St. John's Wort

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St. John's wort has been used to treat a variety of conditions. Several brands are standardized for content of hypericin and hyperforin, which are among the most researched active components of St. John's wort. St. John's wort has been found to be superior to placebo and equivalent to standard antidepressants for the treatment of mild to moderate depression. Studies of St. John's wort for the treatment of major depression have had conflicting results. St. John's wort is generally well tolerated, although it may potentially reduce the effectiveness of several pharmaceutical drugs. (Am Fam Physician 2005;72:2249-54.

The botanical St. John's wort (Hypericum perforatum) is native to Europe, West Asia, and North Africa, and has been naturalized to North and South America and Australia. The Greeks and the Romans documented its medicinal use in the treatment of nerve-related disorders. In Germany, St. John's wort is the most commonly prescribed antidepressant. In 1984, the German Commission E designated St. John's wort as an approved herb,[1] and its safety and effectiveness are reevaluated periodically.

St. John's wort has been used to treat a variety of conditions. It also has been suggested to alleviate symptoms of premenstrual syndrome[2] and obsessive-compulsive disorder[3]; however, these applications have been studied less extensively. Additional studies of St. John's wort, funded by the National Center for Complementary and Alternative Medicine, are underway.[4] This review focuses solely on the use of St. John's wort for the treatment of depression.

Pharmacology

The main active components of St. John's wort are thought to be hypericin and hyperforin.[5] St. John's wort also contains other common plant constituents (e.g., flavonoids and flavonoid derivatives, xanthone derivatives, amentoflavone, biapigenin, volatile oil) that may have antidepressant effects. Although additional research is needed to definitively understand the effects of these components alone and in combination, most available St. John's wort formulations are now standardized to include hypericin (range: 0.1 to 0.4 percent) and hyperforin (range: 2.0 to 4.0 percent) because these constituents have been researched the most extensively.

Studies[6] have suggested that St. John's wort acts via inhibition of the reuptake of serotonin, dopamine, and noradrenaline, along with activation of gamma-aminobutyrate and glutamate receptors. At high dosages, hypericin is a monoamine oxidase inhibitor; however, these effects have not been demonstrated with the consumption of St. John's wort at dosages recommended for the treatment of depression.[7]

The absorption and elimination of hypericin extract have been researched in healthy volunteers.[8] After oral ingestion, plasma levels were measurable within two to three hours. A steep cumulative rise in plasma levels was seen during the first three days; however, a more gradual rise continued for several weeks. The elimination half-life was 24 to 48 hours.[8]

Effects on Depression

A Cochrane Systematic Review[9] used specific criteria to examine the use of St. John's wort for depression. Study limitations included heterogeneous diagnoses of depression, short trial durations, and low dosages of standard antidepressants in comparison trials. In all

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
St. John's wort is recommended as a safe and effective treatment option for patients with mild to moderate depression.	A	11, 16, 20-22
St. John's wort cannot be recommended for patients with major or severe depression because of inconsistent evidence in clinical trials.	B	17-19

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 2160 or http://www.aafp.org/afpsort.xml.

but one of the 27 clinical studies (n = 2,291) of different hypericum preparations, investigators concluded that St. John's wort was either more effective than placebo or as effective as older pharmaceutical antidepressants in the treatment of mild to moderate depression.

More recently, 13 additional clinical trials have been published, some of which, along with a Cochrane review, are summarized in *Table 1*.[9-19] In 10 of these studies, investigators found that St. John's wort was superior to placebo[11,16,20-22] or as effective as standard antidepressants (e.g., amitriptyline [Elavil],[10] fluoxetine [Prozac],[12,13] imipramine [Tofranil],[11,14] sertraline [Zoloft][15]) in the treatment of mild to moderate depression. Two updated meta-analyses exploring the effectiveness of St. John's wort for the treatment of depression are based on studies published between 1979 and 2003.[23] Although their results suggest the possibility that St. John's wort may be less effective than previously assumed, the meta-analyses indicated that St. John's wort was significantly more effective than placebo (risk ratio for first meta-analysis: 1.97, 95% confidence interval [CI], 1.54 to 2.53; risk ratio for second meta-analysis: 1.73, 95% CI, 1.40 to 2.14).

Studies[17-19] on the use of St. John's wort in patients with major depression have had conflicting results. According to the results of one double-blind, placebo-controlled, multicenter clinical trial[18] (n = 200), St. John's wort was effective in treating outpatients with major depression. Although the number of patients achieving remission in symptoms of depression was significantly higher with St. John's wort therapy than with placebo (P = .02), overall remission rates were low (14.3 and 4.9 percent, respectively).

The Hypericum Depression Trial Study Group conducted a double-blind, randomized controlled trial[19] (n = 340) in 12 academic and community psychiatric research clinics in the United States. Investigators found that St. John's wort and sertraline did not differ from placebo for major depression outcomes or adverse events. The authors of an earlier study[17] (n = 209) concluded that St. John's wort was equivalent to imipramine in patients with severe depression.

Taken together, the data[10-22] continue to support the overall conclusions of the Cochrane review,[9] as well as other published reviews,[24,25] that St. John's wort is more effective than placebo and as effective as standard antidepressants for the treatment of mild to moderate depression.

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Adverse Effects, Contraindications, and Drug Interactions

In clinical trials comparing St. John's wort with other antidepressants, the use of St. John's wort was not associated with any serious adverse events. Authors of a systematic review[26] reported an overall side-effect rate of 2.4 percent, with no severe side effects and only the expected mild side effects (i.e., gastrointestinal upset, increased anxiety, minor palpitations, photosensitivity, fatigue, restlessness, dry mouth, headache, and increased depression). Transient photosensitivity is generally the most common side effect and occurs more commonly at higher dosages.[27] Use of St. John's wort continues among a substantial number of persons without apparent serious adverse events.

Because of the possibility of developing serotonin syndrome, use of St. John's wort in

TABLE 1
Key Studies of St. John's Wort for Depression

Study/location	*Sample/number*	*Agents/dosage*	*Outcome*
Cochrane Review Linde, 1996[9] various locations	Systematic review of 27 studies (n = 2,291) examining the treatment of depression	St. John's wort (350 to 1,800 mg) daily	St. John's wort was superior to placebo and as effective as standard antidepressants.
Wheatley, 1997[10] United Kingdom	Moderate depressive disorder (HAM-D; n = 165)	St. John's wort (900 mg) versus amitriptyline (Elavil; 75 mg) daily for six weeks	Both treatments were equally effective.
Philipp, 1999[11] Germany	Moderate depressive disorder (HAM-D; n = 263)	St. John's wort (1,050 mg) versus imipramine (Tofranil; 100 mg) versus placebo daily	St. John's wort was more effective than placebo and as effective as imipramine.
Harrer, 1999[12] Austria	Older patients with mild to moderate depression (HAM-D; n = 149)	St. John's wort (800 mg) versus fluoxetine (Prozac; 20 mg) daily for six weeks	Both treatments were equally effective.
Schrader, 2000[13] Germany	Mild to moderate depression (HAM-D; n = 240)	St. John's wort (500 mg) versus fluoxetine (20 mg) daily for six weeks	Both treatments were equally effective.
Woelk, 2000[14] Germany	Moderate depressive disorder (HAM-D; n = 324)	St. John's wort (500 mg) versus imipramine (150 mg) daily for six weeks	Both treatments were equally effective.
Brenner, 2000[15] United States	Mild to moderate depression (HAM-D; n = 30)	St. John's wort (900 mg) versus sertraline (Zoloft; 75 mg) daily for six weeks	St. John's wort was at least as effective as sertraline.
Kalb, 2001[16] Germany	Mild to moderate major depressive disorder (HAM-D; n = 72)	St. John's wort (900 mg) versus placebo daily for 42 days	St. John's wort was superior to placebo at days 28 and 42.
Vorbach, 1997[17] multicenter	Severe depression as defined by ICD-10 (n = 209)	St. John's wort (1,800 mg) versus imipramine (150 mg) daily for six weeks	Both treatments were equally effective (HAM-D).
Shelton, 2001[18] United States	Adult outpatients with major depression (baseline HAM-D score of at least 20; n = 200)	St. John's wort (900 mg, increased to 1,200 mg if needed) versus placebo daily for four weeks	Proportion achieving response did not differ between groups.
Hypericum Depression Trial Study Group, 2002[19] multicenter	Adult outpatients with major depression (baseline HAM-D score of at least 20; n = 340)	St. John's wort (900 to 1,500 mg) versus sertraline (50 to 100 mg) versus placebo daily for eight weeks	Neither sertraline nor St. John's wort was significantly different from placebo.

HAM-D = Hamilton Rating Scale of Depression; ICD-10 = International Statistical Classification of Diseases, 10th rev.

Information from references 9 through 19.

conjunction with selective serotonin reuptake inhibitors is not recommended. St. John's wort should be used cautiously in patients with bipolar disorder because there have been a few case reports of St. John's wort–related mania.[28]

Table 2[29-40] lists the possible drug interactions that may occur with St. John's wort. The results of one report[41] suggest that induction of cytochrome (CYP) P450 3A4 activity by St. John's wort may have a substantial impact on the effectiveness of pharmaceutical agents because at least one half of all marketed medications are metabolized via this pathway.

Given the induction of CYP 3A4, concurrent use of St. John's wort may reduce the effectiveness of oral contraceptives. In a study[35] of 12 healthy premenopausal women who received an oral contraceptive along with 900 mg of St. John's wort daily in three divided doses, researchers noted a shorter estrogen half-life and increased breakthrough bleeding. Women using oral contraceptives should be counseled regarding possible breakthrough bleeding and might consider a barrier method of contraception when taking St. John's wort.[35]

Additional study is needed to establish if and how St. John's wort interacts with specific pharmaceutical agents. Experience to date suggests few clinically significant interactions. Until the results of ongoing studies on this matter have been published, the medications listed in *Table 2*[29-40] should be considered to have potential interactions and should be monitored when used concurrently with St. John's wort. Family physicians should query all patients about the use of St. John's wort and other herbal agents.

Dosage

Findings suggest that 900 mg of St. John's wort (450 mg two times daily or 300 mg three times daily) is needed to reduce symptoms of depression.[8,10,17] Because plasma levels continue to show a gradual rise over

TABLE 2
Possible Drug Interactions with St. John's Wort*

Agent	*Pathway*	*Type of report*	*Effect of St. John's wort on drug levels in the blood*
Amitriptyline (Elavil)	CYP P450 3A4	One-arm trial[29]	Decrease
Carbamazepine (Tegretol)	CYP 3A4	One-arm trial[30]	None
Cyclosporine (Sandimmune)	CYP 3A4	One-arm trial[31]	Decrease
Digoxin	CYP 3A4	Clinical trial[32]	Decrease
Indinavir (Crixivan)	CYP 3A4	One-arm trial[33]	Decrease
Irinotecan (Camptosar)	CYP 3A4	Crossover trial[34]	Decrease
Midazolam (Versed)	CYP3A	Clinical trial[35]	Decrease
Nevirapine (Viramune)	CYP 3A4	One-arm trial[36]	Decrease
Oral contraceptives	CYP 3A4	Clinical trial[35]	Decrease
Sertraline (Zoloft)	CYP P450 3A4	One-arm trial[37]	Decrease
Simvastatin (Zocor)	CYP 3A4	Clinical trial[38]	Decrease
Tacrolimus (Prograf)	CYP 3A4	One-arm trial[31]	Decrease
Theophylline	CYP 1A2	Case report[39]	Decrease
Warfarin (Coumadin)	CYP 2C9	Case report[40]	Decrease

CYP = cytochrome.

**—These possible interactions are based on preliminary results and may or may not prove to be clinically meaningful. Information from references 29 through 40.*

TABLE 3
Key Points About St. John's Wort

Effectiveness
Effective for the treatment of mild to moderate depression
Insufficient evidence to establish effectiveness for the treatment of major depression
Adverse effects
Most common*: transient photosensitivity
Less common: gastrointestinal upset, increased anxiety, minor palpitations, photosensitivity, fatigue, restlessness, dry mouth, increased depression
Dosage
Standardized pills: 900 mg daily (divided into two or three doses)
Cost†
$10 to $25 for a 30-day supply of standardized hypericum
Bottom line
Generally safe, well-tolerated herbal medicine for the treatment of mild to moderate depression

**—Occurs in less than 3 percent of patients.*

†—Estimated cost to the pharmacist based on average wholesale prices in Red Book. Montvale, N.J.: Medical Economics Data, 2005. Cost to the patient will be higher, depending on prescription filling fee.

several weeks, the full clinical effect of St. John's wort may take two to four weeks to manifest.

Final Comment

St. John's wort represents an effective therapy for the treatment of mild to moderate forms of depression. Standardized formulations are available for $10 to $25 for a one-month supply. It is important to emphasize that not all St. John's wort products are systematically standardized. Drug interactions with St. John's wort have been demonstrated in a variety of pharmacologic studies, although the clinical importance of these observations is uncertain given the widespread use of this agent. *Table 3* outlines the effectiveness, safety, tolerability, dosage, and cost of standardized St. John's wort formulations.

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