Review Article

Herbal Medicines In The Treatment of Psychiatric and Neurological Disorders

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Objective: This review will indicate the quality of the evidence supporting the clinical effects of a number of commonly used types of herbal medicines for psychiatric and neurological disorders.
Method: We conducted a review of literature to understand the biochemical and evidential bases for the use of herbs in psychiatric and neurological disorders as follow:
1) Alzheimer's disease, 2) Depression, 3) Anxiety, 4) Insomnia, 5) Substance use disorders, 6) Attention deficit/hyperactivity disorder (ADHD), 7) Migraine.
Results: Evidences support use of Ginkgo biloba, Huperzine A, Galantamine, Melissa officinalis,and Salvia officinalis for Alzheimer's disease; St. John's wort, Lavender, and Saffron for depression; Passionflower, and Kava, for anxiety disorders; Valerian, and English Lavender for sleep disorders; Hypericum for substance related disorders; Ginkgo biloba, and Passionflower for ADHD; and feverfew, and Butterbur root for migraine. The highest level of confidence derives from well-designed, randomized, double blind controlled studies.
Conclusion: Herbs may have beneficial effects in variety of psychiatric and neurological disorder; however we must consider their potential side effects and drug-drug interactions.
Keywords:
Anxiety , Dementia, Depression, Herbal medicine, Psychiatry

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Herbal medicines include a range of pharmacologically active compounds: in some cases it is not well understood which ingredients are important for a therapeutic effect. The supporters of herbal medicine believe that isolated ingredients in the majority of cases have weaker clinical effects than whole plant extract, a claim that would obviously require proof in each case.
Generalizations about the efficacy of herbal medicines are clearly not possible. Each one needs systematic research including a variety of animal studies and also randomized clinical trials. Indeed, clinical trials of herbal medicines are feasible much in the same way as for other drugs. Numerous randomized clinical trials of herbal medicines have been published and systematic review and meta-analyses of these studies have been available.
Many of today's synthetic drugs originated from the plant kingdom, and only about two centuries ago, the major pharmacopoeias were dominated by herbal drugs. Herbal medicine went into rapid decline when basic and clinical pharmacology established themselves as leading branches of medicine. Nevertheless, herbal medicine is still of interest in many diseases in particular psychiatric and neurological disorders.
There are some reasons for this issue: 1) patients are dissatisfied with conventional treatment; 2) patients want to have control over their health care decision; and, 3) patients see that herbal medicine is congruent with their philosophical values and beliefs. It has been reported that most patients with a mental disorder sought herbal medicine treatment for somatic problems rather than for their mental and emotional symptoms and the best example is somatic symptoms of depression.
Physicians need to understand the biochemical and evidential bases for the use of herbs and nutrients to diagnose and treat patients safely and effectively, to avoid interactions with standard medications, and to provide patients with the benefits of alternative treatments.
Although a multitude of pharmaceutical agents are available for the treatment of mental disorders, physicians find that many patients cannot tolerate the side effects, do not respond adequately, or eventually lose their response. In comparison, many therapeutic herbs have far fewer side effects. They can provide an alternative treatment or be used to enhance the effect of prescription medications.
This review will indicate the quality of the evidence supporting the clinical effects of a number of commonly used types of herbal medicines for psychiatric and neurological disorders as follow:
1) Alzheimer's disease 2) Depression 3) Anxiety 4) Insomnia 5) Substance use disorders 6) Attention deficit/hyperactivity disorder (ADHD) 7) Migraine.
The highest level of confidence derives from well-designed, randomized, double blind controlled studies.

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of severe mental deterioration (dementia) in the elderly (1, 2). AD was known to occur occasionally in families, but was not necessarily related to the more frequent occurrence of cognition impairment in late life. The latter condition was known as senile dementia. When results of careful pathology studies emerged in the 1970s and 1980s showing that the pathology of the brains of patients with early-onset (before the age of 65 years) and late-onset AD was the same, research into the pathologic process as well as the clinical manifestations accelerated (1, 2). The incidence and prevalence of AD rose with increasing age, especially for those over the age of 65 years. The incidence of AD ranges from 1% to 4% of the population per year, rising by half a decade from its lowest level at ages 65 to 70 years to rates that may approach 6% over the age of 85.

Prevalence of AD has been a subject of discussion. Prevalence rates of AD also increase by half decade or decade; reports in the literature of how many cases exist at any one period vary. Estimates of the prevalence of AD range from 3% of the population between the ages of 65 and 75 to the highest reported estimate of 47% of people over the age of 85 years. In general, all studies report a progressive increase in the prevalence of dementia as a function of age between 65 and 85 years; more conservative estimates at the higher end are in the range of 30% to 35%, which is still a significant number. Whatever the current estimates are, all researchers agree that the number of AD cases will probably triple over the next 30 to 40 years (1, 2).

Definitions of AD

There are three widely used criteria-based approaches to the diagnosis of AD: the International Classification of Diseases, 10th revision (ICD-10); the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); and the National Institute of Neurological and Communicative Disorders and Storke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) work group criteria (3). Not surprisingly, the three definitions share many common features.

Three common misconceptions exist regarding AD: that it is a global disorder, that it is a diagnosis of exclusion, and that it can be a diagnosed only at autopsy. All these misconceptions are challenged by the three diagnostic frameworks, which require that attention be sufficiently good to exclude delirium as the cause of the mental status changes, whereas a global disorder would include attentional abnormalities. All the definitions specify expected findings, i.e., memory impairment, thus utilizing inclusionary criteria in the diagnosis rather than approaching the disorder as a diagnosis of exclusion. All definitions are predicted on the feasibility of clinical diagnosis, and most series find accuracy rates of 85-90% based on these criteria. Diagnosis of AD should begin with detailed interviews of both the patient and an informant who is familiar with the patient. The medical history can provide relevant information, such as the timing of onset of symptoms, level of functional impairment, rate of deterioration, and any alterations in mood (2). A complete physical examination should include an in-office cognitive assessment, such as the Mini-Mental State Examination, and a brief neurological examination. The presence of depression should also be evaluated; useful screens include Geriatric Depression Scale and the Zung Self Rating Scale for Depression. Laboratory evaluations should include blood chemistries; a complete blood cell count; tests for neurosyphilis, thyroid, kidney and liver function; and serum levels of vitamin B_{12}. Some neuroimaging is generally recommended. Computerized tomography is usually sufficient to eliminate subdural hematoma or tumors as a potential cause; however, magnetic resonance imaging (MRI) may be necessary to detect the presence of white matter ischemic lesions. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are useful in distinguishing AD from other dementias through quantifying metabolism or to assessing general blood flow (2).

Pathophysiology of AD

Neuroimaging of the patient with AD or other dementias may reveal atrophy of the brain, such as enlarged ventricles and sulci and narrowed gyri, although these features are not always present (2). Neuronal loss is the main neuropathologic feature underlying the symptoms of AD. Microscopically, AD is characterized by the presence of senile plaques and nerofibrillary tangles (NFTs). Plaques are extracellular deposits of filamentous ß-amyloid, a protease cleavage product of amyloid precursor protein (2).

NFTs are formed intracellulary by an abnormal rearrangement of microtubule-associated proteins, such as tau. Both NFTs and senile plaques, although diagnostic of AD when observed in large numbers, are also present to some degree in the brains of normal elderly persons. However, the plaques seen in normal brains or early-stage AD are diffuse and relatively benign deposits of ß-amyloid; whereas at later stages, the plaques assume a compact b-pleated conformation and subsequently become associated with dystrophic neuritis. These later-stage plaques are thought to represent a more neurotoxic form (2).

The cholinergic hypothesis

The first neurotransmitter defect discovered in AD involved acetylcholine (Ach). As cholinergic function is required for short-term memory, the cholinergic deficit in AD was also believed to be responsible for much of the short-term memory deficit (4). Markers for cholinergic neurons, such as choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), which are enzymes responsible for synthesis and degradation of Ach, are respectively decreased in the cortex and hippocampus, areas of the brain involved in cognition and memory. The earliest loss of neurons occurs in the nucleus basalis and the entorhinal cortex where

cholinergic neurons are preferentially affected. As the illness progresses, up to 90% of cholinergic neurons in the nucleus basalis of Mynert may be lost. Preclinical studies have demonstrated that loss of cholinergic functions in these areas is associated with declines in learning capacity and memory. The resultant decrease in Ach-dependent neurotransmission is thought to lead to the functional deficits of AD, much as dopaminergic deficits underlie Parkinson's disease and its clinical manifestations (4). Clinical drug trials in patients with AD have focused on drugs that augment levels of Ach in the brain to compensate for losses of cholinergic function in the brain. These drugs have included acetylcholine precursors, muscarinic agonists, nicotinic agonists, and acetylcholinesterase inhibitors (AChEIs) (5).

The most highly developed and successful approaches to date have employed AChE inhibition. The first drug approved for general clinical use in AD was tacrine, followed a few years later by donepzil. Most recently, rivastigmine has been used in several countries around the world, and was launched in the US by June 2000. Another launched AChEI is galantamine, and metrifonate was being developed by Bayer Corp as an AChE inhibitor (6, 7). All of these drugs have been tested primarily on patients with AD, with most trials studying treatment in patients with mild to moderately severe illness.

Pharmacological treatment

Pharmacological treatment strategies in AD include three classes of agents: (a) mechanism-based disease-modifying therapies such as vitamin E and selegiline; (b) mechanism-based therapies that compensate for transmitter deficits such as AChEIs; and (c) psychotropic agents administered to relieve behavioral symptoms of AD (8). Various other agents have been used in an attempt to modify the course or improve the symptoms of AD, including Ginkgo biloba and anti-inflammatory agents (8). The majority of FDA-approved drugs for Alzheimer's disease (AD) (e.g., tacrine, donepezil, rivastigmine, galantamine) act by countering the cholinergic deficit associated with the cognitive dysfunction, and are based on inhibition of the AChE (8).

Peripheral cholinergic (gastrointestinal) adverse effects for currently used cholinesterase inhibitors are common as well as other side effects such as hepatotoxicity (tacrine). More recently, the uncompetitive NMDA (N-methyl-aspartate) antagonist memantine that improves functioning and behavioral symptoms in patients with AD has been approved.

Other targets including anti-inflammatory, antioxidative and estrogenic mechanisms, nicotinic receptors, nerve growth factors and the formation of neurofibrillary tangles and plaques are the most important research activities in this field (8). There are several studies and documents that indicate a unique role of herbal medicines in the treatment of Alzheimer's disease.

Ginkgo biloba

Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments for thousands of years in China. An extract of Ginkgo biloba has been found in several studies to improve the symptoms and slow the progression of Alzheimer's disease. A study of 309 patients with mild dementia was performed. The patients were given either 120 mg of Ginkgo biloba extract or placebo every day for up to a year (9).

At the six-month point, 27 percent of those using ginkgo had moderate improvement on a variety of cognitive tests.

Only 14 percent of those using placebo had an improvement on these tests. In a separate trial, 112 patients with chronic cerebral insufficiency received 120 milligrams per day of Ginkgo biloba extract (10). The researchers found that the use of this extract led to significant improvements in blood and oxygen flow. Restricted blood and oxygen flow to the brain may be an important factor in the development of Alzheimer's. Ginkgo biloba extract (GBE) appears to be most effective in the early stages of Alzheimer's. This could potentially mean that patients with early Alzheimer's may be able to prevent being placed in a nursing home and to maintain a reasonably normal life. GBE has been shown to have the ability to normalize the acetylcholine receptors in the hippocampus area of the brain (the area most affected by the disease) in aged animals (11). GBE has also demonstrated the ability to increase cholinergic activity and to provide improvements in other aspects of the disease (12).

A double blind study of 216 Alzheimer's patients or dementia caused by small strokes found that 240 mg of GBE daily led to significant improvements in a variety of clinical parameters when compared to placebo. The most effective form of GBE is one that is standardized to a concentration of 24 percent Ginkgo flavoglycosides. A study compared the effectiveness of the most common Alzheimer's drugs, such as donepezil and rivastigmine, to that of a Ginkgo extract called EGb 761.

The researchers determined that EGb761 was as effective as any of these commonly prescribed drugs are in treating the symptoms of Alzheimer's patients. In general, various forms of Gingko have been found to be safe, but in individuals who take aspirin or other anticoagulant drugs, Gingko should be taken with great caution and with the advice of a physician. Ginkgo is sold as a drug and regulated in Germany, and it is used in many other parts of the world to slow the progression of various forms of dementia. EGb 761 is the most commonly sold form of Gingko in Europe (10, 13).

A different study found that EGb761 prevents beta-amyloid toxicity to brain cells, a key part of the development of the disease. All forms of Gingko need to be taken consistently for at least 12 weeks, a potentially difficult task for Alzheimer's patients, to determine whether the supplement is working. A recent double blind, placebo-controlled randomized study of patients

with Alzheimer's found that EGb 761 produced significant improvements in cognitive function compared to a placebo group. Other recent comprehensive surveys of multiple clinical trials found similar results with EGb 761 in these patients. An additional study found that EGb 761 produced cognitive improvement compared to placebo over a 26-week period using a variety of research measures. This study also demonstrated that EGb 761 was as safe as placebo during the study period (10, 13).

Huperzine A

Huperzine A is a chemical derived from a particular type of club moss (*Huperzia serrata*). Like caffeine and cocaine, huperzine A is a medicinally active, plant-derived chemical that belongs to the class known as alkaloids. This substance is really more a drug than an herb, but it is sold over the counter as a dietary supplement for memory loss and mental impairment. According to three Chinese double blind trials enrolling a total of more than 450 people, use of huperzine A can significantly improve symptoms of Alzheimer's disease and other forms of dementia. One double blind trial failed to find evidence of benefit, but it is a relatively small study (14, 15).

Vinpocetine

Vinpocetine is a chemical derived from vincamine, a constituent found in the leaves of common periwinkle (*Vinca minor*) as well as the seeds of various African plants. It is used as a treatment for memory loss and mental impairment.

Developed in Hungary more than 20 years ago, vinpocetine is sold in Europe as a drug under the name Cavinton. In the US, it is available as a "dietary supplement", although the substance probably does not fit that category by any rational definition. Vinpocetine does not exist to any significant extent in nature. Producing it requires significant chemical work performed in the laboratory. Several double blind studies have evaluated vinpocetine for the treatment of Alzheimer's disease and related conditions. Unfortunately, most of these suffered from significant flaws in design and reporting. A review of the literature found three studies of acceptable quality, enrolling a total of 728 individuals. Perhaps the best of these was a 16-week, double blind, placebo-controlled trial of 203 people with mild to moderate dementia, which found significant benefit in the treated group. However, even this trial suffered from several technical limitations, and the authors of the review concluded that vinpocetine could not yet be regarded as a proven treatment. Currently, several better quality trials are underway (16).

Galantamine

An alkaloid ChEI originally derived from European daffodils, or common snowdrops, this drug is a competitive and selective AchE inhibitor. Galantamine also allosterically modifies nicotinic Ach receptors, potentiating the presynaptic response to Ach. Like donepezil and rivastigmine, galantamine is brain selective. Galantamine has a half-life of 5 to 6 hours, and is metabolized by the same CYP 450 enzymes as donepezil. Galantamine has not been associated with hepatotoxicity in clinical trials (8).

Melissa officinalis & Salvia officinalis

It has been reported that *Melissa officinalis* (lemon balm) improves cognitive function and reduces agitation in patients with mild to moderate Alzheimer's disease. *Melissa officinalis* is known to have acetylcholine receptor activity in the central nervous system with both nicotinic and muscarinic binding properties (17, 18). A recent study has shown that this plant modulates mood and cognitive performance when administered to young healthy volunteers (19). In addition, a parallel, randomized, placebo-controlled study assessed the efficacy and safety of *Melissa officinalis* in 42 patients with mild to moderate AD (20). Subjects were treated for four months. The main efficacy measures were the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinical Dementia Rating-Sum of the Boxes (CDR-SB) scores. The CDR-SB provides a consensus-based global clinical measure by summing the ratings from six domains: memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care. The results revealed that patients receiving *Melissa officinalis* extract experienced significant improvements in cognition after 16 weeks of treatment. Improvements were seen on both the ADAS-cog and CDR-SB scores. The researchers observed no significant difference in the frequency of side effects between the placebo group and those receiving the herb extract. However, the frequency of agitation was higher in the placebo group compared to those receiving active treatment (20). Moreover, another study showed that patients with mild to moderate Alzheimer's disease receiving *Salvia officinalis* (sage) extract experienced statistically significant benefits in cognition after 16 weeks of treatment (21).

The clinical relevance of these findings was emphasized by the improvements seen in both the ADAS-cog and CDR-SB measures in the S. officinalis extract group on both observed case and Intention to treat analyses. The side effects associated with Salvia in this study were generally those expected from cholinergic stimulation, and similar to those reported with cholinesterase inhibitors (22). Frequency of agitation appeared higher in the placebo group and this may indicate an additional advantage for *Salvia officinalis* in the management of patients with Alzheimer's disease.

Depression

Depression is a serious disorder in today's society with estimates of lifetime prevalence as high as 21% of the general population in some developed countries. As defined by the American Psychiatric Association, depression is a heterogeneous disorder often manifested

with symptoms at the psychological, behavioral and physiological levels. Such patients are often reluctant to take synthetic antidepressants in their appropriate doses due to their anticipated side effects including inability to drive a car, dry mouth, constipation and sexual dysfunction. As a therapeutic alternative, effective herbal drugs may offer advantages in terms of safety and tolerability, possibly also improving patient compliance (23). The advent of the first antidepressants, the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), in the 1950s and 1960s represented a dramatic leap forward in the clinical management of depression. The subsequent development of the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine in the past decade and a half has greatly enhanced the treatment of depression by offering patients medications that are as effective as the older agents are, but that are generally more tolerable and safer in an overdose. The introduction of atypical antidepressants, such as bupropion, nefazadone, and mirtazapine, has added substantially to the available pharmacopoeia for depression. Nonetheless, rates of remission tend to be low and the risk of relapse and recurrence remains high. Thus, there is a need for more effective and less toxic agents (23). Plants extracts are some of the most attractive sources of new drugs, and have been shown to produce promising results for the treatment of depression (24)

***Hypericum perforatum* (St. John's Wort)**

As one of the best-studied botanicals of all time, St. John's wort (SJW) is notable for its ability to treat mild-to-moderate depression and is also known to be safe and effective for children. As a result, SJW has become very popular in the U.S., where it is available over the counter. In Germany, physicians prescribe SJW to patients with mild-to-moderate depression (25, 26). The possible action of SJW stems in part from its hypericin and hypericin-like constituents, which may act on acetylcholinesterase by decreasing the degradation rate of acetylcholine. Sedative actions come from the hypericins, biflavones, and hyperforin. Other reports demonstrate a serotonergic activity, by which it can act as a weak serotonin-reuptake inhibitor (SSRI) that leads to fewer side effects.

In addition, sigma-1 receptors, which are affected by antidepressant medications in animal studies, may also be affected by SJW. Most likely, the demonstrated efficacy of this botanical in treating depression is through its synergistic effects, orchestrated by the multitude of components in the whole herb working both within and peripheral to the central nervous system (27-30).

A meta-analysis of 23 randomized trials, which included 1757 outpatients with mainly mild or moderately severe depressive symptoms found that *Hypericum* extracts were significantly superior to placebo and similarly effective as standard antidepressants. Side effects occurred in 19.8% of patients on *Hypericum* and 52.8% of patients on standard antidepressants (23), and data analysis revealed a dropout rate of 0.8% for SJW and 3.0% for standard antidepressant drugs due to side effects (25, 26).

The action of SJW has been well characterized in direct comparisons with leading antidepressant medications. In a randomized controlled double blind trial, 70 patients suffering from mild-to-moderate depression received one tablet of either SJW extract or fluoxetine twice a day for 6 weeks. Patients were rated by the 17-item Hamilton Rating Scale for Depression (HAMD) and the von Zerssen depression scale (ZDS). HAMD scores significant decreased ($p<0.001$) in the SJW group (50%) and in the fluoxetine group (58%), and ZDS also decreased in both treatments (42% and 52%, respectively).

Assessments by physicians and patients indicated considerable improvement with no between-treatment differences.

The conclusion of that study is that SJW was therapeutically equivalent to fluoxetine and is therefore a reasonable alternative to synthetic antidepressants. *Hypericum* extract has similarly been tested and showed an efficacy similar to that of sertraline in the treatment of mild-to-moderate depression in a small group of outpatients. Efficacy and tolerability of SJW was also compared with imipramine and was equivalent to that of the drug in treating mild-to-moderate depression. In addition, patients tolerated SJW better than imipramine (25, 26).

In a review of over 3000 depressed patients spanning 34 double blind trials, the effective dosage level of SJW for mild-to-moderate depression was between 500 and 1000 mg of standardized alcohol extract per day (26). For patients with preexisting conductive heart dysfunction or elderly patients, high-dose *Hypericum* extract has been found to be safer with respect to cardiac function than tricyclic antidepressants.

The side-effect profile of SJW extract is minor, especially when compared to the well-known side effects of antidepressant medications. Due to its lack of monoamine oxidase (MAO) inhibition, SJW is not considered to interact negatively with MAO-inhibiting drugs or tyramine-containing foods. However, it has been shown that important SJW–drug interactions may occur. SJW can reduce the circulating levels of certain drugs.

Synergistic therapeutic effects may also lead to complications and unfavorable treatment outcome.

SJW is a potent inducer of cytochrome P450 (CYP) enzymes, particularly CYP 3A4 and/or P-glycoprotein, and it may also inhibit or induce other CYPs (31). Although SJW induces photosensitivity in some patients, this is not likely to happen with standard dosages; it has occurred mainly in HIV patients using larger-than-normal quantities for an antiviral effect. SJW is not recommended for use during pregnancy, because its safety in pregnancy has not been studied (31).

***Lavendula angustifolium* (lavender)**
Lavender is used principally as an aromatic essential oil for relaxation. In a single-blind randomized control trial, 80 women who took daily baths with lavender oil experienced improved mood, reduced aggression, and a more positive outlook (24). Furthermore, the combination of lavender (60 drops/day of a lavandula tincture) and imipramine (100 mg/day) was found to be more effective in the treatment of depression than either treatment alone, according to a double blind randomized control trial. The findings of this study suggested that taking a moderate amount of lavender might help reduce the amount of tricyclic antidepressants needed to treat depression, leading to fewer side effects (31).

***Crocus sativus* (Saffron)**
Saffron is the world's most expensive spice and apart from its traditional value as a food additive, recent studies indicate its potential as an anti-cancer agent and memory enhancer (32-34). The value of saffron (dried stigmas of Crocus sativus L.) is determined by the existence of three main secondary metabolites: crocin and its derivatives, which are responsible for color; picrocrocin, responsible for taste; and safranal responsible for odor. This plant belongs to the Iridaceae family and as a therapeutic plant, saffron is considered an excellent aid for stomach ailments and an antispasmodic, helps digestion and increases appetite. It also relieves renal colic, reduces stomachache and relieves tension (32, 35). Saffron is used for depression in Persian traditional medicine (36). Indeed, it is a Persian herb with a history as long as the Persian Empire itself. Iran, the world's largest producer of saffron has been investing in research into saffron's potential medicinal uses. Much of the work surrounds its traditional application for alleviating depression. The clinical findings suggest that saffron is a safe and effective antidepressant. For example, in a randomized, double blind study, 30 mg of saffron extract (in capsules) given for 6 weeks resulted in significant alleviation of depression compared to those on placebo, and did so without evident side effects. This study was a follow-up to a preliminary trial in which the same saffron preparation performed as well as imipramine for treating depression in a double blind trial. In further preliminary work, saffron was compared to the drug fluoxetine; it was found that saffron performed as well as the drug in the treatment of depression (36, 37).

Anxiety Disorders

Generalized Anxiety Disorder (GAD) is the most common anxiety disorder but being generally less severe than panic disorder. GAD is probably the disorder most often found with a coexisting mental disorder, usually another anxiety disorder or a mood disorder. The ratio of women to men is about 2 to 1. The cause of GAD is not known. The primary symptoms of GAD are anxiety, motor tension, autonomic hyperactivity and cognitive vigilance. DSM-IV employs the following criteria for GAD: excessive anxiety and worry, occurring more days than not for at least 6 months, about a number of events or activities that are difficult to control (38). Autonomic symptoms are no longer required for diagnosis. The principal neurotransmitter systems thought to modify anxiety are the gamma-aminobutyric acid (GABA) system, and the noradrenergic, serotonergic, dopaminergic and histaminergic systems. The most effective treatment of patients with GAD is probably one that combines psychotherapeutic, pharmacotherapeutic and supportive approaches. Because of the long-term nature of the disorder, a treatment plan must be carefully thought out. The two major drugs to be considered for the treatment of GAD are buspirone and the benzodiazepines. Benzodiazepines are the drugs most frequently prescribed for the treatment of anxiety disorders. They act through the benzodiazepines-GABA receptor, where they inhibit neuronal activity by increasing the chloride ion influx into neuron. This includes hyperpolarization of the nerve cell, a condition that leads to decreased responsiveness to incoming stimuli (38). Several problems are associated with the use of benzodiazepines (BZDs) in GAD. About 25 to 30% of all patients fail to respond, and tolerance and dependence may occur. Some patients also experience impaired alertness while taking the drugs. In addition, there are several reports that indicate cognition impairment induced by benzodiazepines. The cessation of use of benzodiazepines can induce a withdrawal syndrome, characterized by psychological symptoms of anxiety such as apprehension and irritability, physiological symptoms of anxiety such as tremor and palpitation, and perceptual disturbances such as hypersensitivity to light, sounds, touch or motion. Only one third of patients who have GAD seek psychiatric treatment. Many patients go to general practitioners, internists, and cardiologists, and use herbal medicine like passiflora (38).

Passiflora incarnata
Passionflower (*Passiflora incarnata*) is a woody, hairy, climbing vine reputed to have sedative/anxiolytic properties, and has been used widely as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture. The commission E approved the internal use of passionflower for nervous restlessness and the British Herbal Compendium indicates its use for sleep disorders, restlessness, nervous stress, and anxiety. A double blind and randomized trial showed that that passiflora extract is an effective drug for the management of generalized anxiety disorder and the low incidence of impairment of job performance with passiflora extract compared to oxazepam is an advantage (38).

Kava
Kava is a ceremonial and social drink in the South Pacific, containing approximately 250 mg of kava lactones. Its use is constrained by elaborate rituals in Fiji, Samoa, and Tonga, where it has also been used for analgesia. Kava contains alpha-pyrones, a recently

discovered class of potent skeletal muscle relaxants. In Germany, doses of 70–80 mg kava lactones are given t.i.d. for stress and muscle spasm. For milder symptoms, a dose of 60–70 mg kava lactones q.d. is usually sufficient. When six of the nine major alpha-pyrones found in Kava extract are administered together in animal studies, they create a synergistic effect. Whether or not Kava affects benzodiazepine or GABA-A receptors is controversial. However, it has anti-convulsant properties in animal models. Kava exerts some serotonin blocking activity and sodium channel blocking. In preclinical studies, the primary calming effect is mediated through the amygdale (39-41). Kava's traditional use as an analgesic was confirmed in preclinical studies. Naloxone, when administered in doses that blocked morphine-induced analgesia, did not reverse Kava's antinociceptive effects. The intriguing finding that the analgesia induced by Kava occurs via non-opiate pathways deserves further study. Some double blind, placebo-controlled studies support the efficacy of Kava for anxiety.

In patients with generalized anxiety disorder, Kava worked as well as oxazepam without producing any cognitive dysfunction. "Menopause-related" anxiety in 20 women improved on kava by week 1 compared with no improvement in 20 women on placebo. Anxious patients receiving 70 mg kava lactones t.i.d. improved compared to a placebo group by week 1 and became increasingly better over 28 days, as measured by Hamilton Anxiety ratings, CGI, and self-ratings, with no side effects reported. In the longest study to date, 108 patients were randomized to 70 mg kava lactones t.i.d. or to placebo. By week 25, Hamilton Anxiety scores dropped from 31 to 10 in the 59 patients on kava and fell from 30 to 15 in the 49 on placebo; 75% of the kava group attained significant global improvement with no evidence of dependency compared to 50% in the placebo group. Although the patients had clinically significant anxiety, this study, like the Lehmann et al. (40) study, suffered from lack of precise diagnoses. Recent reviews concluded that kava extract is relatively safe and more effective than placebo. Only three of the studies met criteria for meta-analysis, including the selection of patients by HAM-A >19 and treatment with kava extract WS1490 100 mg t.i.d. (210 kavapyrones/ day). Because of methodological questions in the studies, the authors suggested more rigorous risk-benefit trials (39-41).

Dosage and side effects

Two post-marketing studies of over 3,000 patients found a 1.5% and a 2.3% incidence of side effects. Gastrointestinal complaints, allergic skin reaction, headache, and photosensitivity were the most common side effects. Other complaints included restlessness, drowsiness, lack of energy, and tremor. Schelosky et al. described four cases in whom kava induced symptoms suggestive of central dopaminergic antagonism, including dystonic reactions (eyes, neck, and trunk), oral/lingual dyskinesias, and one case of worsening Parkinsonian symptoms in a woman on levodopa (42). Until more information is available, kava should be avoided in patients with Parkinson's disease and in those at risk for dystonia or dyskinesia. No studies of long-term safety, teratogenicity, or mutagenicity beyond 6 months have been done. Kava should not be combined with alcohol or other sedatives (39-41).

Substance Related Disorders

Herbal medicines are used extensively as sleep aids. A study of the use of nonprescription sleep products in an ambulatory elderly population found that 27% of total respondents had used a nonprescription sleep product in the past year (43).

Valerian

Valerian (*Valeriana officianalis*) is probably the best-known herbal sedative. However, there is only weak research support for its mechanism of action and efficacy. Valerian is thought to act by potently binding to GABA-A receptors. Four small double blind trials in insomnia and five studies in otherwise healthy people with sleep disturbance have been done. It may require 2–4 weeks for valerian to work. In one study, which compared valerian and hops used together (hops has estrogenic effects) with flurazepam, a benzodiazepine, the researchers concluded that valerian and hops did not cause the deficits in attention and reaction time seen with benzodiazepines. There have been some reports of dystonia and hepatitis from valerian, but the preparations most likely contained a mixture of ingredients making it difficult to place the onus on valerian. Patient compliance is a problem since valerian tea and tablets often have the odor of "old gym socks" (44-47).

***Lavandula angustifolia* (English Lavender)**

English Lavender is approved by Germany's Commission E for nervousness and insomnia, as well as for loss of appetite, circulatory disorders and dyspeptic complaints (PDR for Herbal Medicines, 2000). Like hops, lavender is sometimes put into a pillow or beneath the pillow to promote sleep. There are some preclinical studies suggesting the sedative qualities of English Lavender (48).

Substance use disorders

Many existing pharmacological and psychosocial interventions for substance use disorders are solidly evidence-based. Yet, there is a need to identify additional treatments. The use of natural and complementary therapies fits well within a range of existing theoretical frameworks for understanding and treating drug dependence. They could fulfill a variety of roles: (1) As adjunctive treatments to existing pharmacological or psychosocial interventions; (2) As treatment alternatives for substance users who are not eligible for existing treatments, who are nonresponsive to existing treatments, or who refuse existing treatments; (3) As treatment options in countries or

regions where evidence-based interventions are not routinely available; and (4) As treatment options for disorders where there is no current gold standard treatment. It has been estimated that up to 45% of substance users employ natural and complementary therapies. Surveys suggest that more than three-quarters of substance users contacting treatment services find complementary or alternative treatments acceptable (49).

Substance withdrawal syndrome

The traditional aim of detoxification is to achieve a safe and humane withdrawal from a drug of dependence. Although unlikely to produce long-term abstinence in itself, detoxification is an attractive treatment option for many substance users, and may permit individuals to reduce their drug use, or prepare them for other treatment programs.

Pharmacological interventions

Pharmacological management of substance withdrawal is standard practice in many countries, and an important component of comprehensive treatment provision. Use of complementary medicines with relevant pharmacological properties fits well within existing models of withdrawal management (49).

Hypericum (Hypericum perforatum)

Hypericum has also been investigated for its effects on nicotine withdrawal. Similar pharmacological effects to existing treatments such as bupropion have partly contributed to the interest in hypericum.

In a clinical study, 45 adult smokers were randomized to receive an oral spray containing hypericum or placebo spray, in addition to brief counseling sessions and nicotine replacement patches. Although abstinence rates were similar in each group after 1 month, hypericum was associated with lower craving scores, and less anxiety, restlessness and sleeplessness compared with controls (50). An animal study also reports that high doses of hypericum attenuated effects of nicotine withdrawal in mice. This effect was greatest when hypericum was initiated prior to nicotine cessation rather than delayed until emergence of withdrawal symptoms (51).

Other herbs

Numerous complementary medicines are utilized for their putative sedative properties. Some, such as valerian (*Valeriana officinalis*), have evidence to support their use in insomnia. Sedative compounds have a potential role in the management of agitation, insomnia or anxiety associated with substance withdrawal. Pilot studies have reported beneficial effects of passionflower (*Passiflora incarnata*) for opiate withdrawal (49) or melatonin for benzodiazepine or nicotine cessation (49, 52). However, there are few recent clinical studies of these agents focusing on withdrawal management.

One review discusses the mechanisms of passionflower in the treatment of substance use disorders, focusing on one particular constituent, a benzoflavone moiety, which animal studies have shown to reduce withdrawal severity from various substances (52).

Unfortunately, this review does not address the comparative effects between this constituent and whole plant preparations typically utilized for sedative and anxiolytic effects. Morphine withdrawal signs in mice has been reported for rosemary (Rosmarinus officinalis) and the corn poppy (Papaver rhoeas), which may possess opioid and anticholinergic effects. Positive effects in animal studies do not necessarily translate to clinical effectiveness.

These studies may contribute to our understanding of the pharmacology of these compounds; however, without ongoing research, they provide little to inform treatment (49).

Attention Deficit/Hyperactivity Disorder (ADHD)

ADHD is a loosely defined assemblage of neuropsychiatric symptom clusters that emerge in childhood and often persist into adulthood. Though the means to its diagnosis is only empirical, ADHD is being increasingly employed as a diagnostic label for individuals who display a wide range of symptoms, such as restlessness, inability to stay focused, mood swings, temper tantrums, problems completing tasks, disorganization, inability to cope with stress, and impulsivity (53).

The etiology of ADHD is not understood, yet potent drugs are being employed for its medical management while safe and effective alternatives are being neglected. Neurochemical studies suggest alterations in catecholaminergic (mainly dopaminergic and noradrenergic) transmitter functions markedly contribute to the symptoms of ADHD. The symptoms of ADHD are significantly ameliorated by agents that specifically influence these neurotransmitter systems, and animal studies implicate areas of the brain in which these neurotransmitters are most dominant (53).

ADHD is the most prevalent behavioral disorder in children and frequently its symptoms are commingled with learning problems, oppositional conduct, and depression, which altogether compound the family's emotional burden. Psychostimulant medications are generally the first choice in medication of ADHD. Approximately 70 percent of the children treated show improvement in the primary ADHD symptoms and in comorbidity such as conduct disorder, although the benefits may not hold beyond two years.

Despite the well-established efficacy and safety of stimulants for ADHD, alternative medicines are still needed for several reasons. About 30% of children and adolescents with ADHD may not respond to stimulants or may be unable to tolerate potential adverse events such as decreased appetite, mood lability and sleep disturbances. Although stimulants do not increase risk for later substance abuse in ADHD, concerns have been raised about special prescription rules, and a potential for abuse by persons other than the ADHD subjects (53, 54).

Herbal medicines have been shown to ameliorate ADHD-related behaviors in individuals without this disorder. For example, Ginkgo biloba is somewhat effective for disorders like dementia and memory impairment. A review of 40 controlled trials found at least a partial positive outcome in nearly all subjects who had cerebral insufficiency (e.g. difficulties of concentration and memory, absentmindedness). This finding may help to provide support for using Ginkgo in children with ADHD, especially those who are primarily inattentive. Moreover, Ginkgo improves cerebrovascular blood flow and attention may help to reduce hyperactivity due to boredom and lack of focus (53). A recent study showed that Passiflora might be a novel therapeutic agent for the treatment of attention deficit/hyperactivity disorder. In addition, a tolerable side effect profile may be considered as one of the advantages of Passiflora in the treatment of attention deficit hyperactivity disorder (54).

Migraine

Migraine prevalence studies have indicated that more than 17 percent of the female and six percent of the male population in the United States suffer from the condition. In addition to the debilitating effect of a migraine attack, sufferers report a significant impact on their quality of life between attacks. Many migraine patients report that the fear of getting a headache totally disrupts their ability to plan social events, vacations, and other family activities. Available research on the treatment of migraine focuses on acute treatment and prophylactic medications. Advances in acute treatment are well documented. Sumatriptan, a serotonin-1 agonist administered subcutaneously, orally, or intranasally, is effective in alleviating the pain and associated symptoms of the acute migraine attack. In contrast, there has been limited progress in the prophylactic treatment of migraine. Herbal medicine approaches to migraine prevention have shown some promise (55).

Feverfew

There is significant comorbidity of migraine with mood and anxiety disorders. Three out of four double blind, placebo-controlled trials found that feverfew reduces the frequency and severity of migraines and the associated nausea and vomiting. The negative outcome of the fourth study was due to its use of a preparation standardized for parthenolide (thought to be the key compound with sesquiterpine lactones), instead of the whole leaf extract of feverfew used by other researchers. Parthenolide is unstable and needs other components for its activity. In fact, the Canadian Regulatory Commission will only certify whole leaf extract of feverfew as an effective medication. Spurred by uncertainty about the ideal preparation and concerned about what effects previous exposure to feverfew has on patient expectations, a recent study reduced the possibility of this bias by selecting only those participants who had never taken feverfew before. In this 4-month, three-phase, crossover study, 57 patients were divided into two groups. The feverfew group experienced significant reduction in migraine pain only when they were on feverfew.

The mechanism of activity is uncertain. However, patients who are not able to obtain relief on standard prescription medications, many of which have undesirable side effects, could benefit from feverfew. Feverfew is generally well tolerated with very few side effects. However, feverfew can affect bleeding time and should not be used with warfarin. Feverfew should be discontinued 2–3 weeks prior to surgery. Doses range from 100 to 200 mg/day (2–4 pills) (55). Feverfew has additional uses including treatment of menstrual irregularities and arthritis. Feverfew plants from different parts of the world contain different substances. For example, the variety in Guatemala is without parthenolide, and has not yet been tested in the study of migraine (55).

This is an example of the different contexts in which experience by accomplished herbalists is needed to guide further scientific research.

Butterbur

Petadolex contains an extract of Petasites hybridus (Butterbur root) with demonstrated benefits for the prophylaxis of migraines. A randomized, double blind, placebo-controlled study of 58 migraine sufferers found a significant reduction in the frequency of headaches (46% at week 4, 60% at week 8, and 50% at week 12) in the group given Petadolex 50 mg b.i.d. compared to those given placebo (24%, 17%, and 10% respectively) (55).

Conclusion

Many factors underlie the growing popularity of herbal treatments for a variety of chronic conditions. Interestingly, people who use alternative therapies are not necessarily uninformed. If anything, they are more "culturally creative" (i.e., comfortable with cultural changes) and more highly educated (56).

Many people using herbal medicines find the health care alternatives are more congruent with their own values, beliefs and philosophical orientations toward health and life. Similarly, it seems likely that many people feel that herbal medicines are empowering by allowing them to treat themselves without seeing a physician (This same attitude may be behind the growing popularity of patient-initiated diagnostic scanning procedures such as whole body scans). The danger is that, many people believe that herbal medicines have no toxicity problems or even side effects. In addition, they are not aware of many possible interactions of herbal medicine with concurrently prescribed medications (47).

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