

St John's Wort (*Hypericum perforatum*) in Major Depression

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The herb St John's wort (*Hypericum perforatum*) has been used for centuries to treat a variety of medical illnesses. In certain areas of Europe, St John's wort has been a commonly prescribed treatment for depression, but, in the United States, it is available for purchase over the counter as an herbal supplement. Some researchers believe that specific chemical constituents of St John's wort produce change in depression in a way similar to that of antidepressant medications, yet this hypothesis is problematic. In addition, studies that support the efficacy of St John's wort in patients with mild-to-moderate depression have limitations that may affect the accuracy of their conclusions. Studies measuring the effect of St John's wort in major depression have reported conflicting results and need to be reexamined. Because St John's wort is considered by some to be an alternative to conventional therapies, clinicians need to know whether it is an effective and safe treatment for different levels of severity of depression. Current evidence does not support its use, and, because of potential drug interactions, St John's wort is not a benign treatment.

(*J Clin Psychiatry* 2009;70[suppl 5]:23–27)

In the late 1980s and early 1990s, St John's wort (*Hypericum perforatum*) gained popularity as an alternative treatment for depression. The herb became especially popular in certain areas of Europe, particularly in Germany, where it has been widely prescribed to individuals with depression.^{1,2} During the same period in the United States, many people began to purchase St John's wort over the counter as a dietary supplement. However, at the peak of the herb's popularity in the late 1990s, researchers started to thoroughly examine the evidence for the efficacy of St John's wort in depression.

MECHANISM OF ACTION HYPOTHESIS

Some people believe that the active ingredients of St John's wort produce change in depression. A number of chemical constituents are present in St John's wort, including naphthodianthrone (eg, hypericin), flavonoids (eg, quercetin),

biflavonoids (eg, biapigenin), and phloroglucinol (eg, hyperforin), but the ones that have received the most attention in research are hypericin and hyperforin. These 2 constituents have been studied extensively, primarily in animal models. Both hypericin and hyperforin have certain chemical actions that are similar to those of antidepressants, including monoamine oxidation inhibition, serotonin uptake inhibition, dopamine/norepinephrine uptake inhibition, and sodium channel efflux inhibition (a mechanism of action of tricyclic antidepressants).

Although St John's wort contains certain ingredients with chemical actions that resemble those of antidepressants, the hypothesis that these mechanisms prove that St John's wort is effective in treating depression is problematic because of dosing issues. For instance, a study² in animals compared the mechanisms of action of several antidepressants—imipramine, clomipramine, desipramine, nomifensine, and amineptine—with those of LI 160, a standardized St John's wort extract. In that study, rats were administered one of several antidepressants or LI 160 for 14 days. The dose of imipramine was about 10-fold higher than that given to humans, whereas LI 160 was dosed at approximately 20 times the human dose. In spite of this dosing difference, LI 160 produced less down-regulation of β -adrenergic receptors (about 15%) than imipramine (25%). In another study,³ the dose of imipramine that was used in animals would be equivalent to about 700 mg/d in humans, which is approximately 3 to 5 times the typical dose prescribed to treat depression. The dose of St John's wort that was used would be equivalent to about 21,000 mg/d, which is about 15 to 40 times the standard dose in humans. Therefore, although some pharmacologic constituents of St John's wort appear to

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This article is derived from the planning teleconference series "The Use of Complementary and Alternative Medicines to Achieve Remission in Major Depressive Disorder," which was held in May 2009 and supported by an educational grant from Pamlab, LLC.

Dr Shelton is a consultant to Eli Lilly, Evotec, Forest, Gideon-Richter, Janssen, Novartis, Merck, Otsuka, Pamlab, Pfizer, and Repligen; and has received grant/research support from Bristol-Myers Squibb, Eli Lilly, Evotec, Forest, Janssen, the National Institute of Mental Health, Merck, Novartis, Otsuka, Pamlab, Pfizer, and Repligen.

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doi:10.4088/JCP.8157su1c.05

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FOR CLINICAL USE

- ◆ When treating patients with depression, select treatments that have shown efficacy in adequate controlled clinical trials.
- ◆ Inform patients who are taking or considering taking St John's wort that it is not a benign treatment and may interact with other medications.

produce antidepressant effects in animal models, the doses that would be needed to produce the same results in humans are unlikely to be achieved. St John's wort may have other mechanisms of action that are unknown or that have not been extensively studied, but the identified mechanisms at standard doses would not explain an antidepressant effect.

STUDIES OF ST JOHN'S WORT IN MILD-TO-MODERATE DEPRESSION

In 1996, Linde et al⁴ conducted a meta-analysis of randomized controlled trials to determine the efficacy and safety of St John's wort in depression. Twenty-three controlled trials of St John's wort in depression were identified (N = 1,757); 15 were placebo-controlled, and 8 compared St John's wort with another medication (a tricyclic antidepressant, a benzodiazepine, or maprotiline). Twenty studies used single preparations of St John's wort, and 3 studies used a combination of the herb and other plant extracts. Most patients had mild-to-moderate depression.

These data⁴ indicated that St John's wort extracts were significantly superior to placebo (OR = 2.67; 95% CI, 1.78–4.01) and were comparable to antidepressant medications (single preparations: OR = 1.10; 95% CI, 0.93–1.31; combinations: OR = 1.52; 95% CI, 0.78–2.94). Also, fewer patients who received St John's wort experienced side effects than did those who received antidepressants (19.8% vs 52.8%, respectively). However, the researchers concluded that, because of methodology limitations, the studies did not sufficiently prove that St John's wort is as effective as antidepressants or that it has fewer side effects.

Various limitations of these trials were identified.⁴ External validity problems existed, such as nonsystematic diagnoses. Although most patients were described as having milder depression, scores on the Hamilton Depression Rating Scale (HDRS) suggested greater severity in some studies. Also, internal validity problems were evident; for example, adequacy of blinding was a concern because 6 trials used fluid preparations of St John's wort extracts, which have a distinct taste that may be distinguished from placebo. In addition, the evaluators in some of these studies (ie, primary care physicians, internists, gynecologists) would have been inexperienced with the HDRS, which was the scale most often used. The daily doses of St John's wort (in different preparations) ranged considerably, and doses of the comparator drug were often inadequate to produce strong

antidepressant action. The trials that used a comparator did not include a placebo arm, which is necessary to determine assay sensitivity, ie, placebo response rate. Further, the studies were of low power (ie, only 7 had sample sizes of 100 or more), and only 4 of the trials lasted 8 weeks or longer.

STUDIES OF ST JOHN'S WORT IN MAJOR DEPRESSION

A few large trials⁵⁻⁷ with long-term components have been conducted on St John's wort in major depressive disorder (MDD). Two trials^{5,7} had acute phases of 8 weeks, and 2 had continuation phases of 24 weeks⁶ and 18 weeks.⁷ A recent meta-analysis⁸ was also conducted.

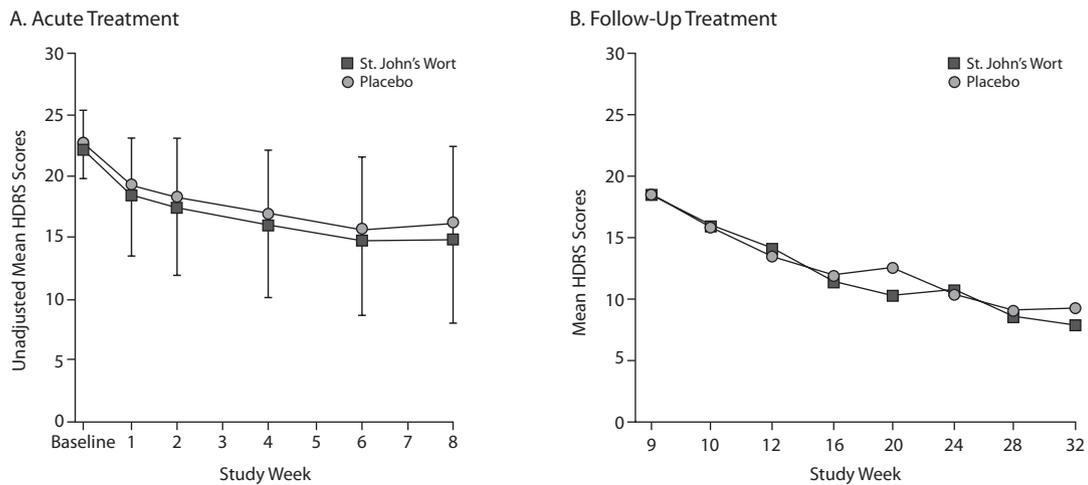
A Randomized Controlled Trial

Design. Shelton and colleagues⁵ conducted a randomized, double-blind, placebo-controlled trial to measure the efficacy and safety of St John's wort in outpatients with major depression. After being screened for MDD (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV] criteria and a score of ≥ 20 on the 17-item HDRS), patients with certain comorbid diagnoses and characteristics that could affect responsiveness to treatment were excluded from the study, such as those who had taken St John's wort within the last month, those with a history of resistance to antidepressant medications, and those with borderline, antisocial, or schizotypal personality disorders. Individuals who qualified to participate in the study were given placebo for 1 week, and those who achieved either a 25% improvement or a score of < 20 on the HDRS were dismissed to prevent a high placebo response rate and a failed clinical trial.

Participants were randomly assigned to 8 weeks of treatment with St John's wort (900 mg/d for at least 4 weeks, which was increased to 1,200 mg/d for the next 4 weeks if needed; n = 98) or placebo (n = 102). Individuals who responded to St John's wort were continued on the extract for an additional 6 months (n = 17), while patients who did not respond to either St John's wort or placebo were assigned to an open antidepressant trial for 6 months (n = 95).⁶ Placebo responders were terminated from further participation.

Results. Throughout the 8-week trial,⁵ no significant differences were seen between the 2 treatment groups on the HDRS (the primary outcome measure; Figure 1), the Hamilton Anxiety Rating Scale, the Clinical

Figure 1. Mean Change in HDRS Scores During Acute Treatment and Follow-Up After Nonresponse With St John's Wort or Placebo^a



^aAdapted with permission from Shelton et al⁵ (1A) and Gelenberg et al⁶ (1B). Abbreviation: HDRS = Hamilton Depression Rating Scale.

Global Impressions-Improvement scale, the Clinical Global Impressions-Severity scale, or the Beck Depression Inventory. Some minor differences existed between St John's wort and placebo. In study completers, response and remission rates were nonsignificantly higher in St John's wort-treated patients (32.9% and 20.3%, respectively) compared with placebo-treated patients (20.7% and 10.3%, respectively). In the intent-to-treat sample, the remission rate was significantly higher in the St John's wort group (14.3%) than in the placebo group (4.9%; $P = .02$); however, this analysis was exploratory and did not survive correction for multiple testing. Although there was not an active comparator control in the study, placebo response and remission rates were low, indicating sufficient assay sensitivity. Generally, the placebo response rate is around a third to almost a half for patients with depression.

Headache and abdominal discomfort were reported by at least 10% of subjects in both treatment groups. However, only headache was reported significantly more often in the St John's wort group than in the placebo group ($P = .02$).

During the follow-up phase, the majority of patients who did not respond to either St John's wort or placebo in the acute phase responded to antidepressant medication, indicating that they were not resistant to treatment (see Figure 1).⁶ Although 17 patients had initially responded to St John's wort, 29.4% of those had a relapse while continuing St John's wort during the follow-up period, so only 18.7% of all patients treated with St John's wort were able to achieve and maintain a response.

Conclusions. According to these data,^{5,6} St John's wort is not more effective than placebo in individuals with MDD of at least moderate severity. The differences in the response and remission rates between St John's wort and

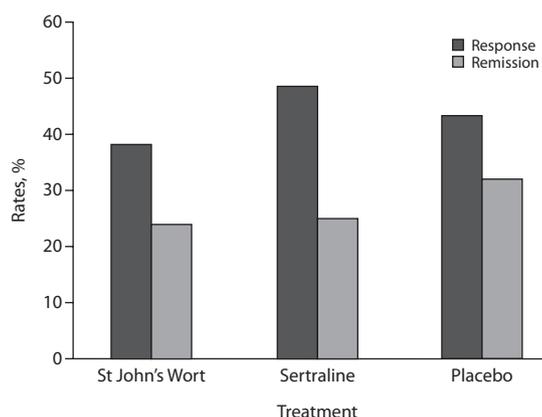
placebo leaves open the possibility that there may be a subpopulation of depressed patients who may respond to the herbal treatment.

Limitations. This trial^{5,6} has limitations that may leave it vulnerable to criticism. For example, a relatively high proportion of chronically depressed individuals participated in the study; however, this patient population was similar to that of the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D), and these patients seem to be representative of the typical depressed population. Because of the low placebo response rate, some have suggested that the participants were a chronically, severely ill group of people who were unlikely to respond to St John's wort. However, a low placebo response rate provided an optimal chance for St John's wort to separate from placebo. Additional suggestions that have been expressed are that the dose of St John's wort should have been higher (some studies use 1,600–1,800 mg/d) and that a comparator drug should have been used, but placebo was considered to be the definitive comparator.

Hypericum Depression Trial Study Group

Design. The Hypericum Depression Trial Study Group⁷ conducted a randomized, double-blind, placebo-controlled trial to examine the efficacy and safety of St John's wort in outpatients with major depression ($N = 340$). This trial compared the herbal extract not only with placebo but also with sertraline. As in the Shelton et al trial,⁵ the participants had an MDD diagnosis as defined by the *DSM-IV* criteria and a score of ≥ 20 on the HDRS. Also, as in the Shelton et al study,⁵ patients with certain diagnoses and characteristics, such as those who were suicidal or had a history of suicidality, those with a history of resistance to antidepressants,

Figure 2. Response and Remission Rates Following Acute Treatment With St John's Wort, Sertraline, or Placebo^a



^aData from the Hypericum Depression Trial Study Group.⁷

and those who had taken St John's wort or sertraline daily for at least 4 weeks within 6 months of the trial, were excluded from participation. As in the Shelton et al study,⁵ to prevent a high placebo response rate, patients were given placebo for 1 week and dismissed if they showed a greater than 25% decrease in HDRS total score.

Participants were randomly assigned to receive St John's wort (900–1,500 mg/d; n = 113), sertraline (50–100 mg/d; n = 111), or placebo (n = 116) for 8 weeks. After week 8, responders could choose to participate in an 18-week continuation phase (N = 129). The maximum daily dose of St John's wort following week 8 was 1,800 mg/d, and the maximum daily dose of sertraline was 150 mg/d.

Results. At the end of the acute phase, overall response and remission rates did not significantly differ between the 3 treatment groups. Compared with the rates reported by Shelton et al,⁵ the response and remission rates with both St John's wort and placebo were substantially higher. Response rates for St John's wort, placebo, and sertraline were 38.1%, 43.1%, and 48.6%, respectively, while remission rates were 23.9%, 31.9%, and 24.8%, respectively; none were significantly different (Figure 2). Adverse events that were reported significantly more often in the St John's wort group than in the placebo group were anorgasmia ($P = .04$), frequent urination ($P = .003$), and swelling ($P = .02$).

Conclusions. This study⁷ does not support the efficacy of St John's wort for the treatment of moderately severe MDD.

Limitations. External and internal validity concerns regarding this study⁷ have been raised. For instance, it may be that St John's wort would be more effective for patients with less severe MDD than many of the participants involved in this particular study. Still, the major concern about this study involved the dosages. Patients taking St John's wort could theoretically receive as much as 1,800 mg/d after week

Table 1. Medications That Interact With St John's Wort^a

Type of Agent	Medications
Anticancer	Imatinib and irinotecan
Anti-HIV	Indinavir, lamivudine, nevirapine, and others
Anti-inflammatory	Ibuprofen, fexofenadine, and others
Antimicrobial	Erythromycin, voriconazole, and others
Cardiovascular	Digoxin, ivabradine, warfarin, verapamil, nifedipine, talinolol, and others
Central nervous system	Amitriptyline, buspirone, phenytoin, methadone, midazolam, alprazolam, sertraline, and others
Hypoglycemic	Tolbutamide, gliclazide, and others
Immunomodulating	Cyclosporine, tacrolimus, and others
Oral contraceptives	...
Proton pump inhibitor	Omeprazole and others
Respiratory system	Theophylline and others
Statins	Atorvastatin, pravastatin, and others

^aBased on Di et al.¹²

Abbreviation: HIV = human immunodeficiency virus.

Symbol: ... = not provided.

8, and patients taking sertraline could receive up to 150 mg/d, yet the mean maximum daily doses were 1,382 mg/d and 89 mg/d, respectively, during the continuation phase. The proportion of patients who achieved the highest daily dose in the first 8 weeks was significantly less in the sertraline group (36%) compared with the other 2 groups (54% for both; $P = .005$). The dose of sertraline was controlled to avoid side effects, but, as a result, it may not have received a fair chance to separate from St John's wort and placebo.

Meta-Analysis of Studies in Major Depression

A number of controlled clinical trials have been published since the original meta-analysis⁴ described above. To determine the effectiveness of St John's wort compared with placebo and antidepressants in major depression, a recent meta-analysis by Linde et al⁸ reviewed results from 29 controlled studies (N = 5,489); 18 of the studies compared St John's wort with placebo and 17 compared St John's wort with antidepressant medications.

Overall response risk ratios (RRs) were higher with St John's wort compared with placebo, but results varied depending on sample size. The combined RR for St John's wort compared with placebo in the larger studies was 1.28 (95% CI, 1.10–1.49) and in the smaller studies was 1.87 (95% CI, 1.22–2.87). However, if the German clinical trial⁹ that reported an RR that was extremely out of range (10.25; 95% CI, 3.88–27.09) was excluded from the smaller trials, the overall comparison would suggest a modest effect of St John's wort compared with placebo (RR ≈ 1.3). Compared with antidepressants, St John's wort was not more effective, regardless of sample size.

In addition, the meta-analysis⁸ compared the results by German studies and non-German studies. The combined RR from studies conducted in German-speaking countries was substantially higher than that of studies conducted in non-German-speaking countries (1.78 vs 1.07). In fact, the

majority of favorable studies (whether larger or smaller) were from German-speaking countries; the reason for this is unknown. Possibly, people with Germanic backgrounds respond better to St John's wort than do people from other ethnic groups. However, this also raises concerns about internal validity with these studies. Nonetheless, the overall evidence does not support a significant effect of St John's wort in MDD.

THE EFFECT OF ACTIVE CONTROLS ON STUDY RESULTS

People may perceive a pharmacologic effect from St John's wort, even if it is not necessarily related to an antidepressant action, which may enhance placebo response. A meta-analysis¹⁰ of studies that compared antidepressants with active placebo controls (ie, drugs that mimic side effects of the medication being tested but do not produce the intended antidepressant effect) found that only 2 of 9 studies produced a significant difference in effect size. St John's wort may have an effect similar to that of active placebo controls. In the Shelton et al study,⁵ the patients treated with St John's wort had numerically higher response and remission rates than placebo-treated patients, which may be due to the perceived pharmacologic effects of St John's wort.

ST JOHN'S WORT INTERACTIONS

Concerns have been raised about possible interactions of St John's wort extracts with other medications. For example, St John's wort activates the pregnane X receptor,^{11,12} an orphan nuclear receptor that regulates the expression of cytochrome P450 3A4, and P-glycoprotein,¹² an efflux protein, thus increasing the removal of drugs from the central nervous system. Many drugs have been reported to interact with St John's wort (Table 1),¹² so it cannot be considered a benign treatment. St John's wort may interact with 1 or more of the medications that a patient is taking or that he or she will take in the future.

SUMMARY

Current evidence does not support the efficacy of St John's wort in major depression, and the evidence in mild/minor depression is insufficient to draw any conclusions. The modest efficacy of St John's wort that has been found in placebo-controlled trials suggests an active control effect

rather than superiority to placebo. Further, St John's wort interacts adversely with numerous medications, which would argue against its use to treat depression.

Drug names: alprazolam (Niravam, Xanax, and others), atorvastatin (Lipitor), buspirone (BuSpar and others), clomipramine (Anafranil and others), cyclosporine (Gengraf, Neoral, and others), desipramine (Norpramin and others), digoxin (Lanoxin and others), erythromycin (Eryc, Eryderm, and others), fexofenadine (Allegra and others), imatinib (Gleevec), imipramine (Tofranil and others), indinavir (Crixivan), irinotecan (Camptosar), lamivudine (Epivir), methadone (Methadose, Dolophine Hydrochloride, and others), nevirapine (Viramune), nifedipine (Procardia, Adalat CC, and others), omeprazole (Prilosec and others), phenytoin (Dilantin, Phenytek, and others), pravastatin (Pravachol and others), sertraline (Zoloft and others), tacrolimus (Prograf and Protopic), theophylline (Theochron, Uniphyll, and others), verapamil (Verelan, Isoptin, and others), voriconazole (Vfend), warfarin (Coumadin, Jantoven, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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