are included.

Available Dosage Forms of Valerian: Dosages for oral administration (adults) for traditional uses recommended in standard herbal reference texts are given below;

- **Dried rhizome/root:** 1- 3 g as an infusion or decoction up to three times daily.
- **Tincture:** 3-5 mL (1:5; 70% ethanol) up to three times daily.
- **Extracts:** Once to several times daily; 2-6 mL of 1:2 liquid extract daily.

Doses given in older texts vary. For example: Valerian Liquid Extract (BPC 1963) 0.3-1.0 mL; Simple Tincture of Valerian (BPC 1949) 4-8 mL; Concentrated Valerian Infusion (BPC 1963) 2-4 mL. Clinical trials investigating the effects of valerian root extracts on sleep parameters have used varying dosages, for example, valerian extracts 400 mg/day (drug to extract ratio of 3:1) and 1215 mg/day (drug to extract ratio of 5-6:1).

Recommended Time for Usage:

- Capsules: 400 to 900 mg by mouth at bedtime.
- Tea: single dose, 2 to 3 grams of herbs or dry extract by mouth.
- Tincture: 1 to 3 ml (20 to 60 drops) by mouth.

Can Valerian be Harmful? Few adverse events attributable to valerian have been reported for clinical study participants. Headaches, dizziness, pruritus, and gastrointestinal disturbances are the most common effects reported in clinical trials but similar effects were also reported for the placebo. In one study an increase in sleepiness was noted the morning after 900 mg of valerian was taken. Investigators from another study concluded that 600 mg of valerian did not have a clinically significant effect on reaction time, alertness, and concentration the morning after ingestion. Several case reports described adverse effects, but in one case where suicide was attempted with a massive overdose it is not possible to clearly attribute the symptoms to valerian. Valepotriate, which is a component of valerian has cytotoxic activity *in vitro* but were not found carcinogenic in animal studies [22-24, 27, 81-85].

Side effects of Valerian: Some people taking valerian may experience a paradoxical effect; that is, they may feel agitated or jittery instead of relaxed or sleepy. This side effect is not dangerous, but it should be reported to the patient's health care provider. If the dosage is too high, an individual could experience longer sleep than usual, and wake up not feeling well-rested [86]. Prolonged use of valerian results in tolerance, and increasing the dose may have serious side effects. According to some researchers, long-term use of valerian may cause psychological depression, damage to the liver, or damage to the central nervous system. High short-term doses of valerian have been reported to cause headaches, muscle spasms, dizziness, digestive upsets, insomnia, and confusion [87]. Although valerian has been regarded as a relatively safe herb because few interactions with prescription medications have been reported, newer research indicates that it should be used cautiously following surgery. Like St. John's wort, valerian can interact with anaesthetics and other medications given to patients after surgery. Because valerian has a mild sedative effect, it should not be taken together with alcoholic beverages, benzo-diazepines, barbiturates, or antihistamines. Some components of valerian are metabolized in the liver. This herb has the potential to interact with liver metabolized prescription medicines [88-89]. More recently, a review conducted by researchers from an evidence-based complementary and alternative medicine website suggested that valerian is “safe and effective” for treating insomnia [90]. More than half of these studies included very small sample sizes, and evidence suggests that small positive trials are more likely to be published than small negative trials.

Valerian has also been suggested for the treatment of anxiety, but there is limited evidence to support its effectiveness. In their randomized, double-blind, placebo- controlled trial evaluating the use of valerian for generalized anxiety disorder, Andreatini and colleagues found that Contraindication/allergies: Valerian is contraindicated in patients who are pregnant or lactating. It also should not be administered to children less than 12 years. Most herbs and supplements have not been thoroughly tested for interactions with other herbs, supplements, drugs, or foods. The interactions listed below are based on reports in scientific publications, laboratory experiments, or traditional use. You should always read product labels. If you have a

medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy [91].

Drug interactions and Drug-Disease Interactions:

Drug Interactions: Alcohol, barbiturates, benzodiazepines. Valerian can also inhibit CYP_{450} enzyme. This is because valerian may increase levels of drug metabolized by CYP_{450} e.g. lovastatin, ketoconazole, itraconazole, fenofenadine, triazolam, chemotherapeutic agent. This has not been reported in humans so caution should be taking when recommending in patients taking these drugs.

Adverse Effects: Headaches, nausea, trouble sleeping nervousness, palpitation, and morning drowsiness are the acute side effects of valerian. Hepatotoxicity is a chronic side effect, which may be due to idiosyncratic reactions. Other side effects include breathing problems or chest tightness, chest pain, skin hives, rash, or itchy or swollen skin. Increase in dose of Valerian may lead to increase in adverse effects [92-93].

Potential Dangers: Valerian is listed by the FDA as a food supplement and is, therefore, not subject to regulatory control beyond labeling requirements. According to Commission E monographs, there are no contraindications to valerian. Reported adverse effects of valerian are rare. In a 14 day, multiple-dose study of 16 patients, there were only two adverse events (migraine and gastrointestinal effects) in patients receiving valerian compared with 18 events in patients receiving placebo. A randomized, controlled, double-blind study of 102 subjects evaluated reaction time, alertness, and concentration the morning after using valerian root extract (600 mg) and found no negative effect in single- or repeated-dose administrations of valerian. Only one adverse effect (dizziness) was attributed to the valerian extract. No evidence of potentiating of valerian effects by concomitant ingestion of alcohol has been found in animal and human studies, but the combination should still be avoided. Valerian may potentiate the sedative effects of barbiturates, anesthetics, and other central nervous system depressants. One case report suggests that sudden cessation of long-term high dose valerian therapy (530 mg to 2 g, five times daily) may result in withdrawal symptoms similar to those occurring with benzodiazepine use. Perhaps because of the poorly defined effects of valerian on GABA neurotransmission, valerian appears to attenuate benzodiazepine withdrawal symptoms in animals and humans [94-95].

Allergies: People with allergies to plants in the *Valerianaceae* family may be allergic to valerian. Few side effects have been reported when valerian is used at recommended doses. Rare problems may include headaches, excitability, decreased ability to concentrate, inability to sleep, uneasiness, dizziness, shakiness, unsteady walking, lower-than-normal body temperature (hypothermia), stomach discomfort, nausea or vomiting. It is not clear if valerian causes drowsiness or sedation, although early studies suggest that this may not be a major problem. Nonetheless, you should avoid driving or operating heavy machinery, especially within a few hours of each dose. Although not extensively studied, it is possible that valerian may cause adverse effects on the liver or heart, especially if high

doses are used for long periods of time. If you have been diagnosed with a heart or liver disorder and are considering taking valerian, discuss this with your health care provider [96-101].

Valerian Effect on Pregnancy and Breast-Feeding: Valerian cannot be recommended during pregnancy or breast-feeding because there is not enough information available. In theory, valerian may cause birth defects. Pregnant women should avoid ethanol (alcohol) extracts. Because there is limited human safety data, valerian use during pregnancy and breastfeeding is not recommended. There are theoretical concerns over the adverse effects of chemical components that are toxic in laboratory studies.

No adverse effects have been reported when taken in typical doses, but safety during pregnancy and lactation has not been established. Some tinctures contain 40-60% alcohol. Mutagenic effects on bacteria were reported from the decomposition products of valtrate and isovaltrate, but these compounds are unstable in aqueous solution [99-100] the implications for human use of this finding in bacteria are uncertain. In pregnant rats given valepotriates for 30 days, there was no impact on fertility, fetotoxicity or other adverse effects on mother or offspring [101]. Long-term administration to pregnant rats and their offspring did not lead to any adverse effects [50].

Fetal Risk Summary for Valerian: Reproductive studies in animals with valerian have not shown antiovulation, antifertilization, or embryotoxic effects. Further, the valepotriates exhibit low toxicity in mice, producing no deaths in doses of up to 1600 mg/kg intraperitoneally or 4600 mg/kg orally. Toxicity in mice was characterized by ataxia, hypothermia, and increased muscle relaxation. The cytotoxic activities of three valepotriate compounds, valtrate, didrovaltrate, and baldrinal (a degradation product of valtrate), in cultured rat hepatoma cells were described in a 1981 Reference. Both valtrate and didrovaltrate demonstrated much greater cytotoxic activity than did baldrinal, with rapid and irreversible toxicity. In addition, the antitumor activity of didrovaltrate was demonstrated in vivo on female mice ascitic tumors. Five surviving mice were then bred with normal male mice 50 days after treatment with didrovaltrate. Each had a normal pregnancy and produced normal offspring.

In a 1988 report, two cases of attempted suicide with valerian dry extract plus other drugs were described. In one case, a woman at 10 weeks' gestation ingested 2.5 g of valerian dry extract and 0.5 g of phenobarbital. An apparently normal, 4350 g female infant was delivered at 42 weeks' gestation. Examination of the child (age not specified) indicated an IQ in the range of 111 to 120. In the second case, the mother ingested a combination of valerian dry extract (3.0 g), phenobarbital (0.6 g), glutethimide (5.0 g), amobarbital (5.0 g), and promethazine (0.3 g) at 20 weeks' gestation. A mentally retarded, 2650-g male infant was born at 36 weeks' gestation. About 2 years later in her next pregnancy, this woman again attempted suicide at 20 weeks' gestation, by ingesting glutethimide (3.75 g), amobarbital (3.75 g), and promethazine (0.23 g). It was delivered to another mentally retarded, 2650-g male infant at 43 weeks'. The infant also had a unilateral undescended testicle. Of interest, none of the

woman's other 10 children is mentally retarded. Two additional cases of self-poisoning with valerian were described in 1987 by the same group responsible for the above report. In both cases exposure occurred early in gestation, with ingestion of 5 g and 2 g of valerian at 3 and 4 weeks of foetal development, respectively. No congenital abnormalities were observed in the offspring. In summary, the very limited animal and human data do not allow a conclusion as to the safety of valerian during pregnancy.

Moreover, as a natural, unregulated product, the concentration, contents, and presence of contaminants in valerian preparations cannot be easily determined. Because of this uncertainty and the potential for cytotoxicity in the foetus and hepatotoxicity in the mother, the product should be avoided during pregnancy. Other authors have arrived at the same conclusion. The risk to a foetus from short-term or inadvertent use during any part of gestation, however, is probably low, if it exists at all.

Breast Feeding Summary: No reports describing the use of valerian during lactation have been located. For the reasons cited above, the use of this herbal product should be avoided during breast-feeding [102].

Effects of Valerian observed on Cats and Rats: An unusual feature of valerian is that the essential oil of valerian root is a cat attractant similar to catnip. The active compound in valerian for this is actinidine. Cat attractants might mimic the odour of cat urine which is caused by 3- mercapto- 3 - methylbutan- 1 - ol (MMB). Anecdotes state that valerian is also attractive to rats, so much so that it had been used to bait traps. Some versions of the legend of the Pied Piper of Hamelin have him using valerian, as well as his pipes, to attract the rats. This might be related to the change of aversion into attraction to cat urine in rats infected with the parasite *Toxoplasma gondii* [103].

Interaction Study of Valerian: Interactions with drugs, supplements and other herbs have not been thoroughly studied. The interactions listed below have been reported in scientific publications. If you are taking prescription drugs, speak with your health care provider or pharmacist before using herbs or dietary supplements.

Interactions with Drugs: In theory, valerian may increase the side effects, including the amount of drowsiness, caused by sedative drugs. Examples include benzodiazepines, such as lorazepam (Ativan); barbiturates, such as phenobarbital; narcotics, such as codeine; antidepressants, such as fluoxetine (Prozac); antihistamines, such as diphenhydramine (Benadryl); alcohol; and possibly some antiseizure or antidiarrheal drugs. Caution is advised while driving or operating machinery. The alcohol content in some valerian extracts may lead to vomiting if used with the drug disulfiram (Antabuse) or metronidazole (Flagyl).

Based on animal and human studies, valerian may increase the amount of drowsiness caused by some drugs, although this is an area of controversy. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery. In one human study, a combination of valerian and the

beta-blocker drug propranolol (Inderal) reduced concentration levels more than valerian alone. A brief episode of confusion was reported in one patient using valerian with loperamide (Imodium) and St. John's wort (*Hypericum perforatum* L). An episode of agitation, anxiety, and self-injury was reported in a patient after taking valerian with fluoxetine (Prozac) for a mood disorder (the person was also drinking alcohol). In theory, valerian may interact with anti-seizure medications, although human data is lacking.

Valerian tinctures may contain high alcohol content (15-90%) and theoretically may cause vomiting if taken with metronidazole (Flagyl) or disulfiram (Antabuse). Valerian may interact with certain drugs metabolized by the liver or vasopressin. Although valerian has not been reported to interact with any drugs or to influence laboratory tests, this has not been rigorously studied. No evidence of potentiation of valerian effects by concomitant ingestion of alcohol has been found in animal and human studies, but the combination should still be avoided [31-98]. Valerian may potentiate the sedative effects of barbiturates, anesthetics, and other central nervous system depressants [114]. One case report suggests that sudden cessation of long-term high dose valerian therapy (530 mg to 2 g, five times daily) may result in withdrawal symptoms similar to those occurring with benzodiazepine use. Perhaps because of the poorly defined effects of valerian on GABA neurotransmission, valerian appears to attenuate benzodiazepine withdrawal symptoms in animals and humans [91, 105, 115].

Interactions with Herbs and Dietary Supplements: Very few interactions between valerian and herbs or supplements have been reported. Valerian may increase the side effects or the amount of drowsiness caused by some herbs or supplements, such as St. John's wort or melatonin. Caution is advised while driving or operating machinery. Valerian may have effects that counteract stimulations caused by caffeine [104]. Based on theoretical concerns, valerian may increase the amount of drowsiness caused by some herbs or supplements. A brief episode of confusion was reported in one patient during use of valerian with loperamide (Imodium) and St. John's wort (*Hypericum perforatum L*.). Nausea, sweating, muscle cramping, weakness, elevated pulse, and high blood pressure were reported after a single dose of a combination product with St. John's wort, kava, and valerian. Valerian may interact with certain herbs and supplements that are metabolized by the liver.

- Studies suggested valerian to be safe for short term use (4 to 6 weeks).
- No information is available about the long-term safety of valerian.
- Valerian can cause mild side effects, such as headaches, dizziness, upset stomach, and tiredness in the morning after its use.

Valerian may cause excessive sleepiness or daytime drowsiness if combined with other drugs that cause drowsiness, such as the benzodiazepines Ativan (lorazepam) or Valium (diazepam), some antidepressants, narcotics such as codeine, and barbituates such as phenobarbitol, or with over-the-counter (OTC) sleep and cold products containing

diphenhydramine and doxylamine [105]. It may also cause excessive sleepiness if taken with herbs thought to have a sedative effect, such as hops, catnip and kava. Valerian is broken down in the liver. Theoretically, it could interfere with the effectiveness of medications that are broken down by the same liver enzymes, such as:

- Allergy medications like Allegra (fexofenadine)
- Cholesterol medication such as Mevacor (lovastatin)
- Antifungal drugs such as Sporanox (itraconazole) and Nizoral (ketoconazole)
- Cancer medications such as Camptosar (irinotecan), Etopophos, Vepesid (etoposide), Gleevec, Taxol (paclitaxel), Velbe (vinblastine) or Oncovin (vincristine) [106].

Clinical Studies Done on Valerian and Sleep Disorders: In a systematic review of the scientific literature, nine randomized, placebo-controlled, double-blind clinical trials of valerian and sleep disorders were identified and evaluated for evidence of efficacy of valerian as a treatment for insomnia. Reviewers rated the studies with a standard scoring system to quantify the likelihood of bias inherent in the study design. Although all nine trials had flaws, three earned the highest rating (5 on a scale of 1 to 5) and are described below.

Unlike the six lower-rated studies, these three studies described the randomization procedure and blinding method that were used and reported rates of participant withdrawal [107-108]. The first study used a repeated-measures design; 128 volunteers were given 400 mg of an aqueous extract of valerian, a commercial preparation containing 60 mg valerian and 30 mg hops, and a placebo. Participants took each one of the three preparations three times in random order on nine non-consecutive nights and filled out a questionnaire the morning after each treatment. Compared with the placebo, the valerian extract resulted in a statistically significant subjective improvement in time required to fall asleep (more or less difficult than usual), sleep quality (better or worse than usual), and number of night-time awakenings (more or less than usual).This result was more pronounced in a subgroup of 61 participants who identified themselves as poor sleepers on a questionnaire administered at the beginning of the study. The commercial preparation did not produce a statistically significant improvement in these three measures. The clinical significance of the use of valerian for insomnia cannot be determined from the results of this study because having insomnia was not a requirement for participation. In addition, the study had a participant withdrawal rate of 22.9%, which may have influenced the results [109].

In the second study, eight volunteers with mild insomnia were evaluated for the effect of valerian on sleep latency (defined as the first 5-minute period without movement). Results were based on night-time motion measured by activity meters worn on the wrist and on responses to questionnaires about sleep quality, latency, depth, and morning sleepiness filled out the morning after each treatment. The test samples were 450 or 900 mg of an aqueous valerian extract and a placebo. Each volunteer was randomly assigned to receive

one test sample each night, Monday through Thursday, for 3 weeks for a total of 12 nights of evaluation. The 450 mg test sample of valerian extract reduced average sleep latency from about 16 to 9 minutes, which is similar to the activity of prescription benzodiazepine medication (used as a sedative or tranquilizer). No statistically significant shortening of sleep latency was seen with the 900 mg test sample. Evaluation of the questionnaires showed a statistically significant improvement in subjectively measured sleep. On a 9 point scale, participants rated sleep latency as 4.3 after the 450 mg test sample and 4.9 after the placebo. The 900 mg test sample increased the sleep improvement but participants noted an increase in sleepiness the next morning.

Although statistically significant, this 7 minute reduction in sleep latency and the improvement in subjective sleep rating are probably not clinically significant. The small sample size makes it difficult to generalize the results to a broader population [77]. The third study examined longer-term effects in 121 participants with documented nonorganic insomnia. Participants received either 600 mg of a standardized commercial preparation of dried valerian root or placebo for 28 days. Several assessment tools were used to evaluate the effectiveness and tolerance of the interventions, including questionnaires on therapeutic effect (given on days 14 and 28), change in sleep patterns (given on day 28), and quality and well-being (given on days 0, 14, and 28). After 28 days, the group receiving the valerian extract showed a decrease in insomnia symptoms on all the assessment tools compared with the placebo group. The differences in progress between valerian and placebo increased between the assessments done on days 14 and 28. The reviewers concluded that these nine studies are not sufficient for determining the effectiveness of valerian to treat sleep disorders. For example, none of the studies checked the success of the blinding; none calculated the sample size necessary for seeing a statistical effect, only one partially controlled pre bedtime variable, and only one validated outcome measures. In a randomized, double-blind study, 75 participants with documented nonorganic insomnia were randomly assigned to receive 600 mg of a standardized commercial valerian extract or 10 mg oxazepam (a benzodiazepine medication) for 28 days. Assessment tools used to evaluate the effectiveness and tolerance of the interventions included validated sleep, mood scale, and anxiety questionnaires as well as sleep rating by a physician (on days 0, 14, and 28).

Treatment result was determined via a 4-step rating scale at the end of the study (day 28). Both groups had the same improvement in sleep quality but the valerian group reported fewer side effects than did the oxazepam group. However, this study was designed to show superiority, if any, of valerian over oxazepam and its results cannot be used to show equivalence [78]. In a randomized, double-blind, placebo-controlled crossover study, researchers evaluated sleep parameters with polysomnographic techniques that monitored sleep stages, sleep latency, and total sleep time to objectively measure sleep quality and stages. Questionnaires were used for subjective measurement of sleep parameters. Sixteen participants with medically documented nonorganic insomnia were randomly assigned

to receive either a single dose or a 14-day administration of 600 mg of a standardized commercial preparation of valerian or placebo. Valerian had no effect on any of the 15 objective or subjective measurements except for a decrease in slow-wave sleep onset (13.5 minutes) compared with placebo (21.3 min). During slow-wave sleep, arousability, skeletal muscle tone, heart rate, blood pressure, and respiratory frequency decreased. Increased time spent in slow-wave sleep may decrease insomnia symptoms. However, because all but 1 of the 15 endpoints showed no difference between placebo and valerian, the possibility that the single endpoint showing a difference was the result of chance must be considered. The valerian group reported fewer adverse events than did the placebo group [110].

Although the results of some studies suggest that valerian may be useful for insomnia and other sleep disorders, results of other studies do not. Interpretation of these studies is complicated by the fact the studies had small sample sizes, used different amounts and sources of valerian, measured different outcomes, or did not consider potential bias resulting from high participant withdrawal rates. Overall, the evidence from these trials for the sleep-promoting effects of valerian is inconclusive.

Safety concerns: Pregnant or nursing women and children should not use valerian. People taking medications for insomnia or anxiety, such as benzodiazepines, should not combine these medications with valerian. Side effects of valerian may include headache, dizziness, itchiness, upset stomach, drowsiness during the daytime, dry mouth and vivid dreams. Rarely, liver damage has been associated with the use of valerian. It's not certain whether the cause of the liver damage was due to valerian itself or to contaminants in the product. Until we know more, people should use valerian only under the supervision of a qualified health care practitioner and those with liver disease should avoid it. Although liver damage doesn't always produce noticeable symptoms, if excessive tiredness, intense itching, nausea, vomiting, diarrhoea, pain or discomfort in the upper right side of the abdomen, or a yellowing of the whites of the eyes or skin occurs, see your doctor immediately [111]. The U. S. Food and Drug Administration do not strictly regulate herbs and supplements. There is no guarantee of strength, purity or safety of products and effects may vary. You should always read product labels. If one have a medical condition, or are taking other drugs, herbs, or supplements, one should speak with a qualified healthcare provider before starting a new therapy. Consult a healthcare provider immediately if you experience side effects [38, 112-113].

Precautions and Warnings with Usage of Valerian: Persons who take valerian should consult an experienced herbalist about dosage and about reliable sources of the herb. Because herbal preparations are not regulated by the U. S. Food and Drug Administration, consumers cannot be certain of the freshness and potency of commercial herbal products. In July 2001, an independent laboratory published the results of its tests of 17 valerian products; only nine contained the amount of valerian that their labels claimed. Of the remaining eight products, four contained only half the amount of valerian that they should have, and the other four

contained none at all [38]. Although valerian has a good reputation for safety when used as directed, it should not be used in high doses or taken continuously for longer than two to three weeks. Studies report that valerian is generally well tolerated for up to four to six weeks in recommended doses. Valerian has occasionally been reported to cause headache, excitability, stomach upset, uneasiness, dizziness, unsteadiness (ataxia), and low body temperature (hypothermia). Chronic use (longer than two to four months) may result in insomnia.

Slight reductions in concentration or complicated thinking may occur for a few hours after taking valerian. Use caution if driving or operating heavy machinery. Some research suggests that valerian may not cause sedation. A drug "hangover" effect has been reported in people taking high doses of valerian extracts. "Valerian withdrawal" may occur if you stop using valerian suddenly after chronic high-dose use, including confusion (delirium) and rapid heartbeat. These symptoms may improve with the use of benzodiazepines such as lorazepam (Ativan). Although unknown, valerian may have similar brain activity as benzodiazepines (which are commonly used to treat anxiety and insomnia), through effects on the brain chemical GABA [35, 50, 91].

Valerian has been on the U. S. Food and Drug Administration's (FDA's) GRAS (Generally Regarded as Safe) list, and no deaths due to overdose are currently available. Liver toxicity has been associated with some multi-herb preparations that include valerian. However, the contribution of valerian itself is not clear due to the potential liver toxicity of other included ingredients and the possibility of contamination with unlisted herbs [89-90].

Contraindications of Valerian:

- Women who are pregnant or nursing should not take valerian without medical advice because the possible risks to the foetus or infant have not been evaluated.
- Children younger than 3 years old should not take valerian because the possible risks to children of this age have not been evaluated.
- Individuals taking valerian should be aware of the theoretical possibility of additive sedative effects from alcohol or sedative drugs, such as barbiturates and benzodiazepines.

Obtain a complete patient profile when patients express an interest in taking valerian. Discuss potential risks and benefits, particularly any specific to the patient's drug profile or medical history, empowering the consumer to make an informed choice. Few adverse events have been associated with this herb, but patients should be informed of the potential dangers of driving or operating heavy machinery. Patients should be cautioned regarding concurrent sedative use. Pregnant or lactating women should not use this herb. Patients using valerian root for insomnia can be instructed to take it 30-60 minutes before bedtime. Follow-up is important, and adverse events and drug interactions should be immediately reported to the Natural Health Products Directorate of Health Canada [116].

Threats towards Extinction of Valerian: There are no reports of significant global decline of *Valeriana uliginosa* [117]. Nature Serve in year

2002 indicated that loss of habitat due to logging of cedar swamps and draining of wetlands, which is the most serious threat to *V. uliginosa.* Potential threats include:

- Forest encroachment or succession [117].
- Hydrological alteration
- Logging [118].
- Competition with other plants.
- Invasive exotic plants
- Trampling
- Pollution and climate change [120].

There is little evidence that *V. uliginosa* is threatened by collection, though *V. officinalis* for medicinal purposes. Scientists believe the biggest threats to *Valeriana uliginosa* populations are forest encroachment and continuous flooding from beaver activity. Logging is indicated as a potential threat at several Maine sites, but I believe that selective logging in winter may be beneficial to *V. uliginosa* populations that occur in relatively small openings within northern white-cedar swamps [117].

Additional Sources of Information on Valerian: Medical libraries are a source of information about medicinal herbs. Other sources include Web-based resources such as PubMed [121] for general information on botanicals and their use as dietary supplements. Authors are also referred to see background information about botanical and dietary supplements from the Office of Dietary [122-123].

SUMMARY: This paper provides a systematic overview of the use of valerian for various disorders and it can be concluded that valerian is an herb sold as a dietary supplement through out the world. It is a common ingredient in products promoted as mild sedatives and sleep aids for nervous tension and insomnia. It has been suggested for several conditions but has been most studied as a treatment for insomnia. Valerian may reduce the length of time it takes to fall asleep and may improve sleep quality with fewer adverse effects than commonly used prescription drugs. Valerian is not recommended for pregnant or breast-feeding women or in children and hence must be avoided in such patients. A potential advantage of valerian over benzodiazepines is the lack of sleepiness on awakening when used at the recommended dosages.

Valerian also may be helpful in weaning patients with insomnia from benzodiazepines. The use of valerian as an anxiolytic requires further studies. Under the US Preventative Services Task Force's (USPSTF) classification system for herbs, valerian was rated as probably safe and effective as a sleep aid, based on evidence from randomized clinical trials. But the long-term safety studies are lacking. In respect to its spasmolytic properties, it was rated possibly effective and probably safe, based on animal studies.

While valerian appears to be safe and possibly effective, the literature available in the English language evaluating this herb is limited due to small sample size, short study duration, and some inconsistent results. Valerian's long-term safety has yet to be demonstrated, and therefore restricting its extended use for any indication. Valerian's main attribute may be that it serves as an alternative, with a low incidence of side effects, to synthetic sedative agents.

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