
FOR YOUR INFORMATION



PHARMACY NEWSLETTER



Volume #21, Issue #15 – September, 2001

Drug Interactions Between Select Psychiatric Herbal Remedies

Introduction

Herbal products are derived from plants and when they are used for medicinal purposes, they should be regarded in a similar manner as patented drugs in their potential for causing unwanted effects. A recent survey found that up to 24-49% of consumers use herbal remedies. As use of these products continues to rise, new information about their clinical attributes are being reported in the medical literature. In addition to efficacy and adverse effects, the potential for drug interactions is an important factor to consider among the various herbal products. A full discussion on the effects of each herbal product is beyond the scope of this newsletter. Instead, we will focus on the drug interactions of four commonly used herbal products in the management of psychiatric symptoms: St. John's wort, ginkgo biloba, ginseng, and kava kava.

St. John's Wort (SJW)

St. John's wort is the common name for a perennial flowering plant, *Hypericum perforatum*. Pharmacologically, this product is thought to inhibit serotonin reuptake as well as monoamine oxidase. The major use of SJW is the management of mild to moderate symptoms of depression. SJW is an inducer of the cytochrome P450 metabolic pathway and, as such, has the potential to interact with a number of medications. As well SJW may also inhibit certain P450 isoenzymes.

CYP450 Substrates (e.g. Indinavir, cyclosporine, oral contraceptives, warfarin)

Many medications used to treat conditions such as heart disease, depression, seizures, certain cancers or to prevent conditions such as transplant rejection or pregnancy are metabolized by this cytochrome P450 system. As would be expected, loss of therapeutic effect of drugs metabolized via this pathway can occur when they are used together with SJW.

For example, when SJW is co-administered with the protease inhibitor indinavir, blood levels of latter drug drop dramatically between 49% to 99%. A similar effect is seen when SJW is co-administered with another CYP 3A4 substrate, cyclosporin. In one case report, a 61 year-old heart transplant patient who was stabilized on cyclosporin started to add SJW 300mg three times daily to his medication regimen. Plasma cyclosporin level diminished to sub-therapeutic levels, but after discontinuation of SJW, his plasma cyclosporin level returned to normal. In a study of healthy subjects, SJW decreased the absorption of digoxin by 25%. In another report, co-administration of warfarin and SJW resulted in diminished effect of warfarin, thereby decreasing the INR (or clinically, increasing the risk of thromboembolism). The INR returned to normal after SJW was stopped. SJW may increase the clearance of oral contraceptives and thus decrease the effectiveness of birth control, thereby increasing the risk of pregnancy. There are also reports of unexpected menstrual bleeding in women taking oral contraceptives and SJW.

Olanzapine

An interaction between SJW and olanzapine has been reported in which a patient's olanzapine level increased 300% after starting SJW. In contrast to the effects on the

P450 3A4 isoenzyme, this interaction may have been due to the inhibition of CYP 1A2 by SJW, thus interfering with the metabolism of olanzapine.

SSRIs/MAOIs and other Antidepressants

SJW potentiates the effects of selective serotonin reuptake inhibitors (SSRIs) by excessive elevation of serotonin. Consequently, the risk of serotonin syndrome, a potentially life-threatening reaction, may be increased. Signs of serotonin syndrome include mental status changes, restlessness, muscle twitching, diarrhea, sweating, and high body temperature. This syndrome has been reported when SJW has been used with SSRIs, trazodone, and nefazodone.

SJW is believed to exert a similar influence on monoamine oxidase inhibitors (MAOIs) and therefore the co-administration of these two agents should be avoided since the herb may potentiate the effects of MAOIs. A washout period of two weeks is recommended before any MAOI is started in a patient previously taking SJW. Given the potential MAO inhibition with SJW, it would be wise to restrict the consumption of foods high in tyramine.

Photosensitizing drugs

Phototoxicity manifested as elevated, itching, erythematous lesions has been reported. Reversible, subacute toxic neuropathy has also been noted in association with use of SJW in the presence of sun exposure. In one case report, a 35 year-old female developed stinging pain on sun exposed areas after self-treatment with SJW for four weeks. Her symptoms gradually resolved over a 2-month period after stopping SJW. However, at usual therapeutic doses, it is extremely rare to find reports of photosensitivity induced by SJW.

It is advisable to use caution when combining SJW with other drugs known to cause photosensitivity (eg phenothiazines, tetracycline) as well as limiting sun exposure and other sources of ultraviolet light.

Ginkgo Biloba

The deciduous, slow-growing ginkgo biloba tree is found in certain regions in the United States and China. Among the various biological effects, active compounds

from ginkgo leaf extracts can stimulate increase blood flow to brain and extremities. This herbal product has been used primarily in the elderly for managing symptoms of Alzheimer's disease and cerebrovascular insufficiency. The most common adverse effect reported has been gastrointestinal discomfort. Due to its ability to inhibit platelet aggregation, the use of ginkgo has also been associated with spontaneous bleeding, as several published reports have shown. One report showed that ginkgo use after one week was associated with spontaneous ocular bleeding at dosage of 40mg twice daily. In another patient, use of ginkgo for a longer duration of at least 1 ½ years lead to a bilateral subdural hematoma. Finally, a subarachnoid hemorrhage was described in an elderly patient who took this herb for more than 6 months.

Drugs with anticoagulant or antiplatelet effects

A 78 year-old female who had been treated with warfarin for five years suffered a left parietal hemorrhage after using ginkgo for two months. Patients who are taking drugs with anticoagulant or antiplatelet effects (e.g. nonsteroidal anti-inflammatory agents, Aspirin, valproic acid) should be cautioned about potential interactions with ginkgo products. Patients who are taking ginkgo should inform their physicians about unusual bleeding, bruising, new onset headaches or vision changes.

Ginseng

The active ingredients of ginseng are derived from roots of the plants *Panax ginseng* and *Panax quinquefolius*. Ginseng has been used to improve thinking, combat stress and fatigue, and boost resistance to infections. Though the mechanism of action is not entirely clear, ginseng likely increases ACTH, which stimulates the release of adrenal stress and sex hormones.

Warfarin

A ginseng/warfarin combination may decrease the INR thus resulting in reduced effectiveness of warfarin and increasing the risk of clotting. Such an interaction was reported in a 47-year old male who experienced a decline in INR to below therapeutic range when ginseng was added to his warfarin. Two weeks after ginseng was discontinued, his INR level returned to normal.

Antidepressants/MAOIs

Ginseng can potentiate the adverse effects of certain antidepressants. Concurrent treatment may induce mania in depressed patients. One patient reported experiencing mania, insomnia, headache, and irritability when ginseng was added to his previously stabilized regimen consisting of phenelzine. Ginseng has been reported to cause transient nervousness and excitation and these are the same effects that some antidepressants can cause.

Estrogenic agents

Ginseng may produce estrogen-like effects manifesting as mastalgia and vaginal bleeding. In this regard, use of ginseng can potentiate estrogen-related side effects in women who are stabilized on estrogen-replacement therapy. Such reactions have been reported in postmenopausal women who had been taking modest oral doses of ginseng in combination with their hormone therapy.

Antihypertensive agents

To date, reports showed that ginseng may either increase or decrease blood pressure. It is not clear, however, whether these changes in blood pressure brought on by ginseng is of any clinical significance. Nonetheless, those who have or have disposition to developing hypertension should exercise caution when using ginseng.

Kava Kava

Kava kava (*Piper methysticum*) is a member of the pepper family. This herb is indigenous to the South Pacific where it has been used for its medicinal effects as a sedative, anxiolytic, muscle relaxant, and as a remedy

for nervousness. Unlike non-herbal anxiolytics, kava kava has not been shown to be addictive.

Levodopa

Kava has an antagonistic effects on dopamine and may reduce the effectiveness of levodopa in the treatment of symptoms of Parkinson's disease.

Other psychotropic medications

Use of kava has been associated with disorientation and lethargy and appears to cause certain adverse CNS effects including headaches and drowsiness. Caution should be used when this herbal product is used concurrently with drugs such as benzodiazepines, antihistamines, anticonvulsants, sedative antidepressants, and antipsychotics.

Conclusions

Although evidence of the efficacy of herbal preparations in treating psychiatric conditions is growing, scientific data about their safety and efficacy are lacking in most cases. Due to the chemical complexity of herbal products and the lack of standardization in the manufacturing of these products, not to mention the paucity of well-controlled studies comparing herbal remedies with conventional medications, it is premature to recommend herbal remedies over established conventional treatments. Consumers need to be aware of the adverse effects of herbal remedies and the potential for drug interactions. Therefore it is important for patients to inform their physicians of such use and for health care professionals to ask questions about the use of herbal and non-prescription medications as part of the patients medication history.

Summary

Table 1: Selected examples of Drug/herbal product interactions

HERB	DRUG	Effect/comments
St. John's Wort	Antidepressants: SSRIs MAO inhibitors	Increase risk of serotonin syndrome Increase effect of drug
	Indinavir and other protease inhibitors	Decrease effectiveness of drug
	Cyclosporin	Decrease effect of drug (risk of organ rejection)
	Oral contraceptives	Decrease effect of drug (risk of pregnancy)
	Photosensitizing drugs e.g. Tetracycline, chlorpromazine	Increase photosensitivity
Ginkgo	Anticoagulants/antiplatelet agents	Increase risk of bleeding
	NSAIDs	Increase risk of bleeding
	Valproic acid	Increase risk of bleeding
Ginseng	Warfarin	Decrease anticoagulant effect
	MAOI and other antidepressants	Increase in adverse CNS effects
	Hormonal therapy	Mastalgia & vaginal bleeding
Kava Kava	Levodopa	Decrease control of symptoms of Parkinson's disease
	Other psychotropic medications	Increase adverse CNS effects of drug (can produce deep sedation or even coma)

Compiled by Susy Fung

Reviewed by: Gordon Tse, Pharm. D.

If you would like to be added to the Inpharmation Newsletter mailing list, please call (604) 524-7012 or email address bthompson@bcmhs.bc.ca. Please ensure you include your entire mailing address (including postal code). References available upon request from Pharmacy Services.