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The Scientific Basis for the Reputed Activity of Valerian

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Abstract

The underground organs of members of the genus *Valeriana* (Valerianaceae), as well as related genera such as *Nardostachys*, are used in the traditional medicine of many cultures as mild sedatives and tranquillizers and to aid the induction of sleep. *V. officinalis* is the species most commonly used in northern Europe and still retains its official pharmacopoeial status although it is most commonly encountered as an ingredient of herbal medicines. This plant is still the subject of considerable research aimed at establishing the chemical and pharmacological basis of the activity which has been clearly shown in a number of animal and clinical studies.

The constituents of the volatile oil are very variable due to population differences in genetics and to environmental factors. The major constituents include the monoterpene bornyl acetate and the sesquiterpene valerenic acid, which is characteristic of the species, in addition to other types of sesquiterpene. Some of these have been shown to have a direct action on the amygdaloid body of the brain and valerenic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain resulting in sedation. The non-volatile monoterpenes known as valepotriates were first isolated in 1966 and contribute to the overall activity by possessing sedative activity based on the CNS although the mode of action is not clearly known. The valepotriates themselves act as prodrugs which are transformed into homobaldrinal which has been shown to reduce the spontaneous motility of mice. More recent studies have shown that aqueous extracts of the roots contain appreciable amounts of GABA which could directly cause sedation but there is some controversy surrounding the bioavailability of this compound. Another recent finding is the presence of a lignan, hydroxypinoresinol, and its ability to bind to benzodiazepine receptors.

Valerian is a good example of both the negative and positive aspects of herbal drugs. The considerable variation in its composition and content as well as the instability of some of its constituents pose serious problems for standardization but the range of components which contribute to its overall activity suggest that it may correct a variety of underlying causes of conditions which necessitate a general sedative or tranquillizing effect.

Valerian is the common name given to the crude drug consisting of the underground organs of species of *Valeriana* (Valerianaceae). In northern Europe the official drug in the British and European Pharmacopeias is derived from *V. officinalis* L. but other species are used as crude drugs in other parts of the world, the most notable being Indian Valerian, *V. wallichii* DC, and Chinese and Japanese Valerian *V. angustifolia* Tausch. or *V. fauriei* Briq. A related species which has an important place in traditional medicine in the Indian subcontinent and the Middle East is Nard *Nardostachys jatamansii* DC. Unless specified otherwise, the term 'Valerian' used below refers to *V. officinalis*.

It is remarkable that all these species are used for much the same purposes. The major use is as a tranquillizer and CNS sedative and a secondary use as a treatment for gastrointestinal hyperactivity. Extracts of Valerian made with 25 or 60% alcohol have been used as galenicals for a long time and Potassium Bromide and Valerian Mixture was last included in the BPC 1963. Valerian is the subject of a German Commission E monograph in 1985 which

recommended its use as a tincture or infusion for restlessness and nervous disturbance of sleep, noting that it had calming and sleep-inducing effects (Bisset 1994). In Germany many medical practitioners prescribe herbal preparations and these monographs were developed for herbal drugs to give information about indications where they were considered effective and safe and can be regarded as a type of licensing for herbal medicines.

In the UK, however, very few prescriptions for this type of medication are written and Valerian is mostly bought as an ingredient of over-the-counter preparations whose sales are not restricted. Valerian is included in nearly all 'herbal' products promoted directly or obliquely as tranquillizers and sleep inducers and there are at least 25 products containing Valerian available in the UK, whilst in Germany over 400 products exist which contain Valerian (Reynolds 1996). The products may contain the powdered plant material but more commonly a dried extract, sometimes standardized to a minimum level of particular constituents, is used. It has been noted that different extracts have slightly different effects, i.e. crude extracts made with water alone or with alcohol tend to be sleep-inducing and sedative whilst those made with dilute alcohol, containing a high level of valepotriates, have a tranquillizing action, i.e. they reduce anxiety without causing drowsiness (Bisset 1994). The reasons underlying this will be discussed later.

The continued, and indeed increasing, use of this material has resulted in a steady stream of scientific publications, both as research papers and as reviews (Hobbs 1989; Houghton 1997a). This paper gives an account of the current state of knowledge of the scientifically demonstrated links between the extracts and constituents of these plants and their pharmacological activity in the CNS.

Clinical and animal studies for evidence of efficacy

A great deal of the scientific investigation of medicinal plants which has taken place over the last 150 years is open to the criticism that attention was paid primarily to the chemicals present with little interest in their biological activity. In the last twenty years this has changed dramatically and many researchers now combine in-vitro tests for a particular activity with their isolation of chemical constituents. There may still be, however, a considerable lack of correlation between activity demonstrated in-vitro and the desired clinical effect. This may be due to the in-vitro model being a poor reflection of the clinical condition but factors such as bioavailability and metabolism of the constituents will also play an important part. It is thus important to note that Valerian has been shown to have sleep-inducing, anxiolytic and tranquillizing effects in-vivo both in clinical and animal studies.

The German Commission E monograph was constructed on the basis of clinical trials and several others have been published since then. The most rigorously-designed trials consisting of randomized, double-blind controlled studies are summarized in Table 1.

Several points are worthy of note which arise from these studies. The first is that the extracts produce significant effects but these often take at least two weeks to become apparent. Another is that, in contrast to many other hypnotic agents, there is little hangover effect and there are also no obvious signs of interaction with alcohol. Valerian administration is associated with a reduction in REM sleep during the first part of the night but an

Table 1. Recent placebo-controlled double blind clinical studies on *V. officinalis* extracts (from Schulz et al 1997)

Sample size	Medication	Result	Reference
12,937 multi-centre	45 mg aqueous extract 3–9 times per day	Pre-sleep phase reduced 35 to 60%; evasicated sleep duration improved 29 to 67%	Kamm-Kohl et al 1984
8	450 mg, 900 mg aqueous extract, 1 h before retiring	Significant decrease in latency time to fall asleep with 450 mg compared with placebo ($9{\cdot}0 \pm 1{\cdot}5$ min compared with $15{\cdot}8 \pm 2{\cdot}2$ min)	Leathwood & Chauffard 1985
14 poor sleepers	405 mg aqueous-alcoholic dried extract	Increase in sleep phases 3 and 4; no alteration to REM sleep; K-complex density increase	Schulz et al 1994
121	600 mg alcoholic extract per day for 28 days	Increase in clinical global impression, sleep rating, and von Zerssen's well-being scale	Vorbach et al 1996

increase during the latter stages. In addition to Valerian alone, other studies with a commercial preparation consisting of a mixture of Valerian and hops (*Humulus lupulus*) have also shown significant improvement in sleep quality.

Classical animal models used to demonstrate the effects of Valerian extract include the measurement of the movement of mice (Gstirmer & Kind 1951; Kiesewetter & Müller 1958; Rosecrans et al 1961). Wagner et al (1980) noted that the lipophilic portion of the extract had a greater activity than the more polar fraction but the reverse has been shown in several other studies (Hölzl 1997). The prolongation of barbiturate-induced sleeping time has also been reported in several studies and a recent report showed that a dose of $2\,mg\,kg^{-1}$ of the alkaline aqueous extract increased thiopental-induced sleeping time by a factor of 1·6 compared with 4·7 given by $4\,mg\,kg^{-1}$ for chlorpromazine (Leuschner et al 1993). Later studies on the individual constituents are discussed below.

Other animal studies have shown that administration of a 96% ethanol extract had an anticonvulsive ED50 value of $6\,mg\,kg^{-1}$ in mice treated with picrotoxin (Hiller & Zetler 1996). This compared with an ED50 value of $0{\cdot}03\,mg\,kg^{-1}$ for diazepam.

Other studies have used the Sokoloff method which measures glucose consumption in the brain by postmortem examination of the glucoseun sediment in different brain areas. A significant reduction in sediment levels, indicating reduced neuronal activity, was noted in the cortex and limbic system when the total ethanolic extract was administered (Grusla et al 1986).

Recent receptor-binding studies have produced some interesting results. An aqueous extract of Valerian displaced GABA from receptors in rat brain cortex tissue (Santos et al 1994a). Other work has shown that melatonin is also displaced from receptors but that there seems to be little interaction with the benzodiazepine and μ-opiate receptors (Bodesheim & Hölzl 1997). Inhibition of binding of both types of compounds would be associated with a sedative effect.

The basis for the observed effects

The basis of activity demonstrated by a herbal extract is no different from a single chemical entity drug since it depends on the chemical interaction with receptors or other features of the tissues affected. The explanation of the activities noted must, therefore, involve a knowledge of which compounds are present in the plant extract. It must be emphasized that the extract is often a complicated mixture of different types of compound, each type consisting of several closely related structures. The overall effect is therefore due to this mixture of compounds which, in turn, may exert several direct and indirect activities.

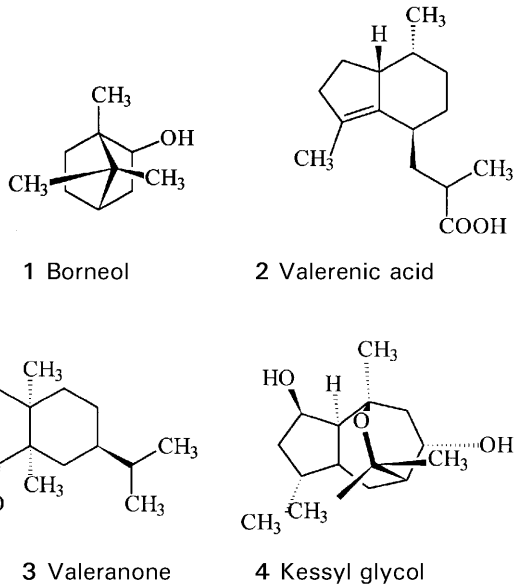
This situation makes it difficult to interpret the activity easily by the reductionist approach employed in modern science since interactions between the components involving synergy and the alteration of bioavailability or metabolism may result in a very different activity profile from that given by a single active component.

Chemical Constituents of Valerian

Volatile oil components

The presence of a volatile oil in Valerian has been known for a long time although its characteristic odour, which many find very unpleasant, is due to the release of isovaleric acid from some volatile oil components and other constituents by enzyme activity rather than to the oil itself.

The composition of the volatile oil is very variable and depends not only on climate and other ecological factors but on the chemical race and polyploidy of *V. officinalis* used for extraction. The oil contains monoterpenes, chiefly consisting of borneol (**1**) and its acetyl and isovaleryl esters, but it is the sesquiterpene components which are distinctive and which have received most attention regarding their biological activity. Three major



1 Borneol **2** Valerenic acid

3 Valeranone **4** Kessyl glycol

Figure 1. Volatile oil constituents of Valerian.

types of sesquiterpene skeleton are found and these are exemplified (Figure 1) by valerenic acid (**2**), valeranone (**3**) and kessyl glycol (**4**). The valerenic acid and kessyl ring systems are unique to the Valerianaceae. Valerenic acid has so far been found in no other organism apart from *V. officinalis* whilst valeranone is found as the major component of the oil of *V. wallichiana* and the related plant Nard (*Nardostachys jatamansii*). Compounds with the kessyl ring system are the major constituents in the volatile oil of Japanese valerian *V. fauriei* but are also found in *V. officinalis* oil (Houghton 1997b).

Valepotriates

In 1966 a novel class of compounds was discovered in *V. wallichiana* and in the closely-related *Centranthus ruber* (Mannenstatter et al 1966; Thies 1966). These compounds were called valepotriates and consist of the furanopyranoid monoterpene skeleton commonly found in the glycosylated forms known as iridoids. The valepotriates (Figure 2) are not glycosides but are esterified, usually at three positions around the ring and contain either one or two ring double bonds. Didrovaltrate (**5**) and valtrate (**6**) are compounds of these two types respectively. Isovaleric acid (**7**) is commonly esterified to the ring and the ester link is easily hydrolysed resulting in the characteristic odour of the dried crude drug which is, however, not detected in freshly-dug samples. The process of degradation of the valepotriates, both by physical means in tinctures and by microbial transformation in the gut, results in products such as homobaldrinal (**8**).

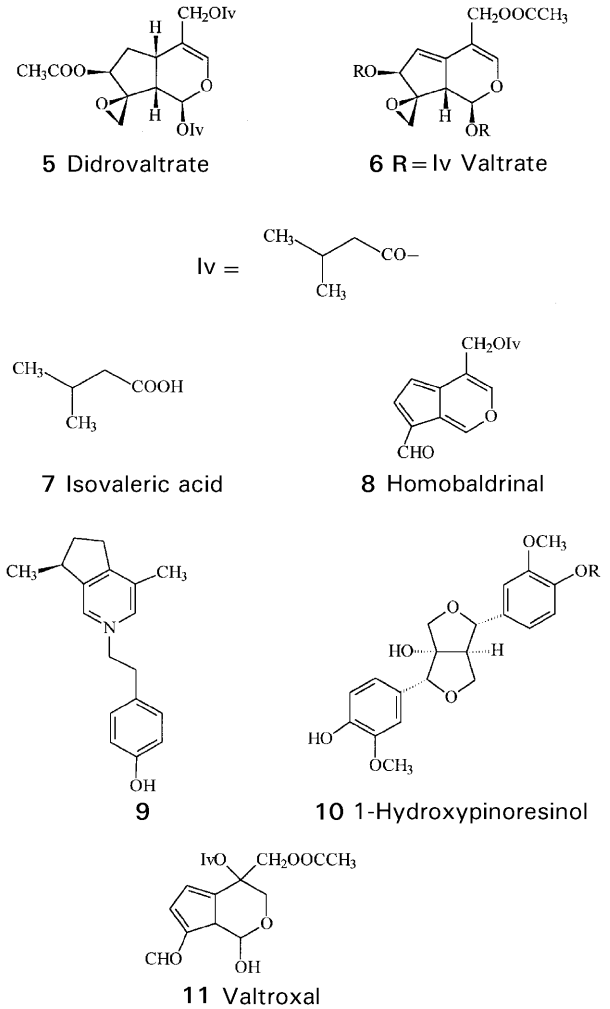


Figure 2. Valepotriates and other constituents of Valerian.

Other constituents

Small amounts of monoterpene alkaloids, e.g. **9**, are also present in the roots of Valerian (Torsell & Wahlberg 1967) and, more recently, furanofuran lignans such as 1-hydroxypinoresinol (**10**) have been isolated (Bodesheim & Hölzl 1997). Substantial amounts of free amino acids, particularly GABA, tyrosine, arginine and glutamine are also present in aqueous extracts of the roots of Valerian.

These components will be extracted with varying efficiency according to the solvent used. The greater the alcoholic strength of the solvent used, the greater will be the concentration of volatile oil components and some of the valepotriates whilst aqueous extracts will have larger amounts of the amino acids.

Biological activities of the constituents

Any study intending to relate activity to constituents present must take account of the amount of the compound present in a plant extract and the concentration which shows activity in a test system. It is not unusual for demonstration of possible clinical efficacy of a herbal preparation to be claimed even though the dose projected from laboratory studies which would show activity in a clinical situation is at least ten or a hundred times higher than that which would exist in a standard recommended dose. This must be borne in mind when considering some of the activities discussed below.

Volatile oil components

These would comprise less than 1% of powdered root material and not more than 5% of an ethanolic extract. Sesquiterpenes are the most important of

the volatile oil components which are responsible for the biological effect.

Valerenic acid (**1**) at 50 mg kg^{-1} was shown to produce a significant decrease in motility of mice (Hendriks et al 1981). Further studies showed that a similar dose increased pentobarbital-induced sleeping time and was slightly less active than standard doses of chlorpromazine and diazepam (Hendriks et al 1985). The profile of activity indicated that valerenic acid had a central, rather than a peripheral effect and this hypothesis has been strengthened by the finding that valerenic acid inhibits the enzyme system causing breakdown of GABA in the brain (Riedel et al 1982). The consequent increase in GABA levels is associated with sedation and a decrease in CNS activity.

The kessane sesquiterpenes have been investigated mainly in Japan. Takamura et al (1973) carried out experiments on the major constituent kessyl alcohol 8-acetate and showed that the motility of rats was decreased and also hexobarbitone-induced sleeping time prolonged. Studies on a range of related compounds were then carried out and these showed that kessyl alcohol 8-acetate was the most active of the series, the parent non-acylated alcohols being less potent (Takamura et al 1975a). Semi-synthetic butyl derivatives were more potent than the natural compounds and this suggests that lipophilicity plays an important part in activity, probably due to bioavailability factors associated with the blood–brain barrier (Takamura et al 1975b).

The valeranone sesquiterpenes are not as important as the valerenic acid and kessane types in *Valeriana* spp. but are major constituents in the oil of Nard *Nardostachys jatamansii*. Barbitone-induced sleeping time and a decrease in motility of mice have been noted at doses of 100 mg kg^{-1} and 50 mg kg^{-1}, respectively and this was attributed to the observed reduction in levels of 5-hydroxytryptamine and noradrenaline in the brain examined post mortem after administration of valeranone (Arora & Arora 1963; Hendricks et al 1981) but it should be noted that the corresponding doses in man would be large and the quantities present in a standard Valerian preparation would give a dosage well below this level. An indication of a tranquillizing effect at 31·6 mg kg^{-1} was noted for valeranone in rats using the electric shock avoidance test but it was not so strong as a 10-mg kg^{-1} dose of chlorpromazine (Rücker et al 1978). Hazelhoff et al (1982) have shown that valeranone acts primarily on the muscles rather than on the CNS.

It can therefore be seen that the major sesquiterpenes responsible for CNS sedation are the valerenic acid and kessane types. The former is of most importance in European Valerian whilst the latter plays a major role in Far Eastern species.

The valepotriates

Much interest was aroused in 1966 by the isolation of a novel type of iridoid-like monoterpene from two genera of the Valerianaceae, *Centranthus* and *Valeriana* (Mannenstatter et al 1966; Thies 1966). Unlike most iridoids, these compounds were not glycosides but were esters and had only moderate polarity so they were extracted mainly using alcoholic solvents rather than water alone. The presence of these compounds helped explain the discrepancies which had commonly been observed between low volatile oil content and relatively high activity in tinctures made from Valerian. Mexican Valerian *V. edulis* subsp. *procera* had large roots containing as much as 8% of valepotriates and was used as a source of a standardized mixture called Valmane which consisted of 15% valtrate, 80% didrovaltrate and 5% acevaltrate. This mixture has been used for a large number of pharmacological investigations. Von Eickstedt (1969) and Von Eickstedt & Rahman (1969) first reported on the pharmacology of the valepotriates and showed that they decreased spontaneous motility in mice though not to such a great extent as the sesquiterpenes of Valerian. The tranquillizing effect at 31 mg kg^{-1} given orally in mice was significant although not as effective as 10 mg kg^{-1} chlorpromazine but motor co-ordination, measured by the rotating-rod test, was better with Valmane than chlorpromazine. Tests with cats confirmed the findings since no decrease in reactivity was observed but there was a decrease in restlessness, anxiety and aggressiveness.

One of the experiments reported by von Eickstedt (1969) compared the effect on performance of alcohol co-administered with diazepam, chlorpromazine or the valepotriates. Unlike the other two drugs, the valepotriates lessened the effects of alcohol on mice.

The valepotriates decompose rapidly to give homobaldrinal (**8**) and related products. It is thought that the same process occurs in the intestines due to the bacterial flora present. Wagner et al (1980) compared the effects of the parent valepotriates and homobaldrinal on spontaneous motility of mice following oral administration of 100 mg kg^{-1}, a higher dose than would be expected from normal administration of the extract. Homobaldrinal had a greater effect and this has led to the suggestion that the valepotriates act as prodrugs. A similar effect following intraperitoneal administration was noted by Schneider & Willems (1982) and

valtroxal (**11**), a decomposition product of didrovaltrate, has also been shown to have a greater effect on spontaneous motility than didrovaltrate itself (Veith et al 1986).

The basis of the observed effect is still not very clear. The valepotriates have been shown to exert a strong spasmolytic effect at doses below those observed for any direct CNS effect (Wagner & Jurcic 1979). This activity explains the secondary use of some *Valeriana* species for gastrointestinal disturbances but may also account for some of the decrease in motility since the animals would be more relaxed. The valepotriates have also been found to bind to dopamine receptors and thus may inhibit the stimulatory effect of endogenous dopamine in the CNS (Godau 1991).

It should be noted that, in spite of the first work reported by Wagner et al (1980), there is some doubt about the oral bioavailability of homobaldrinal and related breakdown products. In light of the fact that the valepotriates hydrolyse rapidly in an aqueous environment, such as that offered by a traditional tincture or infusion, it is questionable whether they exist in appreciable amounts in products which have been stored for some time under normal conditions. This may account for the notorious unreliability of efficacy of Valerian preparations in former days.

The presence of an epoxide group, and its alkylating potential, in many of the valepotriates has raised concerns about their cytotoxicity and consequent potential carcinogenicity. Cytotoxicity has been demonstrated in-vitro (Bouthanh et al 1981; Braun et al 1982) and it has been demonstrated that valtrate inhibited the incorporation of thymidine and leucine into DNA (Bouthanh et al 1983). Rather surprisingly, studies using other valepotriates showed that the C5-C6 double bond was more important for this activity than the epoxide group. In-vivo studies have failed to show carcinogenic effects, even when the compounds were given intraperitoneally at 1350 mg kg^{-1} in mice (Braun et al 1982) but the in-vitro findings have made the presence and use of valepotriates in Valerian undesirable factors.

Alkaloids and amino acids

The alkaloids present in Valerian exist in small amounts and are not presently considered to make a significant contribution to its overall effect. Tests have shown that they possess cholinesterase activity (Torsell & Wahlberg 1967) and this would reduce levels of acetylcholine in the CNS which would produce stupor similar to that induced by the anticholinergic tropane alkaloids such as scopolamine. A recent study has shown that the alkaloids do not bind to a range of CNS receptors including those associated with 5-hydroxytryptamine, GABA, benzodiazepine and opiates (Bodesheim & Hölzl 1997).

The ability of an aqueous extract of Valerian to decrease radiolabelled GABA uptake in isolated synaptosomes prompted interest in the possible presence of substances which would thereby increase GABA levels and produce a sedative effect (Santos et al 1994a). The valerian extract was subsequently shown to contain high levels of GABA and glutamine, which could be metabolized to GABA, and these are now thought to be the substances causing the effect (Santos et al 1994b; Cavadas et al 1995). It is doubtful whether these amino acids would reach the CNS if taken orally.

Lignans

Bodesheim & Hölzl (1997) have recently reported that the lignan 1-hydroxypinoresinol inhibits 5-hydroxytryptamine binding to its receptor in isolated brain tissue but has little effect on the benzodiazepine receptor. Little information is available about the amounts of this compound in Valerian or its preparations but the possibility of yet another factor leading to CNS sedation, i.e. inhibition or agonism of 5-hydroxytryptamine depending on the part of the brain, is an interesting aspect of the chemical basis for the observed effects of Valerian.

Conclusions

Regarding the chemical basis for the observed sedative and tranquillizing activity it can be clearly seen that Valerian is a classical example of a herbal drug where the overall effect is due to several types of constituent and modes of activity. The activity of any particular Valerian preparation will be due to both the profile of the types and amounts of the constituents present and this underlines the importance of standardizing such preparations both qualitatively and quantitatively, not only in terms of one constituent. The variety of activity indicates that Valerian constituents act on several different mechanisms causing sedation and this may be an advantage in situations such as those requiring a tranquillizer or sedative, where the clinical effect, but not the underlying cause, is known.

Some general conclusions can be drawn from the knowledge that has so far been accumulated.

Firstly, there seems to be considerable evidence for the sleep-inducing effects of Valerian. Aqueous extracts appear to be better than those made with alcohol although the nature of the compounds

responsible is not fully known. Valerenic acid plays some part in the activity of *V. officinalis*, together with other more polar compounds, and the mechanism is likely to be associated with increased levels of GABA in the brain.

The sedative effects, i.e. relaxant activity and suppression of CNS activity leading to decreased response to stimuli, are associated with volatile oils and valepotriates and recent findings implicate the possible contribution of the lignans. These types of compounds would be found in alcoholic extracts. The major compounds responsible for decrease in anxiety, without a major suppression in alertness, are the valepotriates which are therefore classed more as tranquillizers than sedatives. They are likely to play a significant role only when freshly-prepared extracts are used since they decompose quickly on storage. They are likely to be more stable in dry extracts incorporated into solid oral dosage forms.

Summary – the past, present and future use of Valerian

The decline in the prescribing of Valerian extract in the 1960s in the UK was due to the introduction of the synthetic tranquillizers and sedatives such as the benzodiazepines. It should be noted, however, that the decline was also due to the variation in effect, and therefore the unreliability of preparations, to achieve a therapeutic effect and also to the unpleasant smell and taste of preparations linked with the inconvenience of liquid dosage forms.

Although Valerian has been re-introduced to the British Pharmacopoeia, it is now only rarely prescribed. In contrast, its use for self-medication as a constituent in most proprietary medications has increased dramatically. Although Valerian has been shown to be generally safe, even when taken in fairly large doses, there are still concerns over its safety, quality and efficacy which need to be addressed.

The possible carcinogenicity of the valepotriates awaits further clarification and current moves to produce valepotriate-free preparations are not unnecessarily cautious (Bos et al 1998). Another area which needs further research is the interaction of Valerian with other medication intended to act on the CNS. Valerian may exert an additive, synergistic or antagonist response in these situations and thus potentiate tranquillizers and sedatives or reduce the effect of antidepressants. This is particularly pertinent in the light of the large number of CNS-active medicines prescribed and the increasingly large number of people who are self-medicating with herbal preparations such as Valerian.

The evidence for the efficacy of Valerian is fairly strong and it would appear to be a relatively safe substitute for drugs such as the benzodiazepines as a mild tranquillizer and to aid onset of sleep, particularly as it does not seem to produce a hangover effect. If it is used more widely it is very important that standardized extracts are used and it is encouraging that some manufacturers are now introducing solid oral dosage forms containing standardized extracts. Since the chemical basis of the observed activities is still not fully known, more work needs to be carried out before a satisfactory standard can be formulated which relates to activity.

The continued use in pharmacy of this interesting plant seems more likely than it did twenty years ago and further scientific study may mean not only that it can be used with more confidence, but that it may provide lead molecules for more conventional therapy.

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