Considerations for the Use of Alternative Therapies in the Treatment of Depression

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Approximately 65%–75% of patients with major depression will respond to drug therapy. However, conventional antidepressants may be costly and have side effects and drug interactions that may inconvenience the patient, limit the use of the particular drug, or require the discontinuation of a particular therapy. In this past decade, there has been a renewed interest in alternative medicines, especially for depression, that are available without a prescription. The ability of patients to self-medicate depression presents a risk of inappropriate treatment, thereby increasing the morbidity and mortality rates associated with this sometimes fatal disease. In addition, herbal products are not regulated by the government, leading to problems with batch-to-batch consistency and adulteration, even for products that have evidence of efficacy in depression. The potential for herbal-pharmaceutical grade drug interactions increases the need for input and follow-up from health care practitioners. There is limited quality evidence describing the efficacy and optimal dosing for these products. Clinicians must acknowledge that patients are using herbal products and educate on their use to avoid negative outcomes in patients with depressive disorders.

KEY WORDS: alternative therapies, depression, herbals, St. John's wort, Sam-E, mood.

INTRODUCTION

APPROXIMATELY 19 MILLION people will experience a depressive episode in any given year, but only a third of these patients actually seek medical treatment.[1] It is estimated that by the year 2020, major depression will be the second most important cause of disability worldwide.[2] Eisenberg and associates found that between 1990 and 1997, nearly 41% of adults who had severe depression and anxiety used alternative therapies within 12 months of their diagnosis. [3] There are several hypotheses that explain the lure of using alternative approaches instead of Food and Drug Administration (FDA)—approved or conventional antidepressants. Cultural traditions, lack of governmental regulation, accessibility, adverse effects of pharmaceutical-grade products, drug interactions, and stigma associated with certain mental disorders all contribute to patients seeking alternative treatment.[4] More than $4–$6 billion are spent on these therapies annually. Pharmacists should be an integral part of the educational process for patients and practitioners because of the potential of drug-herbal inteactions, disease exacerbations, and adverse reactions that could result from use of these products. This article will discuss and examine the benefits and risks associated with the use of herbal medicinals for treating depression.

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Herbal Therapies as Primary Treatment for Depression

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

H. perforatum is the most popular herbal product used to treat mild to moderate depression. *H. perforatum* is the dried herb of the flowering top of a member of the St. John's wort family, native to Europe and naturalized in Asia, Africa, North America, South America, and Australia. It was so named because the blooms are at their brightest golden-yellow color coincidentally with the feast day of John the Baptist on June 24.

Ancient Greeks used *H. perforatum* as a diuretic, wound-healing herb and for treatment of menstrual disorders. Today, *H. perforatum* is used orally for the treatment of mild to moderate depression. Externally, the oil is used for the treatment of wounds, abrasions, and first-degree burns.[5–8]

H. perforatum *is the most popular herbal product used to treat mild to moderate depression.*

There are various proposed mechanisms of action for *H. perforatum*, although the precise mechanism is unclear. Hypericum extracts contain more than 10 constituents that could provide its antidepressant effects including naphthodianthrones (i.e., hypericin and hyperforin), flavanoids (i.e., quercetin), xanthones, and bioflavanoids. Hypericin and pseudohypericin have demonstrated considerable antiretroviral activity in both in vitro and in vivo testing, which are believed to help inhibit viral infections, especially retroviruses such as HIV and herpes. Hyperforin is a potent inhibitor of serotonin, dopamine, noradrenalin, and gamma aminobutyric acid. It is not clear whether hyperforin inhibits the reuptake and synthesis or affects neurotransmitter receptors otherwise. The flavonoids and xanthone components may be responsible for monoamine oxidase inhibition.[6–12]

H. perforatum is available in a variety of dosage forms including capsules, tablets, teas, and extracts; however, the extract is most commonly employed for treating depression.[5] The extract LI 160 has been associated with clinical efficacy for depression.[8] A hypericin content of 0.3% is the standard for pharmaceutical quality of the *H. perforatum* extract. This standardization may not offer any guarantee of pharmacologic benefit, as hypericin may not be the primary active constituent, and the active components of hypericum teas cannot be standardized. Most studies disregard the activity of hyperforin and adhyperforin. The fruits of the plants are not typically harvested in the extract form, and they are unstable when exposed to heat and light. Most of hyperforin and adhyperforin are found predominantly in the reproductive parts of the plant (2% in the flowers, 4.5% in the unripe fruits, and 4.4% in ripened fruits).[6–10]

Adverse effects of *H. perforatum* are mild compared to conventional antidepressants. In an open-label study of 3250 patients, the most common side effects noted over a 4-week period were gastric-related symptoms, allergic reactions, and fatigue. Photosensitivity reactions were first observed in cattle grazing in Europe but have been noted in fair-skinned individuals and patients receiving injectable forms of *H. perforatum*. Other adverse effects associated with hypericum include dry mouth, dizziness, constipation, confusion, drowsiness, lethargy, peripheral neuropathy, and restlessness.[6,7] Despite its proposed monoamine oxidase and serotonin-reuptake inhibiting action, there have been no reports of hypertensive crisis, cardiotoxicity, or sexual dysfunction.

The dose of *H. perforatum* most commonly used is 300 mg two to three times a day, taken with water at mealtime. Studies suggest that adults with mild to moderate depression will benefit from 0.9–2.7 mg of hypericin/day. Higher doses of up to 1800 mg/day have been studied in individuals with severe depression.

No studies have been done on children to date.[6] In 1984, the German Commission E monographs cited hypericum as an experimental monoamine oxidase inhibitor in daily doses of 2–4 grams/day or 0.2–1.0 mg/day of total hypericin. Despite these citations, clinicians should remember that these monographs were translated from dated German medical practices that may not be applicable to current medical practices. Despite a number of studies, pharmacokinetic data are limited. The t 1/2 of hypericin and pseudohypericin is around 24 hours, which implies that the extract may be administered once daily. Antidepressant effects are not reported to occur until after 2 to 4 weeks of continuous treatment.[10]

H. perforatum has been compared to placebo, maprotiline, imipramine, amitriptyline, desipramine, and bromazepam in clinical studies. More than 3000 patients have been evaluated for clinical efficacy of the extract and injectable formulations. A meta-analysis of randomized clinical trials suggests that *H. perforatum* extracts were superior to placebo and similarly effective as standard antidepressants. Unfortunately, none of the studies were longer than 12 weeks.[21,22] Larger studies comparing the extract to more contemporary antidepressants and doses are needed.

***Drug interactions are of concern when patients take* H. perforatum.**

There have been no human studies evaluating the teratogenic effects of hypericum. Anecdotal reports in humans suggest that hypericum may be safe during pregnancy. Animal studies suggest that prenatal exposure causes no long-term deficits in growth, physical maturation, or future reproduction compared to placebo. It is noted that hypericin and pseudohypericin cross the placenta, so it is not recommended for women using hypericum to breast-feed.[13]

Drug interactions are of concern when patients take *H. perforatum*. Reports have been documented that suggest that *H. perforatum* is a potent inducer of the cytochrome P4503A metabolic pathway and may increase metabolic activity 2-fold, resulting in decreased plasma concentrations of other medications when taken concomitantly.[14–17] Yue and associates reported on 8 females who were taking either cyclosporine, theophylline, ethinylestrodiol/ desogestrel, or warfarin. Three of the patients had decreased serum concentrations of cyclo-sporin. One patient had a lowered concentration of theophylline. Three of the females taking ethinylestrodiol/desogestrel experienced breakthrough bleeding. The last patient had a lowered serum concentration of warfarin. Interestingly, there have been at least 7 reports of reduced anticoagulant effects when *H. perforatum* is coadministered with hypericum since 1999, so it is recommended to monitor bleeding time and INR when using the two together. At least 8 cases of intermenstrual bleeding or change in menstruation were reported in women ages 23 to 32. All of the women were taking oral contraceptives with hypericum.[6,18] Other important interactions include reduced concentrations of digoxin, some of the steroidal hormones, and HIV-1 protease inhibitors.[17–20]

Additive toxicity with other antidepressants may occur resulting in serotonin syndrome–like reactions. There have been reports that this syndrome is characterized by mental status changes, tremor, gastrointestinal upset, headache, myalgia, and restlessness. The syndrome has also occurred when *H. perforatum* was taken with selective serotonin reuptake inhibitor antidepressants or nefazodone.[6,14] Because of these risks, clinicians should consider a 5 to 7 day wash-out period when switching between conventional antidepressants. In moderate to severely depressed patients, a gradual cross-titration is recommended.

Although studies imply that *H. perforatum* is efficacious compared to tricyclic antidepressants, more research is needed comparing it to other antidepressants, and further evaluation of its exact mechanism of action is needed to min-

imize adverse effects like serotonin syndrome. Its side effect and drug interaction profile also should be considered in patients taking other medications.

Sam-E (*S*-adenosylmethionine)

S-adenosylmethionine has been marketed as a promising alternative to St. John's wort. It is known in European countries as ademethionine and is used for the treatment of depression, arthritis, cholestasis, fibromyalgia, and migraine headaches. *S*-adenosylmethionine, unlike *H. perforatum*, is naturally produced by the body and is involved in a number of biochemical pathways. It was first discovered in the 1950s, but due to its lack of chemical stability, it was not studied in clinical trials until 20 years later in the injectable form of the stable salt. In 1999, General Nutrition Companies, Inc. and Pharmavite Corporation marketed mass production of an enteric-coated oral formulation as a nutritional supplement.[15,23,24]

S-adenosylmethionine is found in every cell in the body, particularly in the brain and liver, and is essential to numerous metabolic processes in the body. The synthesis of *S*-adenosylmethionine is directly linked to folate and vitamin B metabolism. Deficiencies in these vitamins are associated with reduced concentrations of *S*-adenosylmethionine in central nervous system (CNS) and neuropsychiatric disorders.[24]

Animal studies suggest that the antidepressant effects of *S*-adenosylmethionine may be due to an increase of the turnover of catecholamines (norepinephrine, serotonin, and dopamine) and weak effects on monoamine oxidase. Intravenous administration resulted in suppressed orthostatic rise in pulse rate and decreased plasma norepinephrine. Levels of 5–hydroxyindoleacetic acid were elevated in the cerebrospinal fluid of depressed patients who received injections of *S*-adenosylmethionine, suggesting activation of the central serotonergic system. It appears to inconsistently inhibit monoamine oxidase type B in the brain but increases monoamine oxidase activity in the heart and brain tissue. All of these effects could theoretically improve the mood.[15,23]

There have been studies comparing the injectable form of *S*-adenosylmethionine to other antidepressants and using it as augmentation. Intramuscular and intravenous administration of *S*-adenosylmethionine proved to be more significantly effective than placebo; however, the enteric-coated oral formulation is the only form available in the United States. A metaanalysis of 6 placebo-controlled clinical trials in a total of 200 patients and 7 trials, concluded in 3 weeks or less, showed that *S*-adenosylmethionine was at least as effective as imipramine, desipramine, amitriptyline, or clomipramine and more effective than placebo. Although the studies were placebo controlled, the short duration and lack of appropriate psychometric testing make the results unreliable.[15,23,24]

The usual dose of *S*-adenosylmethionine recommended for depression is 200–800 mg twice daily. Most of the published studies used doses of 1600 mg/day. The bioavailability of *S*-adenosylmethionine is low, implying that the oral administration results in a significant first-pass effect. *S*-adenosylmethionine is metabolized by the liver but does not bind to plasma proteins. No drug interactions have been reported as of yet between *S*-adenosylmethionine and other drugs. After intravenous doses of 50 mg/kg in humans, the half-life is approximately 80 minutes, with urinary metabolites being noted after 48 hours and fecal tracings noted after 72 hours.[23]

There are less adverse effects and drug interactions with use of *S*-adenosylmethionine compared to *H. perforatum*. The most common adverse effects include gastrointestinal discomfort such as flatulence, nausea, vomiting, diarrhea, anxiety, and headache. A switch to hypomania was reported in a few patients by Carney and associates.[23]

S-adenosylmethionine may have a role in treating depression, but more studies are needed comparing it to conventional therapies

outside of the tricyclic antidepressants as well as comparing it to *H. perforatum* and other herbals.

DHEA (Dehydroepiandosterone)

DHEA is an endogenous hormone secreted by the adrenal cortex and is a precursor to androgenic steroids. It is synthesized de novo by the CNS, and concentrations are found higher in the brain compared to other organs. It is commonly known as the "fountain of youth," and is used as a natural aphrodisiac. Although DHEA is considered a banned substance, athletes use DHEA for its anabolic effects. The over-the-counter sale of DHEA was banned by the FDA in 1984 due to concern over hepatotoxicity. The Dietary Safety Health and Education Act of 1994 allowed DHEA to be marketed as a nutritional supplement, although its true nutritional value is doubtful.[15,19]

DHEA is promoted for possible antidepressant effects because of its excitatory activity on gamma aminobutyric acid (GABA) and NMDA. Bloch and colleagues found that DHEA may have antidepressant effects in patients with midlife-onset dysthymia and major depression. There have been at least 2 case reports linking DHEA to manic episodes in patients with no previous psychiatric history.[15] Wolkowitz and associates showed >50% decrease in Hamilton Depression Rating Scale scores in 5 of 11 patients with major depression compared to 11 patients given placebo.[26] Since more rigorous studies are needed to establish doses, clinical efficacy data, and information regarding drug interactions and side effects of DHEA, it is not recommended to use this product as first line for the treatment of depression.[19]

HERBALS AS ADJUNCTIVE THERAPIES

Other herbal therapies are commonly used as adjunctive treatments in depression because depression often involves sleep disturbances and anxiety. It is common practice for patients to combine herbal remedies such as kava kava and valerian root with each other, with *H. perforatum*, or with prescription antidepressant agents, increasing the risks of drug interactions. The bulk of evidence in the literature exists for valerian and kava, primarily for use as sedatives and/or anxiolytics.[4]

Valerian

The plant name for valerian is *Valeriana officinalis*. Valerian has been also referred to as garden heliotrope, all heal, amantilla, and set wall.[27,30] Valerian is commonly indicated for insomnia and anxiety and possibly as an anticonvulsant. Active ingredients are thought to include volatile oil (sesquiterpines), iridoids (valepotrieates), and alkaloids.

The mechanism of action of valerian is proposed to be inhibition of the breakdown of GABA. Valerian may also have an affinity for the serotonin 2a (5HT2a) receptor. Valerian may affect calcium entry or binding in muscle tissue. Of the valepotriates, valtrate and isovaltrate have antidepressant properties, and the didrovaltrate has a tranquilizing effect similar to that of the benzodiazepines.[16]

Valerian is commonly indicated for insomnia and anxiety.

Precautions for the use of valerian are similar to those with benzodiazepines, barbiturates, and other CNS depressants. The significance of interaction between al-cohol and valerian is still under evaluation; therefore, caution is advised with the combination of valerian and alcohol.[29,30] Valerian has also been shown to prolong thiopental- and pentobarbital-induced sleep.[29,30] Patients should also be cautioned when driving or operating machinery. Valerian should be avoided during pregnancy and lactation.

Adverse effects associated with the use of valerian include headaches, hangover effects,

excitability, insomnia, uneasiness, and cardiac disturbances. Ataxia, decreased sensibility, hypothermia, hallucinations, and muscle relaxation have also been noted with valerian therapy but are not common.[16] The recommended dosage is typically 2–3 g of the dried herb or extract 1 to 3 times per day and at bedtime.[27–30] Valerian is also used as a tea with 2–3 g per cup, 1 to 3 times daily. Recommended dosage of the tincture is 0.5–1 teaspoons (1–3 mL) 1 to 3 times per day.[27–30]

Valerian should not be considered for use in patients receiving CNS-depressing medications. There are limited studies evaluating its efficacy in depressed patients. Further study is needed to determine the exact role of valerian adjunctively with other herbals in the treatment of depression.

Kava Kava

Kava kava, or simply kava, is derived from the root of the pepper plant, *Piper methysticum*, which is found in the South Pacific islands and Australia.[27,31,32] Kava is also known as ava, intoxicating pepper, and ava pepper. Kava is commonly prepared as a ceremonial beverage, which acts as a CNS depressant that causes a tranquil state of intoxication.[5,27] Kava is primarily indicated as an anxiolytic and sedative.

Kava is also said to promote sociability in a similar manner as alcohol. Kava has also been reported to have anticonvulsant and muscle relaxant properties, but these are not as well supported in the scientific literature. The primary active ingredients in kava are thought to be kavalactones (α-pyrones). The mechanism of action for kava is proposed to be binding at GABA and benzodiazepine receptor sites.[4,27,31,32] Kava was reported to produce changes in the electroencephalogram similar to those produced by diazepam.[4]

Adverse effects associated with chronic, high-dose use of kava include scaling of the skin on the extremities, eye disturbances, muscle weakness, and vitamin B deficiency. Kava use has also resulted in hepatotoxicity, macrocytosis of the red blood cells, neurologic effects, anorexia,and pulmonary hypertension. Extrapyramidal symptoms and exacerbation of Parkinson's disease have been reported with the use of doses of 100–450 mg/day. Clinical trials with kava have used doses of standardized preparations (WS 1490) that typically contain 100–200 mg of kavalactones, given daily in divided doses or as a single dose at bedtime.[4] The recommended adult daily dose is 60–120 mg kava pyrones.[5]

Potential drug interactions with kava kava include synergistic sedative activities with alcohol and prescription sedative/hypnotics.[16,31,32] Kava may be detrimental to cognitive function.[31,32] There is one case report of a drug interaction between alprazolam and kava. A 54-year-old man was hospitalized in a lethargic and disoriented state. The patient's medications included alprazolam, cimetidine, and terazosin. An interaction between kava and alprazolam was thought to be the most likely explanation of the patient's condition.[34] Kava is contraindicated in pregnancy and lactation.

Kava may be detrimental to cognitive function.

The use of kava kava is not recommended in patients taking concomitant benzodiazepines, and further study is needed to establish its exact role in treating depression.

Passionflower

Passionflower is made from the plant *Passiflora incarnata* and is also called apricot vine, grenadille, maypop, passiflora, and passion vine.[5,29] Passionflower is noted to possess sedative, hypnotic, antispasmodic, and analgesic properties. The proposed mechanism of action of passionflower is monoamine oxidase inhibition, leading to central stimulant activity.

This action is commonly attributed to the active constituent of harman alkaloid. The sedative effects of the maltol and ethylmaltol constituents are thought to mask the stimulant actions of the alkaloids.[5,29]

Adverse effects associated with passionflower use include hypersensitivity vasculitis and altered consciousness.[4,5,29] Due to sedative effects, the usual precautions regarding operation of machinery and driving of motor vehicles should be observed. Use during pregnancy and lactation is not recommended.

Passionflower is typically given 3 times daily in doses of 0.25–1 g of dried herb, 0.5–1 mL of liquid extract (1:1 in 25% alcohol), or 0.5–2 mL of tincture (1:8, 45% alcohol).[5,29]

It is not known if passionflower will interact with tyramine-containing foods and other medications that conserve catecholamines, so caution should be exercised in the use of passionflower for depression.

Skullcap

Plants of the species *Scutellaria lateriflora*, commonly referred to as skullcap, helmet flower, hoodwort, quaker bonnet, and scutellaria, are often used in Chinese medicine. Skullcap is indicated for use as a sedative and anticonvulsant. The mechanism of action and active constituents of skullcap remain unclear.

Adverse effects associated with skullcap include giddiness, stupor, confusion, and seizures. Hepatotoxic effects have also been reported, but these may have been attributable to ingredients of the preparation in the particular case.[4,5] Skullcap use is not recommended during pregnancy and lactation due to its hepatotoxic effects and limited information about pharmacological activity (lack of clinical trials in humans).[5]

Skullcap is taken 3 times daily in doses of 1–2 g of dried herb, 2–4 mL of liquid extract, and 1–2 mL of the tincture.[5]

There are no studies proving the clinical efficacy of adjunctive use of skullcap for insomnia associated with depression.

Hops

Although hops (*Humulus lupulus*) is commonly known for its use by the brewing industry to produce beer, the female flowers of the plant have a long history of medicinal use as a mild sedative. The sedating effects of hops are thought to be due to volatile oil constituents. Active ingredients increase when the herb is stored for 1 to 2 years. Adverse effects associated with hops include respiratory allergy, contact dermatitis, and disruption of the menstrual cycle. The sedative action of hops may potentiate the effects of other sedative therapies or alcohol. It has been stated that hops should not be given to those suffering from depressive disorders because sedative properties of hops may accentuate depressive symptoms. Hops are commonly given as 1–2 g of dried strobile for hypnotic purposes, 0.5–2.0 mL of the liquid extract, and 1–2 mL of the tincture.[5,29] Hops are often used in combination with other herbal therapies. Hops have been reported to improve sleep disturbances when used in combination with valerian.[4,5,16,29]

Hops have a long history of medicinal use as a mild sedative.

Melatonin

Melatonin is a popular herbal used for its sedative properties. Melatonin is a hormone produced primarily by the pineal gland. It is used commercially by consumers to aid in the regulation of sleep. Its principal function appears to be the inhibition of reproductive activities by inhibiting gonadotropic hormones. Melatonin has been evaluated as an option to taper older patients off benzodiazepines; however, more studies are needed to establish specific protocols.[35] It is commercially available as a synthetic product or derived from ani-

mal pineal tissue. It is recommended to use the synthetic version because of an increased risk of contamination or viral transmission associated with the nonsynthetic product.[4,5,19,27,35]

Melatonin has also been noted to reduce the efficacy of nifedipine resulting in increased blood pressure and heart rate.[5,35] Melatonin is a metabolite of serotonin, so patients receiving monoamine oxidase inhibitors (including selegiline) should be warned against using melatonin and excessive amounts of tyramine-containing foods. It is also recommended to caution its use in immunocompromised patients, patients with autoimmune disorders, children, and pregnant or lactating women.[5,35] Transient depression or aggravation of depressive symptoms has been reported with this product, so use in psychiatric patients is not recommended.[5] Depressed patients may experience therapeutic failure from conventional or herbal therapy. Despite its popularity, the use of melatonin is not recommended in patients with depression.

Ginseng

Ginseng has been used for more than 2000 years for its purported efficacy in depression, stress management, energy enhancement, infection resistance, and aphrodisiac properties. Adverse effects that may complicate its efficacy in depressed patients include insomnia, nervousness, and poor concentration. The nervous excitation is transient, but other side effects associated with ginseng after long-term use include hypoglycemia, anticoagulation, mammary nodularity, vaginal bleeding, and gynecomastia. There is also controversy surrounding the potential for "ginseng-abuse syndrome." The syndrome is characterized by CNS stimulation, insomnia, hypertension, diarrhea, skin eruptions, and increased motor and cognitive efficiency.[5,16] Ginseng appears to enhance adrenal gland function, thus lending itself to stress management, but it negatively affects the hypothalamic-pituitary axis resulting in elevated plasma corticotropin and corticosteroid levels. Ginseng may potentiate the effects of monoamine oxidase inhibitors, stimulants (including caffeine), and haloperidol.[4] There are no clinical studies proving efficacy on ginseng alone or in combination with other therapies. Long-term use of ginseng may have greater risks than benefits, and consumers should be cautious about differences within each species.

Ginkgo

Ginkgo has been used to treat cerebrovascular insufficiency, impotence, and antidepressant-induced sexual dysfunction and as an augmenting agent with conventional antidepressants. An in vitro study suggests that the dried and fresh ginkgo leaves contain flavonoids (ginkgo- flavone glycosides and bioflavanoids) that inhibit monoamine oxidase A and B, indirectly stimulate norepinenephrione release by upregula- ting alpha-2 adrenergic receptors, and may stimulate choline uptake in the hippocampus. Side effects associated with ginkgo include headache, gastrointestinal upset and potentiation of anticoagulants.[4,36]

The risk of bleeding may eliminate the benefits of ginkgo as an adjunctive therapy for treating depression or any other ailment.

CONCLUSION

Despite the wide availability of herbal and dietary supplements, consumers should be cautious about using these products for the treatment of depressive disorders. Clinicians should warn patients about the potential risks associated with purity, potency, self-prescribing, and the variances associated with product formulation. Drug interactions and side effects of these products should also not be ignored. Little is known about the utilization of homeopathy, Ayurvedic, and other Chinese herbal preparations. More scientifically controlled studies are needed to assess clinical efficacy of these products compared to conventional products as well as the efficacy of certain herbal combinations.

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