St. John’s Wort

SILVANA LAWVERE, PH.D., and MARTIN C. MAHONEY, M.D., PH.D.
Roswell Park Cancer Institute, Buffalo, New York

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. Copyright © 2005 American Academy of Family Physicians.)
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 placebo11,16,20-22 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 suggested 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).

Studies17-19 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 trial18 (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 trial19 (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 study17 (n = 209) concluded that St. John’s wort was equivalent to imipramine in patients with severe depression.

Taken together, the data10-22 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.

The Authors

SILVANA LAWVERE, PH.D., is a postdoctoral fellow in the Department of Clinical Prevention, Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute in Buffalo, N.Y. Dr. Lawvere obtained her Ph.D. from the School of Medicine and Biomedical Sciences, State University of New York (SUNY), Buffalo.

MARTIN C. MAHONEY, M.D., PH.D., F.A.A.F.P., is chair of the Department of Clinical Prevention, Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, and associate professor in the Departments of Family Medicine and Social & Preventive Medicine at SUNY, Buffalo. Dr. Mahoney received his medical degree from SUNY, Buffalo, where he also completed a family practice residency program and a faculty development fellowship.

Address correspondence to Martin C. Mahoney, M.D., Ph.D., Department of Clinical Prevention, Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute–Carlton 307, Elm and Carlton Streets, Buffalo, NY 14263 (e-mail: Martin.Mahoney@roswellpark.org). Reprints are not available from the authors.
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 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. 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

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

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 lists the possible drug interactions that may occur with St. John’s wort. The results of one report41 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 study35 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 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

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**TABLE 2**

**Possible Drug Interactions with St. John’s Wort***

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pathway</th>
<th>Type of report</th>
<th>Effect of St. John’s wort on drug levels in the blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>CYP P450 3A4</td>
<td>One-arm trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>CYP 3A4</td>
<td>One-arm trial</td>
<td>None</td>
</tr>
<tr>
<td>Cyclosporine (Sandimmune)</td>
<td>CYP 3A4</td>
<td>One-arm trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Digoxin</td>
<td>CYP 3A4</td>
<td>Clinical trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Indinavir (Crixivan)</td>
<td>CYP 3A4</td>
<td>One-arm trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Irinotecan (Camptosar)</td>
<td>CYP 3A4</td>
<td>Crossover trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>CYP3A</td>
<td>Clinical trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Nevirapine (Viramune)</td>
<td>CYP 3A4</td>
<td>One-arm trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>CYP 3A4</td>
<td>Clinical trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>CYP P450 3A4</td>
<td>One-arm trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>CYP 3A4</td>
<td>Clinical trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Tacrolimus (Prograf)</td>
<td>CYP 3A4</td>
<td>One-arm trial</td>
<td>Decrease</td>
</tr>
<tr>
<td>Theophylline</td>
<td>CYP 1A2</td>
<td>Case report</td>
<td>Decrease</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>CYP 2C9</td>
<td>Case report</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

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.
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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Members of various family medicine departments develop articles for “Complementary and Alternative Medicine.” This is one in a series coordinated by Sumi Sexton, M.D.

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

REFERENCES

15. Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. Comparison of an extract of hypericum (LI 160) and ser-
St. John’s Wort


