A Role for Phytotherapy in the Treatment of Benzodiazepine and Opiate Drug Withdrawal

back Materia Medica

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This paper will discuss the pathophysiology and symptomatology associated with dependency and withdrawal from two main classes of drugs, benzodiazepines (e.g. Valium) and opiates (e.g. heroin). An outline of orthodox treatment regimes used during withdrawal from these substances will be given, followed by a list and discussion of specific phytomedicines used by the author in his work as a phytotherapist in a Medical Detoxification Unit operating in Auckland, New Zealand. Part 1 of this paper will discuss treatment approaches and agents used primarily for benzodiazepine withdrawal, and Part 2 (to be published in the following issue of this journal), those for opiate withdrawal.

Introduction

"Psychoactive substance dependence" is defined by the American Psychiatric Association's Diagnostic and Statistical Manual, as having the essential feature of "a cluster of cognitive, behavioural, and physiologic symptoms that indicate that the person has impaired control of psychoactive substance use and continues use of the substance despite adverse consequences".

Over the centuries, a large number of plant derived or synthetically produced substances have been responsible for dependency syndromes or addictions. Society's attitudes to addiction or "chemical dependency" vary substantially from one country or decade to the next, and relate largely to cultural influences.

General pathophysiological factors in substance dependency and withdrawal

The frequent co-occurrence of substance use disorders with mental disorders ("dual diagnosis"), is pervasive and well documented. In particular, the incidence of depression, anxiety, and "antisocial personality" disorder is high among substance abusers relative to non-drug abusers. Moreover, the differential diagnosis of patients presenting with drug or alcohol related problems is further complicated by the fact that virtually any psychiatric syndrome can be produced by acute and chronic use of drugs and alcohol, and the fact that dependencies on more than one substance at the same time (polydrug addiction), are common. Taking these factors into account, it is often difficult to determine the relative contribution of dependency on a particular substance to a person's particular symptoms or psychopathology (i.e. the dilemma of "cause or effect").

For the sake of simplicity however, pathophysiological mechanisms behind addictions/ dependencies, can generally be divided into two basic components, psychological and physical. All substance dependency syndromes involve contributions from both of these factors to a greater or lesser degree.

Physical dependency involves the development of tolerance - a markedly diminishing effect from continued use of the same amount of the substance. The person will then take increasing amounts of the substance in order to achieve intoxication or the desired effect. Withdrawal symptoms also have physical and psychological components, but are much more likely to be seen with drugs that cause the development of physical dependence.

In general, withdrawal symptoms tend to be the opposite of those produced by acute intoxication with the drug. These symptoms and tolerance itself can be related to pathophysiological factors produced as a natural consequence of the body's own homoeostatic mechanisms and subsequent "neuro-adaptive" changes in response to the continual presence of the drug and/or its metabolites, in the bloodstream and body tissues. Such changes are likely to be widespread and diverse, but include the following:

Receptor changes

Most, if not all, drugs and active plant components are known to initiate their pharmacological actions through their affinity for specific membrane sites, known as receptors. Adaptive changes in the characteristics of these receptors may be expected from their persistent occupation by agonist (causing receptor activation) or antagonist (inhibiting receptor activation) ligands (molecules which have a tendency to bind to specific receptors). These changes may be in the form of numbers of receptors, affinity for endogenous or exogenous ligands, and so on. For example, persistent activation of endogenous opiate receptors by exogenous agonists such as morphine, is likely to lead to a gradual reduction in the 'sensitivity' (affinity for ligands) or numbers of these receptors (receptor 'down-regulation').

Metabolic factors
A number of drugs, including alcohol, are inducers of liver metabolising enzymes. Induction means causing increased production of enzymes which metabolise and inactivate their own and other drug or phytochemical molecules. Liver enzyme induction will thus result in a faster metabolic breakdown of that substance, and a shorter half life and duration of effect as a result.

A logical consequence of these factors, is that relatively large doses of appropriate phytomedicines are often required to produce a significant effect in alleviating acute withdrawal symptoms in tolerant individuals.

The Detox Unit
The Detoxification Unit of Regional Alcohol and Drugs Services (RADS), is a specialised in-patient unit providing medical detox (medically assisted and monitored drug withdrawal programmes) for people who are drug and/or alcohol dependent (or who are in a toxic state due to these) and who cannot be safely managed or treated by community based agencies. Alcohol is the substance most frequently implicated in admissions to the unit, although opiate or benzodiazepine use is behind a large proportion of all admissions, and many clients present with a 'polydrug' history. The average duration of stay in the Detox Unit is 10 days.

The Phytotherapy Service
Since the Phytotherapy Service was introduced into the unit in mid 1993, more than 500 clients have received its treatments from the previously two, but now one practitioner involved (the author). A physiotherapy and acupuncture service is also available in the unit.

Therapeutic strategy
The aims of the phytotherapy service are generally to:

- help alleviate acute symptoms experienced during drug or alcohol withdrawal (e.g. sleep difficulties, anxiety, muscle cramps, gastrointestinal complaints, sweating etc.).
- make the withdrawal process easier.
- provide supportive treatment for those suffering from ongoing problems such as stress, depression, anxiety and panic attacks, thus reducing the chance of relapse following discharge.
- provide advice on other non-drug treatment options for concurrent physical and psychological health problems.
- help encourage the client to take greater responsibility for managing their own health.

Treatment procedures
An information sheet on the phytotherapy service is available to all clients upon admission to the unit. Requests for treatment are dealt with during the twice weekly visits to the unit by the practitioner, in consultation with other medical staff. Assessments usually take about 20 to 30 minutes, following which the individual prescriptions are dispensed and left in the unit with dosage charts to be administered by nurses in the same manner as orthodox prescribed medication. All clients with alcohol related conditions are restricted to infusions or decoctions of dried herbs, while others receive liquid extracts. Dosage varies depending upon individual needs, but generally ranges from 5 to 10ml b.i.d., and 10 to 15ml nocte of a 1 in 2 strength mixed liquid extract.

Most clients receive concurrent orthodox medication, in particular methadone (opiate addicts), diazepam (benzodiazepine and some opiate addicts, amphetamine and cocaine addicts), chlormethiazole (alcoholics), thioridazine

(psychotic symptoms), and clonidine (some opiate addicts). In a significant number of cases the need for additional ameliorative orthodox medication (especially diazepam and methadone) is avoided through the introduction of phytotherapy, often after consultation between the phytotherapist and medical practitioner.

A brief follow-up consultation (usually no more than 10 minutes per client, due to time restrictions) takes place usually 2-3 days after commencement of phytotherapy, and in some cases further consultations occur every few days. During these follow-ups the prescription is reviewed to take account of changing symptomatology or perceived lack of efficacy. Most clients receive a take-away supply of their herbal medicine sufficient to last 1-3 weeks when they leave the unit, and a small proportion recontact the service for further repeat supplies over the ensuing month. All treatments are funded in full by the service and provided at no cost to the client.

Since the service was introduced nearly 4 years ago, there has been no evidence of abuse of the repeat medicine service, or dependency on the prescribed phytomedicines developing following discharge from the unit. The reasons for this remain speculative, but probably relate largely to the multiple rather than isolated chemical makeup of the plant medicines used. Most medicinal herbs are characterised by the presence of more than one active constituent acting concurrently, and in many cases there is synergy between these. This concept, as opposed to persistent receptor occupation by large numbers of a single drug or drug metabolite molecules, would seem to be associated with a much lower tendency to the development of the neuropathological changes associated with repetitive use of individual psychoactive drugs.

Treatment Approaches to Withdrawal from Specific Drugs
Part 1 - Benzodiazepine Withdrawal

Since the development of the first benzodiazepine (chlordiazepoxide) in the late 1950's, this group of drugs has replaced barbiturates as by far the most frequently prescribed anxiolytic (anti-anxiety) agents. While the level of benzodiazepine use has fortunately declined since its peak in the 1970's, a large number remain in current use, mainly for anxiety and related conditions, and insomnia, but also for their properties as muscle relaxants and anticonvulsants. They are also used in doses up to as much as 300mg of diazepam (Valium) per day, either alone or by opiate users to boost the effects of the opiate or help alleviate symptoms of withdrawal, and by cocaine and other stimulant users to counter unpleasant side effects. In other words, benzodiazepine dependence can be seen in conjunction with dependence to another substance, as well as in response to scripting that exceeds 3 months duration.

Withdrawal symptoms

The withdrawal syndrome is usually long-lasting and symptoms can begin 24 hours after withdrawal of a short-acting drug such as lorazepam or triazolam, but not until 3 to 7 days of stopping a longer-acting agent such as diazepam or chlordiazepoxide. Resolution of symptoms can take days or months, and their severity is related to the dosage and duration of drug use.

The most often seen symptoms are anxiety, insomnia, and irritability. Headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, perceptual disturbances such as hypersensitivity to visual, auditory and cutaneous stimuli and metallic taste, nausea, vomiting, abdominal cramps, palpitations and orthostatic hypotension, can also occur.[1] The sympathetic nervous system is in a general state of overactivity, and the patient frequently feels depressed. Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and delirium tremens.

A major difficulty in evaluating the physiologic dependence on benzodiazepines, is in distinguishing between the considerable overlap in the range of symptoms seen as a direct result of the drug withdrawal, and those reappearing as a consequence of the pre-existing condition no longer being controlled (e.g. anxiety, panic attacks).

Pathophysiology

The main mechanism of action of benzodiazepine drugs is widely attributed to be due to their facilitation of coupling of the neurotransmitter GABA (gamma-aminobutyric acid) to its receptor via the so called benzodiazepine-GABA-A

receptor complex.[2,3]

GABA is a neurotransmitter present throughout the brain, and generally considered the major inhibitory neurotransmitter within the mammalian CNS. Release of endogenous GABA by appropriate nerve stimulation produces postsynaptic hyperpolarisation at synapses in the cerebral cortex, the hippocampus, cerebellum and amygdala, and this is thought to play a crucial role in the body's handling of stress and anxiety.

Apart from anxiolytic agonists such as benzodiazepines, anxiogenic (anxiety-inducing) antagonists and "inverse agonists"(e.g. beta-carbolines) are also ligands at so-called benzodiazepine receptors. It seems likely that like other receptor/ neurotransmitter systems, benzodiazepine receptor subtypes with different functions exist.

The existence of an endogenous ligand has also been proposed in a similar manner to endogenous opioid peptides, the enkephalins and endorphins, and intervention of endogenous agonist compounds is possible during stress or anxiety. An important candidate is the DBI (Diazepam Binding Inhibitor), which displays inverse agonist activity and is present in humans. Inverse agonists, however, do not seem to be implicated in benodiazepine withdrawal and panic disorder mechanisms.[4]

The mechanism of benzodiazepine dependence is still unclear. One likely contributory mechanism, however, is a relative deficiency of functional GABA activity resulting from down-regulation (reduced numbers and/or sensitivity) of the benzodiazepine-GABA receptor complex produced as an adaptive response to persistent stimulation. Larger doses of benzodiazepine are therefore required to occupy sufficient receptors to boost GABA activity to the same degree, and produce the same clinical effects.

Apart from GABA, other neurotransmitter systems are also implicated in the psychopathology of benzodiazepine withdrawal. For example, diazepam withdrawal causes increased release of serotonin (5-HT) from the amygdala of rats, and this may contribute to the anxiogenic response.[5] Exposure to anxiogenic drugs is also associated with increased activity of the neurotransmitter dopamine (DA) in the nucleus accumbens.[6]

Orthodox management of withdrawal
This usually involves a gradual reduction in the dose of the benzodiazepine used or a longer-acting, cross-tolerant drug (e.g. diazepam).

While concurrent administration of antidepressant drugs, as well as carbamazepine, propranolol, and clonidine, seem to help attenuate some withdrawal symptoms in some patients, orthodox medical treatment is largely limited to the tapering diazepam dosage regime backed up by psychological support.

Postwithdrawal syndromes lasting for several weeks or months have been described, and continued support may be required for the first year after withdrawal to prevent relapse. If there is continued anxiety away from benzodiazepines, addressing nutritional and lifestyle issues (e.g. avoidance of caffeine and nicotine, good sleep, hygiene, and regular appropriate exercise), counselling, cognitive/behavioural treatment, relaxation training, physiotherapy and acupuncture, assertiveness training, support, and education about anxiety may help.

Phytotherapy can be especially effective in helping to safely reduce the residual anxiety or nervous system weakness commonly seen in the recovering benzodiazepine user, thus providing much of the supportive treatment necessary to enable these and other more long term issues to be addressed. Experience has shown that in particular, the anxiolytic and antidepressant properties of appropriate phytomedicines can be invaluable in many cases during the period following completion of benzodiazepine withdrawal.

Phytomedicines for benzodiazepine withdrawal
Benzodiazepine receptor ligands
Plants containing components which act as agonist ligands at the benzodiazepine-GABA receptor complex in an

analagous manner to the benzodiazepines themselves, can be expected to be likely to show some efficacy in reducing the effects of benzodiazepine drug withdrawal. Some plants which have shown evidence of having the ability to act as agonists on central benzodiazepine receptors, indicating the presence of ligands for these receptors, include the following:

Cola nitida.[7]
Gentiana macrophyllae.[8]
Leptospermum scoparium (Manuka).[9,10]
Matricaria recutita.[11]
Passiflora incarnata.[7]
Passiflora coerulea.[12]
Piper methysticum.[14]
Paullinia cupana (Guarana).[7]
Salvia miltiorrhiza.[8,13]
Salvia officinalis.[15]
Scutellaria baiacalensis.[8]
Withania somnifera.[16]

Plants used in the Detox Unit
The main plants used in the unit for clients undergoing withdrawal from benzodiazepines, are listed below. Other agents are of course sometimes used, depending on the individual symptomatology and presence of other concurrent drug addictions.

Most are anxiolytic agents, with other pharmacological properties which give them specific indications for particular symptomatologies. Others are more 'adaptogenic' than anxiolytic, and some can be regarded more primarily as sedatives or antidepressants. For many of these agents, evidence of beneficial properties as so-called "nervous system (nervine) tonics", is apparent in their traditional uses and/or pharmacological studies. Obviously, as is intrinsic to the properties of medicinal plants, there is much cross-over in these actions.

- *Bacopa monniera* - nervine and brain tonic; may enhance memory and learning processes; probably anxiolytic.[17]
- *Centella asiatica* - nervine tonic; probable anxiolytic.
- *Glycyrrhiza glabra* - adrenal tonic; may contain a compound which stimulates benzodiazepine-binding;[18] flavouring agent.
- *Humulus lupulus* - sedative; antispasmodic; digestive stimulant.
- *Hypericum perforatum* - antidepressant (takes 2-4 weeks for effect to manifest); hepatoprotective; nervous tonic; possible activity against hepatitis C virus.
- *Leptospermum scoparium* - possible anxiolytic and slight sedative; astringent.
- *Matricaria recutita* - relaxant, antispasmodic, anti-inflammatory to the gut.
- *Melissa officinalis* - anxiolytic; mild sedative; nervine tonic.[19]
- *Passiflora incarnata* - traditionally used as a hypnotic and sedative.
- *Piper methysticum* - anxiolytic; mild sedative; muscle relaxant.
- *Polygala tenuifolia* - anxiolytic; sedative; may help ameliorate memory and learning deficits; contains a DA receptor ligand;[20] useful in cases of concurrent bronchial congestion (expectorant).
- *Salvia officinalis* - anti-hydrotic; possible mild anxiolytic.
- *Schisandra chinensis* - adaptogenic and anti-fatigue agent; nervine tonic; hepatoprotective and hepatorestorative; anti-oxidant; possible slight anti-depressant.
- *Scutellaria lateriflora* - anxiolytic, sedative.
- *Valeriana officinalis* - anxiolytic; sedative; possible slight anti-depressant.
- *Withania somnifera* - adaptogenic; gently anxiolytic; may assist memory deficits.
- *Zizyphus spinosa* - anxiolytic; slightly sedative; nervine tonic; anti-hydrotic and sometimes useful with excessive sweating.[21,22]

Some selected plant agents in detail

Valeriana officinalis (Valerian)

Aqueous extracts of Valerian root in doses ranging from 400-900mg have been shown to improve the quality of sleep in humans and reduce sleep latency, without producing a 'hangover' effect the next morning.[23,24] These effects seem to be especially marked in those who consider themselves to be habitually poor sleepers, and several studies suggest that Valerian is at least as effective in this regard as small doses of barbiturates and benzodiazepines.[25] At higher dosages anticonvulsant and spasmolytic effects are observed.[26]

A recent study found that Valerian in doses of 12.0mg/kg reversed the anxiogenic effect of acute diazepam withdrawal in dependent rats, whereas doses of 6.0mg/kg failed to reverse these withdrawal symptoms.[27] This would seem to reinforce the need for adequate and in some cases comparatively large doses in humans also, to produce a significant sedative effect.

While Valerian does not seem to show affinity for benzodiazepine receptors[7] evidence suggests that it may inhibit the reuptake and/or stimulate the release of GABA from nerve terminals.[28] This could increase the extracellular concentration of the neurotransmitter in the synaptic cleft at levels sufficiently high to activate GABA receptors, in a manner analagous to that of selective serotonin reuptake inhibitors (e.g. fluoxetine or "Prozac") on serotonin.

Interaction of Valerian with melatonin-binding sites, may also contribute to its sedative properties, as shown in recent work conducted by German researchers.[29]

Valerian may also possess mild antidepressant properties[30, 31], which may confer an additional potential benefit in many individuals undergoing benzodiazepine withdrawal.

While properly designed studies into the long-term safety and predisposition to development of tolerance for Valerian do not seem to have been undertaken, a significant degree of physical tolerance has not been evident among the many thousands of individuals consuming copious amounts of Valerian-containing proprietary preparations over many years. Nevertheless, it is my opinion that it is probably wise to avoid regular use of this herb for more than two or three months at a time, and to substitute with other herbs during such breaks if needed.

Piper methysticum (Kava)

The root and rhizome of this plant has in recent years been shown to possess anxiolytic and muscle relaxant properties comparable to those of the benzodiazepines, and this activity has been verified by a number of clinical trials using standardised kava extracts or kavain, one of the active kava lactone constituents.[32-35] A possible antidepressant activity has also been implicated in some patients undergoing these trials, and a mild sedative effect is seen with higher doses. No significant adverse effects were reported at the dosages used (1.5-3.0g/day), and no development of tolerance seems to occur at these dosages when taken over a period of weeks. Standardised Kava preparations are now becoming very popular particularly in Germany, as an ameliorative treatment for mild anxiety and related symptoms.

The mode of action of Kava's anxiolytic and sedative effects remains unknown, but probably involves at least some influence on GABA neurotransmission. Thus while one study using whole brain membranes showed no apparent interaction with GABA or benzodiazepine binding sites,[36] a subsequent study found marked effects by kavapyrones on GABA-A receptor binding in the main target brain centres, the hippocampus, amygdala and medulla oblongata.[14]

Leptospermum scoparium (Manuka)

This New Zealand native has been used traditionally as a relaxant and mild sedative, and a team of German researchers have recently found that flavonoid compounds which it contains interact specifically with benzodiazepine receptors.[9, 10] A sedative and possible anxiolytic effect of an alcoholic extract of Leptospermum was also exhibited in locomotion studies in rats by the same investigators.[9] The dosage required was comparable to that required of more established

anxiolytic agents such as *Hypericum perforatum, Passiflora incarnata, Humulus lupulus* or *Valeriana officinalis*.

In clinical practice, I have found that doses of 1 to 3 grams of *Leptospermum scoparium*, as a hydroalcoholic extract, are very effective in many patients experiencing symptoms of anxiety and related disorders, as well as insomnia. This plant is additionally beneficial in those suffering from associated problems such as nervous diarrhoea or loose bowel motions, due probably to the strongly astringent properties of the large amounts of tannins it contains.

***Passiflora incarnata* (Passionflower)**
This plant has long been used for its sedative and analgesic actions, and a sedative effect has been confirmed in animal studies.[37]

The constituents responsible for this activity remain to be identified. A flavonoid compound, 5,7-dihydroxyflavone (chrysin), found in the related *Passiflora coerulea*, has been found to act probably as a partial agonist at central benzodiazepine receptors,[12] and this or similar constituents may also contribute to the actions of *P. incarnata*. Although Passiflora contains small amounts of beta-carboline alkaloids (harman, harmine, harmol, passiflorine etc.), known to act as potent "inverse agonists" on central benzodiazepine receptors,[7] these do not seem to be the main components responsible for its CNS effects.[37] This is indeed fortunate, as if this were the case, an unwanted anxiogenic rather than anxiolytic effect, might be the net result.

***Withania somnifera* (Ashwagandha)**
The root of this plant is widely used in Ayurvedic medicine to augment the faculty of learning and memory retention, and to attenuate cerebral function deficits in the elderly. It is regarded as being particularly useful as a "nervine restorative" in those who have memory impairment and general debility, both common components of the benzodiazepine withdrawal syndrome. Adaptogenic effects have been shown in several studies, and the increase in numbers of dopamine receptors in the corpus striatum produced due to stress, was prevented by pretreatment with Withania.[38] Withania is also reported to have anxiolytic[39] and slight CNS depressant effects.[40-43]

Radioligand binding and functional studies, have found that an extract of Withania acts probably as an agonist at GABA receptors,[16] and this may account for some of these actions on the nervous system. The combination of these actions, makes Withania ideally suited as a medium-term, gently relaxing adaptogenic agent for many clients to be taken during and after both benzodiazepine and opiate withdrawal.

***Hypericum perforatum* (St John's Wort)**
Several well designed clinical trials have now shown conclusively the anti-depressant effects of this herb (see Harrer and Schultz, 1994; Reuter 1995; Linde et al, 1996, for reviews).[44-46] Its efficacy in mild to moderate depression has been found to be similar to that of currently used anti-depressant drugs, but with less side effects and perhaps taking slightly longer to become apparent in some patients.[47, 48]

The mode of this antidepressant action and constituents responsible remain speculative. Contrary to popular opinion this is unlikely to involve inhibition of the enzyme monoamine oxidase (MAO),[49] and instead may involve serotonin[50] or other neurotransmitter pathways.

Depressive illness is often seen in those with substance dependencies, the substance(s) in many cases being abused partly or largely as a means of "numbing the pain" or producing a temporary euphoric effect. In a significant proportion of all clients seen I believe it to be an important aetiological factor in the addiction itself, as well as appearing quite commonly during the withdrawal period. This is probably due largely to the sudden changes in neurotransmitter and hormonal systems which occur during this period. It is no accident that the once used "animal model" of depression used to consist of the abrupt withdrawal of rats previously dependent on amphetamine.

Needless to say, large amounts of *Hypericum perforatum* are used in the Detox unit, and its antidepressant and mild anxiolytic[45] as well as hepatoprotective[51] properties make it especially useful when treatment continues into the post-

withdrawal period. It also possesses anti-viral action, and seems to be of some benefit where there is concurrent hepatitis C infection, although reasonable doses are required.

***Schisandra chinensis* (Schisandra)**
The berries of this vine are used extensively in China and other countries as anti-fatigue agents, and anti-fatigue properties have been proven in animals including horses.[52] Schisandra is also classified as an adaptogen,[53] and is hepato-protective and helps liver cells regenerate.[54, 55] It exhibits a synergistic effect with pentobarbitone as a CNS depressant in mice,[52] and in clinical practice seems to show a similar synergistic effect with many other herbs used in both benzodiazepine and opiate withdrawal. Antidepressant activity may also be possessed by Schisandra.[55]

Once again, the combination of these actions make Schisandra a valuable agent not only for the acute phase of withdrawal, but as a safe treatment for the post withdrawal period. As an adaptogenic nervine tonic, particularly in cases of fatigue, I find it excellent. Like Hypericum, it is also a herb which may offer additional benefits in those addicts who are positive for hepatitis C.

Clinical studies using proprietary formulations
Properly designed and controlled studies into the ability of herbal compounds or formulations to assist the process of benzodiazepine withdrawal in humans, are unfortunately lacking in the literature to date. However, several studies in both humans and animals confirm the efficacy of plant agents in the treatment of anxiety and its associated symptoms. It is therefore logical to presume a beneficial effect of these same agents in alleviating many of the symptoms associated with benzodiazepine withdrawal. Apart from those studies already mentioned, the following are of interest in this regard:

1. A proprietary French herbal formulation containing a mixture of extracts of *Passiflora incarnata, Valeriana officinalis* and *Cola nitida*, as well as smaller amounts of *Crataegus oxyacanthoides*, *Paullinia cupana* (Guarana) and *Ballota foetida*, was shown in a double blind, randomised study to be as effective as oxazepam in the treatment of patients suffering from generalised anxiety.[57] This mixture of plant extracts has also been found to interact with central benzodiazepine receptors.[7] It is also of some interest that the degree of benzodiazepine receptor binding measured with the complete plant mixture was found to be greater than that of the individual components, suggesting a synergistic effect between these components in the formulation.

2. An Indian preparation, BR 16-A (Mentat), which contains the herbs *Centella asiatica, Asparagus racemosus, Hardestachys jatamansi, Xpomosa digitata, Acorus calamus, Withania somnifera, Tinospora cardifolia, Embelica officinalis, Evolvulus alsinoides*, and *Saussurea lappa*, has been found to reverse the acute effects of diazepam withdrawal in mice, although relatively large doses were required.[58, 59]

3. A Japanese formulation, "Shosaikoto", containing *Bupleurum falcatum* and smaller amounts of *Pinellia ternata, Scutellaria baicalensis, Zingiber officinale, Zizyphus spinosa, Panax ginseng* and *Glycyrrhiza uralensis*, produced similar effects to diazepam in reversing stress-induced effects on the immune system and body temperature in mice.[60] Certain other traditional kampo mixtures used clinically for central nervous problems, also contain *Bupleurum falcatum*, which is best known as an anti-inflammatory, liver and adrenal agent. It seems likely that this formulation may be particularly useful to help minimise the adrenal-mediated components of the stress response seen during benzodiazepine withdrawal, such as immune disregulation (discussed further in the next article).

4. A traditional Chinese formulation, "Kamikihito", which consists of *Astragalus mongholicus, Panax ginseng, Atractylodes japonica, Poria cocos, Polygala tenuifolia, Zizyphus jujuba, Euphorbia longan, Angelica acutilobia, Glycyrrhiza glabra, Zingiber officinale, Saussurea lappa, Bupleurum falcatum* and *Gardenia jasminoides*, is used to treat insomnia, amnesia, palpitations and neurosis brought on by physical overwork.[61] This formulation produced an anxiolytic effect related to enhancement of benzodiazepine binding sites in the brains of aged rats[62] and exerted effects suggestive that it assists memory registration, consolidation and retrieval.[61] Effects on DA and 5-HT receptor binding have also been observed.[63]

Other Possible Agents

From the spectrum of symptoms and pathophysiology described earlier, it is apparent that a large number of other phytomedicines may also assist with the benzodiazepine withdrawal process. Other agents with psychoactive properties potentially of value in assisting benzodiazepine (as well as alcohol and opiate) withdrawal in some cases, are listed in Appendix 1.

Appendix 1: Additional agents with possible benefit in benzodiazepine withdrawal

Acorus calamus - sedative, nervine tonic, possible slight antidepressant.
Azadirachta indica - anxiolytic.[64]
Chelidonium majus - enhances binding of agonists to the GABA-A receptor.[19]
Euphorbia hirta - mild sedative and anxiolytic properties.[65]
Ginkgo biloba - may prevent stress-induced desensitisation of 5-HT1A receptors and detrimental changes in both discrimination learning and plasma hormones,65 and improve memory and other cognitive functions.[66]
Leonurus cardiaca - mild sedative and relaxant, antispasmodic, may help reduce palpitations or tachycardia of nervous origin.
Ligusticum chuanxiong - possible benefit in impaired cerebral function due to cholinergic dysfunction or cerebral circulatory deficiency.[68]
Macropiper excelsum - traditionally used as aromatic digestive, also for urinary problems; closely related to kava.[69]
Morinda citrifolia - antispasmodic, central analgesic activity antagonised by the opiate antagonist naloxone; actions suggestive of sedative properties.[70]
Nardostachys jatamansi - frequently used in Ayurvedic medicine for epilepsy, hysteria and 'mental weakness'; produces increases in brain levels of GABA as well as noradrenaline (NA), DA and 5-HT in rats.[71]
Ocimum sanctum - synergistic effect with pentobarbitone as CNS depressant in mice, dopaminergic, possible anti-depressant action.[72]
Poria cocos (Hoelen) - nervine tonic, sedative, may ameliorate learning and memory deficits.[73]
Pinellia ternata - found in many Chinese nervine formulations; may facilitate neurotransmitter release from pre-synaptic nerves.[74]
Rhazya stricta - sedative and analgesic.[75]
Salvia miltiorrhiza - acts as a partial agonist on central benzodiazepine receptors.[13]
Salvia officinalis - contains diterpenes which bind to GABA/benzodiazepine receptor complex.[15]
Vinca minor and *erecta* - Vinca alkaloids increase cerebral blood flow and protect against cerebral ischaemia.[76, 77]

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