REVIEW ARTICLE

St John's Wort for Depression

A Systematic Review

Barak Gaster, MD; John Holroyd, MD

To address whether St John's wort is useful for the treatment of depression we attempted to retrieve all English-language articles with data on the efficacy, safety, and availability of St John's wort. Randomized, controlled, double-blind trials were selected and assessed for methodological quality using a standardized checklist, and data on pharmacology, cost, regulation, and safety were extracted. Eight studies were identified, found to be of generally good methodological quality, and determined to provide a modest amount of data to suggest that St John's wort is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with the use of St John's wort ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. More data are required to assess both its use in severe depression and its efficacy compared with other antidepressants. Rates of side effects were low. As a dietary supplement, St John's wort is currently largely unregulated, but the Food and Drug Administration is reviewing plans to tighten its regulatory oversight. *Arch Intern Med. 2000;160:152-156*

Depression is one of the most common disorders treated in primary care, with 5.1 million office visits for depression in 1995 alone.[1] There are many barriers to the successful treatment of depression, but two of the main ones are the adverse effects of standard antidepressants and their high cost. An effective, low-cost, well-tolerated antidepressant would thus be of tremendous clinical importance.

Some recent reviews have touted St John's wort to be exactly such a medication,[2,3] although other observers have seriously doubted its usefulness.[4,5] To address the question of whether St John's wort is useful for the treatment of depression, we sought to systematically and critically review the literature regarding its safety and efficacy, as well as to investigate the related issues of its availability and cost.

St John's wort is the common name for the flowering plant, *Hypericum perforatum*, which grows as a common weed in much of the United States. Extracts of the plant have been used for centuries as a therapy for "insomnia and other nervous conditions."[6] Its yellow flower was traditionally gathered for the feast of St John the Baptist, and "wort" is the Old English word for plant—hence, the derivation of its common name.

In the past few years, the use of St John's wort in the United States has been rising exponentially, with annual sales increasing from $20 million to $200 million between 1995 and 1997 alone.[7] It has long been a popular antidepressant in Germany.[8]

METHODS

Data Sources

We performed computerized searches of the MEDLINE, EMBASE, PsychINFO, and Cochrane Library databases, attempting to retrieve all relevant English-language articles published between January 1980 and September 1998 using the following all-text search strategy: wort OR hyperic*. In addition, we manually searched the reference lists of relevant articles; contacted trade journals, manufacturers, and retail sellers in the diet supplement industry; spoke with experts in the fields of depression and herbal medicine; and extracted descriptive and analytical data on the pharmacology and risk of adverse events of hypericum extract from relevant articles.

From the Department of Medicine, University of Washington, Seattle.

Table 1. Randomized, Double-blind Studies of Hypericum vs Placebo

Study	Name of Preparation	Dosage*	N	% Responders, Hypericum vs Placebo	*P*
Sommer and Harrer,[10] 1994	LI 160	300 mg TID (0.3% hypericin)	105	67 vs 28	<.001
Hubner et al,[11] 1994	LI 160	300 mg TID (0.3% hypericin)	40	70 vs 47	.15
Hansgen et al,[12] 1994	LI 160	300 mg TID (0.3% hypericin)	67	81 vs 26	<.001
Schrader et al,[13] 1998	ZE 117	250 mg BID (0.5% hypericin)	162	56 vs 15	<.001

**TID indicates 3 times a day; BID, twice a day.*

Study Selection

To be included in our analysis of efficacy, clinical trials of hypericum extract (1) had to be randomized, controlled, and double-blinded; (2) had to be limited to patients with a depressive disorder; (3) had to test hypericum extract alone and not in combination with other antidepressants; and (4) had to present original data that had not previously been published. Articles that met these criteria were further analyzed for methodological quality using a standard checklist that included whether the study (1) reported baseline demographics of the study groups, (2) described steps taken to ensure blinding, (3) used a standardized outcome measure as defined by the Consensus Conference on the Methodology of Clinical Trials of Antidepressants,[9] (4) performed an intention-to-treat analysis; and (5) provided a full accounting of all study subject dropouts and reasons for dropping out.

This search strategy yielded a total of 388 citations. Twelve of these were clinical trials.[10-21] Four of the trials did not meet our inclusion criteria: 2 were not placebo controlled,[18,19] 1 tested hypericum extract in combination with another agent,[20] and 1 presented data that had previously been published.[21] The results of the remaining 8 randomized controlled trials are presented below.

PHARMACOLOGY

Hypericum extract contains at least 10 substances that have been shown to have biological activity, including hypericin, pseudohypericin, xanthones, monoterpenes, β-sitosterol, quercetin, and catechin. Many of these substances have been shown to bind neuroreceptors in the brain and to inhibit the uptake of various neurotransmitters thought to be involved in depression.[22-24] Although hypericin was originally thought to be the primary active ingredient of the hypericum plant,[25] more recent data by Cott[22] at the National Institutes of Health casts doubt on hypericin's importance. Nevertheless, many extracts of hypericum are still standardized by their hypericin content.

There has been concern that hypericum extract might act as a monoamine oxidase (MAO) inhibitor and so should be subject to the same restrictions on diet and drug combinations that this class of drugs requires. Several recent studies have shown that the relative inhibitory potential of hypericum extract on the MAO system is very small, however, and is well below that of the commonly used MAO inhibitors.[24,26,27]

TRIALS OF EFFICACY

Methodological Quality

The 8 studies that met our inclusion criteria for trials of efficacy[10-17] were generally of high methodological quality: all 8 studies presented comparison demographic data and baseline depression scores for both treatment and control groups; all but one of the studies described steps taken to ensure reliable blinding[10]; all 8 studies gave a full accounting of subject dropouts; and all but one of the studies[14] reported data using a standard definition of "responder," which is commonly used in the assessment of antidepressants.[28] This definition of "responder" is based on the Hamilton Rating Scale for Depression (HAMD) an extensively validated[9] observer-rated scale calculated from a 21-item questionnaire, which focuses primarily on the somatic symptoms of depression. "Responders" are patients whose total score at the end of a study has either fallen to an absolute value less than 10 or to a value that is less than 50% of their baseline score.

All 8 studies included both men and women. The age range of study subjects was 19 to 75 years, with an average age of 47 years. Patients were recruited from a variety of settings including psychiatry, neurology, general practice, and internal medicine clinics.

The 2 most common methodological weaknesses found among these 8 trials were failure to perform an intention-to-treat analysis[10-12,14,15] and failure to test the statistical significance of the differences in responder rates between active and placebo groups.[10-12,14,15]

Efficacy Compared With Placebo

Of 4 trials testing hypericum extract against placebo (**Table 1**), all found a significantly greater improvement in HAMD scores in patients taking hypericum extract. Three of these trials also found a significantly greater responder rate in patients who took hypericum compared with placebo. In the largest of these trials, Schrader et al[13] randomized 162 patients to either 250 mg twice daily of hypericum extract standardized to 0.5% hypericin or placebo. Patients in the 2 groups were evenly matched at baseline and had either mild or moderate depression. At the end of 6 weeks, the percentage of patients classified as responders was significantly higher in the patients who took hypericum extract (56% vs 15%; $P<.001$), and mean scores on the HAMD decreased more in the active treatment group (20.1 to 10.5) than in the placebo group (18.8 to 17.9).

Table 2. Randomized, Double-blind Studies of Hypericum vs Tricyclic Antidepressants (TCA)

Study	Hypericum Dosage*	Comparison Treatment	N	% Responders, Hypericum vs TCA	*P*
Vorbach et al,[14] 1994	300 mg TID (0.3% hypericin)	Imipramine hydrochloride (25 mg TID)	135	Not reported	. . .
Harrer et al,[15] 1994	300 mg TID (0.3% hypericin)	Maprotiline hydrochloride (25 mg TID)	102	61 vs 67	.61
Wheatley,[16] 1997	300 mg TID (0.3% hypericin)	Amitriptyline hydrochloride (25 mg TID)	165	60 vs 78	.06
Vorbach et al,[17] 1997†	600 mg TID (0.3% hypericin)	Imipramine hydrochloride (50 mg TID)	209	35 vs 41	.40

**All studies used hypericum preparation LI 160. TID indicates 3 times a day.*
†Patients were diagnosed as having severe depression; in all other studies, patients were diagnosed as having mild to moderate depression.

In another of the trials, Hansgen et al[12] reported mean HAMD scores decreasing from 21.8 to 9.2 in the active treatment group and from 20.4 to 14.7 in the placebo group ($P<.01$ for the difference in means between the groups). The response rate was 81% in patients taking hypericum extract and 26% for those taking placebo ($P<.001$).

Efficacy Compared With Other Antidepressants

Four trials tested hypericum extract against another antidepressant, with tricyclic antidepressants (TCAs) being the comparison treatment in each of these studies (**Table 2**). The primary weakness of these trials is that they all used very low doses of TCAs. Whereas clinicians commonly initiate therapy with a TCA at a low dose and gradually titrate the dose up to 2 or 3 times the initial dose, 3 of these 4 trials[14-16] used constant TCA doses that were at or below the manufacturers' recommended starting doses.[29] Although the fourth trial used a somewhat higher dose of a TCA,[17] the dose used in this trial was still significantly lower than that which ordinarily would be used in clinical practice given the severe degree of baseline depression in that study.

In the trial by Wheatley,[16] the responder rate in the amitriptyline group was higher than in the hypericum group (78% vs 60%; $P = .064$), despite using a low dose of amitriptyline hydrochloride (25 mg 3 times a day).[16] In addition, there was a greater decrease in the total HAMD score in the amitriptyline group (–15 vs –10; $P<.05$).

In the only study of hypericum extract in patients with severe depression, Vorbach et al[17] randomized 209 patients with a mean HAMD score of 25.7 to either 600 mg thrice daily of a hypericum extract (0.3% hypericin) or imipramine hydrochloride, 50 mg thrice daily. At the end of 6 weeks, the response rate was low in both groups (35% for hypericum vs 41% for imipramine; $P = .40$), which is not surprising given the severity of the depression in this study and the relatively low dose of imipramine that was used. The mean decrease in total HAMD score was larger for the imipramine group (–12.7) than for the hypericum group (–10.9) ($P = .02$).

SIDE EFFECTS

Extracts of hypericum appear to be well tolerated. The most frequently reported side effects are nausea, rash, fatigue, restlessness, and photosensitivity, although even these seem to be rare. In a large, prospective open-label study in which data were systematically gathered from 3250 patients taking hypericum extract, only 2.4% of patients spontaneously reported an adverse effect.[30] The most common side effects reported were nausea (0.6%) and allergic rash (0.5%). Only 1.1% of patients discontinued hypericum extract because of side effects. More than one quarter of the patients in this study were older than 65 years.

In the study by Schrader et al,[13] 7.4% of patients taking hypericum reported an adverse effect compared with 6.2% for those taking placebo. In the 4 trials comparing hypericum with a TCA, patients taking low doses of TCAs were 78% to 33% more likely to experience adverse effects than patients taking hypericum.

Although none of the study patients in these clinical trials reported photosensitivity as an adverse effect, this has been listed as a possible side effect of hypericum extract.[2,3] Brockmoller et al[31] measured the minimum dose of UV light required to cause erythema on the skin before and after ingestion of 600 mg thrice daily of hypericum extract (0.3% hypericin) in 50 healthy volunteers. At the end of 15 days of hypericum treatment, the time required to cause a burn decreased by 21% ($P<.01$).

SEVERE ADVERSE EVENTS

In 5 of the 8 efficacy trials[13-17] that met our inclusion criteria, frequent laboratory monitoring of study subjects was performed, totaling 386 monitored patients treated with St John's wort. No changes in complete blood cell count, liver function test results, or serum creatinine levels were found in patients taking hypericum extract. In addition, no serious adverse events were detected in a large, open-label monitoring study.[30]

In one of the TCA comparison trials,[17] electrocardiograms were performed on study subjects at baseline and again at the end of the study period. Patients who took imipramine had a statistically significant prolongation of conduction intervals and a small increase in the incidence of first-degree atrioventricular block, but no electrocardiographic changes were seen in those taking hypericum extract.[32]

No cases of serotonin syndrome with the use of hypericum extract have been reported, although there has been at least 1 case of severe sedation in an elderly patient who combined paroxetine and hypericum extract.[33] There have been no published reports of hypericum extract causing MAO-type food or drug interactions.

There are few data on the safety of hypericum extract in overdose, although in one trial, healthy sub-

Table 3. Monthly Cost of Several Hypericum Extract Products

Product*	Hypericin Content	Cost per Tablet, $†	Cost per Month, $‡
New Attitude, Physicians Direct Inc, Orlando, Fla	0.3%	0.28	24.99
Zand, McZand Herbal Inc, Los Angeles, Calif	0.3%	0.17	14.99
Nature's Herbs, Twinlab Corp, Hauppauge, NY	0.3%	0.17	14.99
Vesta, Vesta Pharmaceuticals Inc, Indianapolis, Ind	0.3%	0.17	14.99
Adbiotk, Adbiotk, Eugene, Ore	0.3%	0.15	13.50

*All in doses of 300 mg.
†Retail prices collected from mail-order advertising.
‡Calculated based on 1 tablet 3 times a day.

jects were given single doses up to 3600 mg with no reported adverse effects.[31] The long-term safety of hypericum, or its use in pregnant women, has not been studied.

REGULATION

The Food and Drug Administration (FDA) does not classify herbal medications such as hypericum as drugs. According to the 1994 Dietary Supplement Health Education Act, herbal products and vitamins are considered dietary supplements, a subclassification of foods. As such, supplement products are not subject to the same quality-control regulations as standard pharmaceuticals, although new regulations regarding the manufacturing of diet supplements are currently under development.

The United States Pharmacopeial Convention, Inc (USP), which for years has published quality standards for vitamins and minerals products, is now in the process of developing monographs for commonly used herbal products, including hypericum.[34] These monographs will provide guidelines for the standardization of quality, purity, storage, and shelf life. Once completed, manufacturers whose products meet these standards will be able to use the USP seal as an assurance of quality. Guidelines for the enforcement and FDA monitoring of such claims are currently being developed, although their success will depend somewhat on the availability of suitable analytical methods (Robert Moore, MD, FDA, written communication, November 12, 1998).

Until then, hypericum products remain largely unregulated. Although some manufacturers of hypericum extract list the hypericin content on the product label (**Table 3**), these claims may or may not be reliable. In one analysis of commercial extracts, 5 of 10 products tested contained less than 80% of the hypericin content stated on the label, and 3 brands contained less than 50%.[35]

COST

The retail cost of hypericum extract varies depending on the supplier. Table 3 lists the monthly cost of several preparations available in the United States via mail order. These prices are generally lower than the current cost of standard antidepressant therapies, although direct cost comparisons are difficult given the variability in the retail costs of prescription drugs.

COMMENT

Although the 8 randomized controlled trials were of moderately high methodological quality, we were able to identify at least one significant methodological flaw in all but 2 of the studies.[13,16] It is important to note that no published trials have compared St John's wort with a selective serotonin reuptake inhibitor.

In general, the content and dosage of hypericin in the extracts tested were remarkably consistent among these 8 trials. Six of the 8 trials used the same standardized dose of 300-mg thrice daily of 0.3% hypericin, while one of the trials used a preparation with a slightly higher hypericin content.[13] One trial, which enrolled patients with more severe depression, used double this dose.

The results of this review generally agree with the results of a meta-analysis published by Linde et al,[36] which found that patients with mild to moderate depression were 2.67 times more likely to respond to hypericum extract than to placebo (95% confidence interval, 1.78-4.01). Our review includes 3 more recently published trials,[13,16,17] all of which were larger and more methodologically rigorous than those included in the meta-analysis of Linde et al.

The most significant potential weakness of our analysis is the exclusion of non–English-language studies. Since many of the studies included in our analysis were translated from German to English, it raises the possibility of translation bias—the possibility that positive studies may be more likely to be translated into English. On careful review of the summarized results of the studies in the meta-analysis by Linde et al,[36] however, there is no evidence for such bias as there was no significant differences in outcomes between the studies published in English and those published in German.

It is surprising that there have been no studies of hypericum extract in the United States. The National Institute of Mental Health and the National Institutes of Health Office on Alternative Medicine, however, have recently announced the joint funding of a $4.3 million study of its use in the treatment of major depression.[37] This 3-year study will enroll 336 patients and randomize them to hypericum extract, a selective serotonin reuptake inhibitor, or placebo. Results are expected in the year 2002.

Even if there were more data regarding the efficacy of hypericum extract, recommending its use to patients would be complicated by the current lack of regulatory oversight of dietary supplements and the potential for fraud in what is now one

of the country's fastest-growing for-profit industries. As the distinction between "natural" and "synthetic" chemicals becomes increasingly blurred,[38] there is a pressing need for better regulation and standardization of herbal therapies such as St John's wort.

The growing mainstream use of herbal remedies among Americans will increasingly require health care providers to recognize that many of their patients have strong preferences for such therapies.[39] While many questions remain unanswered regarding the use of hypericum extract for the treatment of depression, many patients will want to pursue it as a first-line therapy. Effective physician-patient communication concerning such choices is essential. By serving as knowledgeable counselors, physicians will be better able to recommend more conventional therapies when alternative approaches seem inappropriate or are failing.[40]

CONCLUSIONS

Although larger, more methodologically rigorous studies are needed, there is a modest amount of data that suggests that hypericum extract is safe, well tolerated, and probably more effective than placebo in the treatment of mild to moderate depression. More data are required, however, to assess its use in severe depression and its efficacy in comparison with other antidepressants.

Given the low cost of hypericum extract, it may have a role in the treatment of patients with mild depression who cannot afford standard antidepressants or who cannot tolerate standard antidepressants due to adverse effects. The current lack of regulation and standardization of commercially available preparations, however, remains a significant barrier to recommending its use for such patients at the present time.

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Corresponding author: Barak Gaster, MD, Box 354760, 4245 Roosevelt Way NE, Seattle, WA 98105-6920 (e-mail: barakg@u.washington.edu).

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