

## FPIN's Clinical Inquiries

Clinical Inquiries provide answers to questions submitted by practicing family physicians to the Family Practice Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group ([http://www.cebm.net/levels\\_of\\_evidence.asp](http://www.cebm.net/levels_of_evidence.asp)).

This series of Clinical Inquiries is coordinated for American Family Physician by John Epling, M.D., State University of New York Upstate Medical University, Syracuse, N.Y. The complete database of evidence-based questions and answers is copyrighted by FPIN. If you are interested in submitting questions to be answered or writing answers for this series, go to <http://www.fpin.org> or contact [CI2Editor@fpin.org](mailto:CI2Editor@fpin.org).

## St. John's Wort for Depression

### Clinical Question

Does St. John's wort relieve depression in adult patients?

### Evidence-Based Answer

St. John's wort is safe and effective for short-term (six to eight weeks) relief of mild to moderate depression in adults. [Strength of recommendation: A, based on consistent evidence from high-quality systematic reviews]

### Evidence Summary

Although not widely accepted by physicians in the United States, the extract of the herb *Hypericum perforatum*, known as St. John's wort, is the most commonly prescribed treatment for depression in Germany.<sup>1</sup> Preparations generally are standardized to the hypericum component, with dosages ranging from 500 to 1,800 mg daily. Its mechanism of action is thought to be inhibition of reuptake of serotonin, dopamine, and norepinephrine.<sup>2</sup>

A Cochrane review<sup>1</sup> of 14 randomized controlled trials (RCTs) with a total of 960 patients compared single preparations of St. John's wort with placebo. Patients in the included studies were recruited from practices of psychiatrists, general practitioners, internists, and one gynecologist; most of the patients were diagnosed with mild to moderate depression. All trials lasted four to six weeks and used various dosages of St. John's wort. Treatment response was assessed with one of two widely used instruments, the Hamilton Depression Scale or the Clinical

Global Impression Index. A "responder" was defined as a patient with a clinically significant change in these scales.

The pooled response rate ratio (RR, the ratio of treatment group responders to control group responders) was 2.5 (95 percent confidence interval [CI], 1.7 to 3.6), indicating a significant benefit. The pooled response rate was 56 percent in the treatment group and 25 percent in the control group. The number needed to treat for the combined population was 3.2.

Five studies of 691 patients compared St. John's wort with standard antidepressants (mostly tricyclic antidepressants at relatively low dosages) and found them to be equally effective in relieving symptoms of depression (RR: 1.01; 95 percent CI, 0.87 to 1.16). St. John's wort was better tolerated with 26.3 percent of users reporting side effects compared with 44.7 percent in those taking antidepressants. There also were fewer dropouts from side effects (RR: 0.4; 95 percent CI, 0.2 to 0.8).

#### Effectiveness of St. John's Wort

| Review                      | Number of studies (patients) | Treatment duration | Responder rate ratio* (95% CI) |
|-----------------------------|------------------------------|--------------------|--------------------------------|
| Linde, Mulrow<br>(Cochrane) | 14 (960)                     | 4 to 6 weeks       | 2.5 (1.7 to 3.6)               |
| Whiskey, et al.             | 14 (1,319)                   | 4 to 8 weeks       | 2.0 (1.5 to 2.6)               |

CI = confidence interval.

\*-Responder rate ratio is the ratio of treatment group responders to placebo group responders.

Information from references 1 and 3.

A second, more recent meta-analysis,<sup>3</sup> which included many of the studies of the first meta-analysis and a few others, pooled data from 14 RCTs using 1,319 patients. It had results similar to the first meta-analysis and confirmed that St. John's wort is superior to placebo (RR: 2.0; 95 percent CI, 1.5 to 2.6). When compared with antidepressants in nine studies (1,457 patients), St. John's wort was equally effective (RR: 1.0; 95 percent CI, 0.9 to 1.1). Tricyclic antidepressants were used in eight studies and fluoxetine in a single study of 149 patients. Three studies with 155 patients reported adverse drug reactions and found no significant difference when compared with placebo (RR: 1.0; 95 percent CI, 0.7 to 1.6). Five studies of 324 patients reported St. John's wort had significantly fewer side effects than tricyclic antidepressants (RR: 0.59; 95 percent CI, 0.52 to 0.71), although data are lacking for a comparison with newer antidepressants. These results are supported by a smaller systematic review and meta-analysis.<sup>4,5</sup>

It is important to note that St. John's wort is not effective for treating severe major depression, according to one study.<sup>6</sup>

Side effects of St. John's wort therapy mostly are self-limited and include headache, fatigue, gastrointestinal upset, and restlessness. Photosensitivity is possible, but only with very high

dosages.<sup>7</sup> Interactions with other drugs are not well defined, but cases of induction of hepatic cytochrome P450 have been reported.<sup>8</sup> Serotonin syndrome has occurred when St. John's wort is used with selective serotonin reuptake inhibitors (SSRIs), particularly in older patients.<sup>8</sup> Serotonin syndrome is caused by a systemic excess of serotonin and is defined when at least three of the following signs and symptoms are present: mental status changes, diaphoresis, myoclonus, hyperreflexia, diarrhea, fever, tremor, incoordination, seizures, tachycardia, and QT interval prolongation.<sup>9</sup>

#### Recommendations from Others

According to the American College of Physicians, St. John's wort is an option for short-term treatment of mild to moderate depression although it is not approved by the U.S. Food and Drug Administration.<sup>10</sup> Preparations of St. John's wort vary in content of active ingredients.

The Institute for Clinical Systems Improvement states that St. John's wort is more effective than placebo and as effective as low-dose tricyclic antidepressants for mild to moderate depression. St. John's wort may be as effective as SSRIs for mild to moderate depression (studies are lacking), and it is not recommended for patients with major depression.<sup>11</sup>

#### Clinical Commentary

SSRIs are the most widely used antidepressants in the United States. Barriers to their use include cost, side effects, and the reluctance of some patients to use "drugs" to treat depression. The evidence clearly shows that St. John's wort is an effective and well-tolerated option for short-term relief of mild to moderate depression. It is inexpensive and may be more acceptable to patients who prefer "natural" therapy.

Ideal dosages of St. John's wort are not clearly defined. A typical dosage is 300 mg of a standardized preparation three times daily (average cost is \$10 for one month).

It is not well established how St. John's wort compares with other antidepressants, particularly SSRIs. More studies comparing standard dosages of St. John's wort with SSRIs and other antidepressants for long-term treatment are warranted, as are systematic studies of its long-term side effects and interactions with other drugs.

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