CME CREDIT

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Talking to patients about St. John's wort

ABSTRACT

St. John's wort, an unregulated herbal supplement widely used as a self-treatment for depression, can cause side effects and drug interactions. Physicians should ask their patients about use of over-the-counter products such as St. John's wort and discuss their use in a frank but nonjudgmental manner.

KEY POINTS

St. John's wort appears to have plausible mechanisms of action, including inhibition of reuptake of serotonin, norepinephrine, and dopamine and inhibition of monoamine oxidase.

Most randomized clinical trials found St. John's wort to be superior to placebo in mild to moderate depression, but studies in moderate to severe depression have been less conclusive, and the clinical significance of the effect may be small.

Preparations vary in content and potency. Laboratory-grade hypericum, one of the putative active ingredients in St. John's wort, is available and offers standardized dosing for people who feel they must take St. John's wort.

Like some selective serotonin reuptake inhibitors, St. John's wort can cause nausea, constipation, diarrhea, rashes, fatigue, headaches, restlessness, and sweating. The hypericin component of St. John's wort may cause significant phototoxicity.

St. John's wort appears to induce cytochrome P450 3A4 and can decrease blood levels of cyclosporine, protease inhibitors, digoxin, oral contraceptives, warfarin, and theophylline. When used with serotonin reuptake inhibitors, it can contribute to a serotonin crisis.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

PHYSICIANS NEED TO TALK to their patients about St. John's wort (*Hypericum perforatum*). Many people are using it to treat depression, yet besides questions about its efficacy, there is a potential for a variety of important drug interactions.[3] The challenge is to have the discussion in a nonjudgmental way, to improve the chances of having an open dialogue with patients about the risks and benefits of this herbal drug.

The use of herbal supplements is widespread, and many patients who use them do not tell their doctors about it. More than 50 million Americans use herbal medications,[1] at a cost of $3.5 to $5 billion per year.[2] As the Food and Drug Administration (FDA) has little authority over these agents, patients and physicians need to be educated about them.

This review examines issues clinicians must confront when faced with questions from patients about the benefits and side effects of St. John's wort.

KNOWN IN ANCIENT TIMES

St. John's wort is a small flowering weed that originated in Europe and western Asia and was first described by the Greek physician Euryphon in 288 BC. From ancient Greece to the Middle Ages, its various forms of tea, oil, or cream were used to ward off evil and protect against disease. Maidens used the weed to predict their chances of marriage, while others believed its bright yellow color gave it other powers of divination.

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PREPARATIONS VARY

St. John's wort belongs to the genus *Hypericum*, of which there are over 370 species, which vary in chemical composition of the flowers, stem, and leaves.[3]

The extraction medium greatly influences therapeutic potency. In addition, preparations contain different pharmacologically active compounds, including phenylpropanes, flavonol glycosides, biflavones, tannins, proanthrocyanidins, xanthones, phloroglucinols, essential oils, amino acids, and naphthodianthrones.[4] The compounds that are likely responsible for the herb's pharmacologic activity are hypericin and hyperforin.[5,6]

SUGGESTED MECHANISMS OF ACTION

Suggested mechanisms of action for hypericin include:

- Inhibition of reuptake of serotonin, norepinephrine, and dopamine[7,8]
- Inhibition of monoamine oxidase via increased monoamine reuptake[7]
- Increased gamma-amino butyric acid activity[9]
- Up-regulation of serotonin 1a and 2a receptors[10]
- Modulation of cytokine production (associated with depression in susceptible individuals).[11]

We are concerned that depressed people may forgo effective treatment in favor of St. John's wort

IS ST. JOHN'S WORT EFFECTIVE?

How effectively St. John's wort actually relieves symptoms of depression is not entirely clear, particularly in severe cases.

Studies in moderate to severe depression

The Hypericum Depression Trial group,[12] in a recent multicenter double-blind clinical trial, concluded that St. John's wort is not effective in treatment of moderate to severe major depression. In this study, 340 adults received St. John's wort, sertraline (a selective serotonin-reuptake inhibitor [SSRI]), or placebo. All had a baseline score on the Hamilton rating scale for depression (HAM-D) of at least 20, indicating moderate to severe depression. Based on clinical response, the daily dose of St. John's wort ranged from 900 to 1,500 mg and that of sertraline from 50 to 100 mg (this dose may have been inadequate for some patients). Patients were followed for 8 weeks in the acute phase and for 18 weeks in the continuation phase.

Neither sertraline nor St. John's wort were significantly more effective than placebo. However, subjects on sertraline scored significantly better on the Clinical Global Improvement Scale than did those on placebo.

Shelton et al,[13] in an earlier double-blind, randomized, placebo-controlled study of 200 depressed outpatients, also found that St. John's wort was safe and well tolerated but not effective in treating moderate to severe major depression.

Philipp et al,[14] in contrast, found that St. John's wort 1,050 mg/day was more effective than placebo and equivalent to imipramine 100 mg/day in reducing symptoms of moderate depression. At 8 weeks, the mean HAM-D score had decreased by 15.4 ± 8.1 (SD) points with St. John's wort, compared with 12.1 ± 7.4 with placebo and 14.2 ± 7.3 with imipramine. The authors were generous with St. John's wort but may have used lower doses of imipramine than frequently used.

Studies in mild to moderate depression

Most studies showed St. John's wort to be effective in the treatment of mild to moderate major depression.

Linde and Mulrow[15] performed a meta-analysis of 27 randomized double-blind clinical trials and concluded that St. John's wort is effective in mild to moderate depression. Seventeen of the studies were placebo-controlled; the other 10 studies compared St. John's wort with standard antidepressant or antianxiety medications—maprotiline, imipramine, bromazepam, amitriptyline, and diazepam—with which St. John's wort was apparently equivalent.

Other recent studies and reviews of randomized trials[16–18] found St. John's wort to be more effective than placebo in the treatment of mild to moderate depression and similar in effectiveness to fluoxetine or low-dose tricyclic antidepressants.

Lecrubier et al,[19] in a recent 6-week double-blind placebo-controlled study of 375 outpatients with mild to moderate depression, concluded that St. John's wort was better than

placebo. In that study, patients receiving St. John's wort had a mean reduction in their HAM-D score of 9.9 points, vs 8.1 points with placebo. Although the difference was statistically significant, it might not be clinically significant: physicians might not observe much difference. St. John's wort was more effective in patients with higher baseline HAM-D scores and led to a global reduction of depression-related core symptoms as assessed by the melancholia subscale of the HAM-D scale.

SIDE EFFECTS

Although St. John's wort alone has few side effects, several side effects similar to those of other psychotropic agents have been reported.

Like some SSRIs, St. John's wort can cause nausea, constipation, diarrhea, rashes, fatigue, headaches, restlessness, and sweating.

The hypericin component of St. John's wort may cause significant phototoxicity (chemically induced photosensitization); hence, concomitant use with other photosensitizers such as tetracycline, sulfonamides, thiazides, quinolones, and piroxicam should be avoided. Patients with a history of photosensitivity to various chemicals should be cautious of direct sun exposure.[20]

DRUG INTERACTIONS

St. John's wort appears to induce cytochrome P450 3A4,[21] and significant drug interactions have been reported.[22]

St. John's wort has been reported to decrease blood levels of:

- Cyclosporine, an immunosuppressive medication used in transplant recipients. Cases of acute organ rejection have been reported.
- Indinavir, a protease inhibitor used to treat human immunosuppression virus (HIV) infection. In theory, St. John's wort might interfere with other protease inhibitors and nonnucleoside reverse transcriptase inhibitors as well.
- Irinotecan and other cancer chemotherapeutic agents.[23,24]
- Oral contraceptives
- Anticonvulsants (eg, phenytoin, carbamazepine, phenobarbital—suspected on theoretical grounds)
- Digoxin
- Theophylline
- Warfarin[25]
- Triptans.[25]

Comment. Patients with cancer, HIV, or transplanted organs are advised not to experiment with St. John's wort. Physicians need to understand, however, that these patients are seeking hope and any help with their symptoms, and therefore need to be educated about the risks and benefits of alternative ways of alleviating symptoms.

St. John's wort can increase levels of

- Thyroid-stimulating hormone.

Partial serotonin syndrome when used with SSRIs

Perhaps more frequent is a partial serotonin syndrome, which occurs when patients either switch to or from an SSRI too quickly after their last ingestion of St. John's wort or combine St. John's wort with an SSRI. Serotonin syndrome in its mildest form consists of flulike symptoms of headache, dizziness, or gastrointestinal distress; in its most severe form, it can cause myoclonus, delirium, or death.[26,27]

Hypertensive crises when used with MAOIs

St. John's wort also inhibits metabolism of monoamine oxidase inhibitors (MAOIs).[24] Unlike the MAOIs, St. John's wort does not typically require food restrictions unless the patient uses higher-than-recommended doses. However, simultaneous use of St. John's wort and a MAOI or beta sympathomimetic amine such as ma huang or pseudoephedrine should be avoided to avoid precipitating a hypertensive crisis.[22,27]

Patients with cancer, HIV, or transplants should not experiment with St. John's wort

DOSAGE

The total hypericin concentration of different extracts may vary widely. With St. John's wort, the chemicals believed to be most useful are obtained through alcohol extraction, hence a tea made from St. John's wort may not be as effective.

Research-grade hypericum can be obtained through drug stores, by mail, or a retail outlet. In theory, these preparations are standardized and deliver a more predictable

dose. The cost varies from $0.29 to $1.06 a day. More information is available online at **www.hypericum.com.**

According to the *2000 Physicians Desk Reference for Herbal Medicines*,[20] the dosage of hypericin generally recommended for treatment of depression ranges from 200 to 1,000 mg/day. A typical trial consists of 900 mg of standardized extract (0.3% hypericin content),[28] with clinical effect seen in 2 to 3 weeks.

MORE STUDY NEEDED

With limited evidence-based research and an absence of standard regulatory mechanisms for herbal medicine, questions remain about the efficacy of St. John's wort and its appropriate use. Few published reports in the United States address these issues, although increasing numbers of studies have been funded by the National Institutes of Health over the past several years. These studies are needed to identify the pharmacologically active compounds in St. John's wort, establish a dose-response relationship, and compare its efficacy with other frequently used antidepressants.

Information on St. John's wort can be obtained through several online government-sponsored sites including the Center for Food Safety and Applied Nutrition (**http://vm.cfsan.fda.gov/list.html**), the Food and Drug Administration (**www.fda.gov**), HerbMed (**www.herbmed.org**), and the National Center for Complementary and Alternative Medicine (**http://nccam.nih.gov**) of the National Institutes of Health.

TALK TO YOUR PATIENTS

If patients who are more severely depressed forgo regular medical treatment in favor of self-medication, they may spiral downward, similar to an untreated individual.

Because many patients do not tell their physicians that they are using herbal medications, it is important that physicians educate patients about the use of supplements such as St. John's wort. Part of this education is to urge patients to read the ingredients on labels of supplements.

In addition, critical to patient education is the development of trust between physician and patient. By educating themselves about the use, efficacy, and side effects of herbal and traditional medications, and by discussing this information with patients in a nonjudgmental way, physicians can improve the chances of having an open conversation with patients about herbal supplements and their potential side effects and drug interactions.

Many patients will take St. John's wort safely for mild or moderate depression. It remains the job of clinicians to participate actively in their education about both its risks and benefits.[29]

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