Effect of *Hypericum perforatum* (St John’s Wort) in Major Depressive Disorder
A Randomized Controlled Trial

Hypericum Depression Trial Study Group

_Hypericum perforatum* (St John’s wort) is widely used to treat depression, sometimes in an attempt to avoid adverse effects associated with prescription antidepressants. One meta-analysis in 1996 concluded that hypericum is superior to placebo for treatment of mild to moderate depression.¹ Subsequent studies have found hypericum to be comparable to active controls, such as amitriptyline,² imipramine,³-⁵ and fluoxetine,⁶ and superior to placebo.⁴,⁷ Some studies suggest that it may be an effective treatment for moderately severe depression.³,⁴ Others have been unable to differentiate hypericum from placebo.⁸,⁹ Important issues have been raised regarding existing studies, including limited information about use in clinically defined major depression, lack of placebo-controlled trials that have included a selective serotonin reuptake inhibitor arm, and absence of controlled data for continuation treatment. Concern has been raised about adverse interactions of hypericum with certain drugs.¹⁰,¹¹ Most hypericum in the United States is consumed without physician consultation. Even though many patients prefer to avoid the use of medications with adverse effects, there is a risk that people with clinically significant depression may self-medicate with hypericum rather than receive effective medication or psychotherapy.

This placebo-controlled study was designed to expand on previous trials by studying outpatients with well-defined hypericum rather than receive effective medication or psychotherapy.

Context Exports of *Hypericum perforatum* (St John’s wort) are widely used for the treatment of depression of varying severity. Their efficacy in major depressive disorder, however, has not been conclusively demonstrated.

Objective To test the efficacy and safety of a well-characterized *H perforatum* extract (LI-160) in major depressive disorder.

Design and Setting Double-blind, randomized, placebo-controlled trial conducted in 12 academic and community psychiatric research clinics in the United States.

Participants Adult outpatients (n = 340) recruited between December 1998 and June 2000 with major depression and a baseline total score on the Hamilton Depression Scale (HAMD) of at least 20.

Interventions Patients were randomly assigned to receive *H perforatum*, placebo, or sertraline (as an active comparator) for 8 weeks. Based on clinical response, the daily dose of *H perforatum* could range from 900 to 1500 mg and that of sertraline from 50 to 100 mg. Responders at week 8 could continue blinded treatment for another 18 weeks.

Main Outcome Measures Change in the HAM-D total score from baseline to 8 weeks; rates of full response, determined by the HAM-D and Clinical Global Impressions (CGI) scores.

Results On the 2 primary outcome measures, neither sertraline nor *H perforatum* was significantly different from placebo. The random regression parameter estimate for mean (SE) change in HAM-D total score from baseline to week 8 (with a greater decline indicating more improvement) was −9.20 (0.67) (95% CI, −10.51 to −7.89) for placebo vs −8.68 (0.68) (95% CI, −10.01 to −7.35) for *H perforatum* (P = .59) and −10.53 (0.72) (95% CI, −11.94 to −9.12) for sertraline (P = .18). Full response occurred in 31.9% of the placebo-treated patients vs 23.9% of the *H perforatum*-treated patients (P = .21) and 24.8% of sertraline-treated patients (P = .26). Sertraline was better than placebo on the CGI improvement scale (P = .02), which was a secondary measure in this study. Adverse-effect profiles for *H perforatum* and sertraline differed relative to placebo.

Conclusion This study fails to support the efficacy of *H perforatum* in moderately severe major depression. The result may be due to low assay sensitivity of the trial, but the complete absence of trends suggestive of efficacy for *H perforatum* is noteworthy.

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See also pp 1840 and 1853.

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HYPERICUM IN MAJOR DEPRESSION

major depression of moderate severity and included a 4-month continuation phase and sertraline as an active comparator to calibrate the trial’s validity. The main hypothesis tested whether hypericum would be superior to placebo after 8 weeks of treatment.

METHODS

The study was a randomized, double-blind, parallel-group, 8-week, outpatient trial of hypericum, sertraline, or placebo treatment for major depressive disorder, followed by up to 18 weeks of double-blind continuation treatment in participants meeting response criteria at 8 weeks.

Patients

Outpatients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive disorder were recruited from 12 academic or community clinics between December 1998 and June 2000. Major depressive disorder was diagnosed with the modified Structured Clinical Interview for Axis I DSM-IV disorders (SCID-Hypericum). Inclusion criteria were age at least 18 years; current diagnosis of major depression; minimum total score of 20 on the 17-item Hamilton Depression (HAM-D) scale and a maximum score of 60 on the Global Assessment of Functioning (GAF) at screening and baseline following a 1-week, single-blind, placebo run-in; no more than a 25% decrease in HAM-D total score between screening and baseline; capacity to give informed consent and follow study procedures; and identification of a close personal contact to be notified if warranted by clinical concerns.

Exclusion criteria were a score above 1 on the HAM-D suicide item; attempted suicide in the past year or current suicide or homicide risk; being pregnant, planning pregnancy, breastfeeding, or not using medically acceptable birth control; clinically significant liver disease or liver enzyme levels elevated to at least twice the upper normal limit; serious unstable medical illness; history of seizure disorder; SCID diagnoses indicating alcohol or other substance-abuse disorder within the past 6 months or lifetime diagnoses of schizophrenia, schizoaffective or other psychotic disorder, bipolar disorder, panic disorder, or obsessive-compulsive disorder; history of psychotic features of affective disorder; evidence of untreated or unstable thyroid disorder; no response to at least 2 adequate trials of antidepressants in any depressive episode; daily use of hypericum or sertraline for at least 4 weeks within the past 6 months; current use of other psychotropic drugs, other medicines, dietary supplements, natural remedies, or botanical preparations with psychoactive properties; use of investigational drugs within 30 days of baseline or of other psychotropic drugs within 21 days of baseline (within 6 weeks for fluoxetine); allergy or hypersensitivity to study medications; positive urine drug screen; introduction of psychotherapy within 2 months of enrollment or any ongoing psychotherapy specifically designed to treat depression; and mental retardation or cognitive impairment.

Study Design

Patients provided written informed consent, and the institutional review board approved the protocol at each site. Patients who remained eligible after a 1-week placebo run-in were randomly assigned to receive 1 of 3 treatments in a 1:1:1 ratio within permuted blocks of size 3 and 6 within site by sex strata. Drug kits were designed to be indistinguishable for the 3 treatments at each dose level.

Patients were assessed weekly or bi-weekly until week 8. Patients who fully or partially responded during these 8 weeks (ie, the acute phase) could enter the continuation phase, with visits at weeks 10, 14, 18, 22, and 26. The HAM-D, GAF, Clinical Global Impressions Scales for severity (CGI-S) and improvement (CGI-I) and Beck Depression Inventory (BDI) were assessed at all visits. The Sheehan Disability Scale (SDS) was completed at baseline and weeks 8 and 26. As a way to evaluate blinding at weeks 8 and 26, clinicians and patients indicated their beliefs about treatment assignment.

Drug accountability, concomitant therapies, vital signs, and self- and physician-rated symptom reports were assessed at every visit. Blood chemistry and hematologic tests and electrocardiography and physical examinations were performed at screening and at weeks 8 and 26. Urine toxicology was performed at screening.

Columbia University biometric staff trained all raters in the use of the SCID and HAM-D. For reliable scoring of the CGI, raters scored case vignettes before the study. Throughout, audiotapes of SCID and HAM-D interviews and of the medication-management sessions were audited by the coordinating center for quality and adherence to the guidelines specified in the operations manual.

Study Medications

Hypericum and matching placebo were provided by Lichtwer Pharma (Berlin, Germany); sertraline and matching placebo were provided by Pfizer Inc (New York, NY). The Lichtwer extract (LI-160) was selected for its well-characterized features and literature supporting its possible efficacy in depression. The extract was standardized to between 0.12% and 0.28% hypericin, and the entire supply came from one batch. The study was conducted under an investigational new drug application filed by the manufacturer.

Medications were given 3 times daily. During the run-in period, patients received placebo tablets in a single-blind fashion. At baseline, patients were randomly assigned to receive hypericum (900 mg/d), sertraline (50 mg/d), or placebo. Daily hypericum, sertraline, or placebo doses could be increased to 1200 mg, 75 mg, or placebo equivalent, respectively, after weeks 3 or 4 and to 1500 mg, 100 mg, or placebo equivalent at week 6 if the CGI-S score was 4 (moderately ill) or more at week 3, or 3 (mildly ill) or more at weeks 4 or 6. After week 8, those eligible to continue could re-
receive maximum daily doses of 1800 mg, 150 mg, or placebo equivalent, respectively. Medication was dispensed in blister packets in double-dummy fashion. Doses could be held or reduced for adverse effects. For insomnia, zolpidem (5 to 10 mg) was permitted up to twice weekly during weeks 1 and 2 and up to 6 times total during continuation.

**Efficacy End Points**
The prospectively defined primary efficacy measures were the change in the 17-item HAM-D total score from baseline to week 8 and the incidence of full response at week 8 or early study termination. Full response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved) and a HAM-D total score of 8 or less. Partial response was defined as a CGI-I score of 1 or 2, a decrease in the HAM-D total score from baseline of at least 50%, and a HAM-D total score of 9 to 12. Secondary end points comprised the GAF, CGI, BDI, and SDS scores.

After week 8, relapse was defined as a HAM-D score of 20 or more and a CGI-S score of 4 or more at 2 consecutive visits. Serious suicidal ideation or the development of psychosis also served as grounds for removal from the study and prompt clinical assessment.

**Safety Assessments**
Any symptom or sign that appeared or became worse after baseline was considered an adverse event. Adverse events were elicited and recorded by the study physician at each visit, based on patient interview and on a 44-item checklist completed by the patient and expanded from an earlier scale.20

**Compliance**
Patients were deemed noncompliant if they had taken less than 80% of the prescribed medication, according to pill counts at each follow-up visit.

**Statistical Analysis**
The principal comparison was between the hypericum and placebo groups. Sertraline served as an active comparator to evaluate the study's sensitivity. Sample-size calculations were based on detecting a difference in full-response rates at 8 weeks, assuming full-response rates of 55% for hypericum and 35% for placebo. Accordingly, a sample size of 336 patients (112 per group) was specified to ensure 85% power with a type I error rate of 5% (2-sided). The sample-size calculation assumed no interactions of treatment with site or sex, the blocking factors for randomization.

The primary analysis was according to assignment at randomization. However, a systematic review of all protocol deviations in patient enrollment, as indicated by the database, was undertaken before the study was unblinded, and patients who did not meet the HAM-D total score of at least 20 entry criteria (n = 2) were excluded from the efficacy analyses as recommended by the scientific advisors. These ineligibilities resulted from mistakes in summing the 17-item scores.

Treatment differences in full-response rates were assessed with Wald $\chi^2$ statistics from logistic regression, with fixed effects for treatment, site, sex, and baseline HAM-D total score. Treatment differences in the change in HAM-D total score from baseline to week 8 were evaluated through a random-coefficient regression model. The longitudinal scores at baseline and weeks 1 through 8 (all available acute-phase data) were modeled as a linear function of fixed effects for treatment, site, sex, study week (linear), and treatment by study week, with random intercept and slope over time for each patient. Under the assumptions of this model, tests of treatment differences for the change in HAM-D total score from baseline to week 8 are equivalent to tests of treatment differences in the linear trends or slopes with time.

These analyses on full response and change in the HAM-D total score were specified in the final protocol as primary in assessment of acute-phase efficacy. Secondary analyses included random-coefficient regression models on secondary outcomes as described above for HAM-D, similar modeling on primary and secondary outcomes but restricted to patients completing the acute phase (completer analysis), and analysis of covariance models on primary and secondary outcomes using the last available acute-phase measurement (last observation carried forward). The analysis-of-covariance models included effects for treatment, site, sex, and the respective baseline scores.

Among the 3 treatment comparisons, those of hypericum vs placebo and sertraline vs placebo were of interest a priori, and their $P$ values (2-sided) are presented. In addition, for efficacy measures, the nominal significance level for the hypericum vs sertraline contrast is noted in the text if $P < .05$ when the 3 treatment groups differed overall (2 df) using a type I error of .05.

Simple tests for treatment differences included $\chi^2$ and Fisher exact tests for categorical variables, Kruskal-Wallis/Wilcoxon-Mann-Whitney tests for ordinal and continuous measurements, and log-rank tests for time to events. These tests were applied to baseline characteristics, protocol deviations, adverse events, attrition, compliance, treatment beliefs, and maintenance of response during continuation. In addition, the nonparametric methods were used on the efficacy measures to substantiate results that rely on distributional assumptions. The consistency of the data with the parametric assumptions was checked for the primary analyses.

All analyses were performed with SAS version 6.12 software (SAS Institute Inc, Cary, NC). The PROC MIXED procedure was used for the longitudinal data models.

**RESULTS**
In all, 428 patients entered the run-in phase, and 340 were randomized (Figure 1). No differences were noted between treatment groups at baseline (Table 1). In addition, with regard to severity of depression, the numbers of patients judged to be mild, moderate, marked, and severe were 3, 261, 70, and 6, respectively, according to the CGIs. Baseline total HAM-D scores ranged from 18 to 33.
There were similar proportions of patients among the treatment groups discontinued before week 8: 27% for hypericum (n=31), 28% for placebo (n=32), and 29% for sertraline (n=32). Likewise, time to early discontinuation did not differ significantly (P = .91, log-rank test), although 17 of the 32 dropouts in the sertraline group (53%) occurred during the first 2 weeks vs 5 of 32 dropouts in the placebo group (16%) and 11 of 31 dropouts in the hypericum group (35%).

Of the 340 acute-phase subjects, 245 (72%) completed 8 weeks, 129 entered the continuation phase, and 79 completed continuation. There were no treatment differences in attrition during continuation. Nine of the 129 patients entering continuation did not meet response criteria. These patients and the 2 who were ineligible for the acute phase were excluded from efficacy analysis in the continuation phase.

The mean (SD) highest daily dose prescribed was 1299 (243) mg (95% confidence interval [CI], 1254-1344 mg) for hypericum and 75 (21) mg (95% CI, 71-79 mg) for sertraline during the acute phase and 1382 (284) mg (95% CI, 1292-1473 mg) for hypericum and 89 (32) mg (95% CI, 80-98 mg) for sertraline during continuation. Fewer patients in the sertraline group achieved the highest daily dose level during the acute phase (36% compared with 54% for hypericum and 54% for placebo; P = .005, Kruskal-Wallis test). Similar proportions of each treatment group required dose reductions during the acute phase because of adverse events (hypericum, 4%; placebo, 5%; and sertraline, 7%).

**Efficacy Outcomes**

The HAM-D total scores throughout the 8-week trial are summarized by treatment group in [Figure 2](#). The random-coefficient regression analysis on the longitudinal HAM-D total scores detected a downward linear trend with time (F1,263 = 565.2; P < .001) and gen-
eral differences in scores by site ($F_{12,328} = 4.56; P < .001$) and sex (lower for men; $F_{1,328} = 8.97; P = .003$). Linear trends with time did not differ significantly by treatment (hypericum vs placebo: $F_{3,265} = 0.30$ and $P = .59$; sertraline vs placebo: $F_{3,265} = 1.83$ and $P = .18$), and no interactions were found between treatment and site or sex. Model estimates for the mean (SE) change in HAM-D total score (week 8 minus baseline) were $-8.68 (0.68)$ for hypericum, $-9.20 (0.67)$ for placebo, and $-10.53 (0.72)$ for sertraline. According to the model estimates for the difference in slopes between sertraline and placebo and the variance estimate for the random slope coefficient, the sertraline effect size was 0.24.

Full response rates at acute-phase exit did not differ between placebo and either hypericum ($P = .21$) or sertraline ($P = .26$) (TABLE 2). Patients with a lower HAM-D total score at baseline had a higher rate of full response ($P = .002$), which did not differ by treatment group. No differences were noted by site or sex. No interactions were found for treatment by site, sex, or baseline HAM-D total score. The ordinal distribution of responses (full, partial, or none) differed significantly across treatments ($P = .04$, Kruskal-Wallis test), with more partial responders among the sertraline patients and more full responders among the placebo patients. Findings were similar for patients completing the acute phase, with percentages (full, partial, or no response) of 30.5%, 17.1%, and 52.4% for hypericum, 41.6%, 14.3%, and 44.0% for placebo, and 52.4% for hypericum; and frequent urination and swelling (hypericum) all were higher than those of placebo. Forgetfulness was less common with sertraline than with placebo. No serious adverse events occurred.

### Safety Evaluation

Hypericum and sertraline were associated with more acute-phase adverse events than placebo. TABLE 4 displays those that differed significantly. Analyses of data from the continuation phase yielded similar results. Rates of diarrhea, nausea, and sweating (sertraline); anorgasmia (sertraline and hypericum); and frequent urination and swelling (hypericum) all were higher than those of placebo. Forgetfulness was less common with sertraline than with placebo. No serious adverse events occurred.

#### Assessment of Blindness to Treatment

At the end of 8 weeks, the proportion of patients guessing their treatment correctly was 55% for sertraline, 29% for

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Table 3. Summary Measures of Acute-Phase Efficacy*

<table>
<thead>
<tr>
<th>Summary Measure†</th>
<th>Hypericum (n = 113)</th>
<th>Placebo (n = 116)</th>
<th>Sertraline (n = 109§)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D total score (week 8−baseline)</td>
<td>−8.68 (0.68) [−10.01 to −7.35]</td>
<td>−9.20 (0.67) [−10.51 to −7.89]</td>
<td>−10.53 (0.72) [−11.94 to −9.12]</td>
<td>.59 .18</td>
</tr>
<tr>
<td>GAF score (week 8−baseline)</td>
<td>12.31 (1.22) [9.92 to 14.70]</td>
<td>11.76 (1.19) [9.43 to 14.09]</td>
<td>14.16 (1.27) [11.67 to 16.65]</td>
<td>.75 .17</td>
</tr>
<tr>
<td>BDI total score (week 8−baseline)</td>
<td>−7.84 (0.91) [−6.92 to −6.06]</td>
<td>−6.83 (0.90) [−5.89 to −5.07]</td>
<td>−8.75 (0.98) [−10.61 to −6.89]</td>
<td>.43 .15</td>
</tr>
<tr>
<td>SDS total score (acute exit−baseline)</td>
<td>−3.34 (0.69) [−4.69 to −1.99]</td>
<td>−3.19 (0.68) [−4.52 to −1.86]</td>
<td>−4.01 (0.70) [−5.38 to −2.64]</td>
<td>.88 .39</td>
</tr>
<tr>
<td>CGI-S score (week 8−baseline)</td>
<td>−1.07 (0.12) [−1.31 to −0.83]</td>
<td>−1.19 (0.12) [−1.43 to −0.94]</td>
<td>−1.47 (0.12) [−1.71 to −1.23]</td>
<td>.48 .11</td>
</tr>
<tr>
<td>CGI-I score (week 8)</td>
<td>2.50 (0.11) [2.28 to 2.72]</td>
<td>2.45 (0.11) [2.23 to 2.67]</td>
<td>2.04 (0.12) [1.80 to 2.28]</td>
<td>.75 .02</td>
</tr>
</tbody>
</table>

*See Table 1 for definitions of the scoring tools. CGI-S indicates Clinical Global Impressions severity score; CGI-I, Clinical Global Impressions improvement score.
†Values are linear model estimates and P values adjusted for site and sex. HAM-D total score, GAF score, BDI total score, and CGI-S score statistics were based on modeling the longitudinal measures at week 0 and weeks 1 through 8 as a linear function of site, sex, treatment, week, and treatment by week, with a random intercept and slope over time for each subject. A similar model was used for CGI-I, but there was no baseline measurement in the longitudinal stream. The SDS was measured at baseline and acute-phase exit. Change was modeled as a linear function of the baseline measure, site, sex, and treatment. The means for CGI-I and SDS are least square.
‡Lower scores denote greater improvement, except for the GAF.
§Two sertraline patients had HAM-D scores below the cutoff of 20 required for enrollment. These patients were excluded from efficacy analysis.

Table 4. Adverse Events That Differed Significantly by Treatment During the Acute Phase*

<table>
<thead>
<tr>
<th>Event, No. (%), Hypericum (n = 112‡) vs Placebo (n = 116) vs Sertraline (n = 111)</th>
<th>Hypericum vs Placebo</th>
<th>Sertraline vs Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea 23 (21) 22 (19) 42 (38)</td>
<td>.81 003</td>
<td>.002</td>
<td>.003</td>
</tr>
<tr>
<td>Nausea 21 (19) 24 (21) 41 (37) 78 .02</td>
<td>.04</td>
<td>.04</td>
<td>.06</td>
</tr>
<tr>
<td>Anorgasmia 28 (25) 16 (14) 35 (32)</td>
<td>.04</td>
<td>.002</td>
<td>.003</td>
</tr>
<tr>
<td>Forgetfulness 28 (25) 26 (22) 13 (12) 75 .04</td>
<td>.003</td>
<td>.003</td>
<td>.90</td>
</tr>
<tr>
<td>Frequent urination 30 (27) 13 (11) 23 (21)</td>
<td>.003 06</td>
<td>.003</td>
<td>.90</td>
</tr>
<tr>
<td>Sweating 20 (18) 14 (12) 32 (29)</td>
<td>.02</td>
<td>.003</td>
<td>.90</td>
</tr>
<tr>
<td>Swelling 21 (19) 9 (8) 9 (8)</td>
<td>.02</td>
<td>.003</td>
<td>.90</td>
</tr>
</tbody>
</table>

*No attributions made with respect to the relationship to treatment.
† Wilcoxon-Mann-Whitney test for difference in distribution of severity between treatments (absent, mild, moderate, or severe).
‡Excluding 1 patient who lacked a symptom report.

Hypericum, and 31% for placebo (P = .02 for differences between treatment groups). Correct guesses for clinicians totaled 66% for sertraline, 29% for hypericum, and 36% for placebo (P = .001 for differences between treatment groups). The change (mean) in HAM-D total score from baseline to week 8 did not differ for patients who were in the sertraline group and either had guessed the correct treatment (−11.6; 95% CI, −13.1 to −10.1) or had not (−11.9; 95% CI, −13.9 to −9.9).

COMMENT

As with 2 other trials,8,9 we have found no evidence for a superior effect of hypericum relative to placebo. Neither hypericum nor sertraline could be differentiated from placebo on the primary efficacy measures. Although the efficacy of sertraline was demonstrated on the secondary CGI-I measure, resulting on average in much improvement, hypericum had no efficacy on any measure. Although not designed to compare sertraline with hypericum, the study showed superiority of sertraline on the CGI-I. Responders who entered continuation treatment maintained their improvement equally in each treatment group.

The overall effect size for sertraline on the HAM-D total score was 0.24, which is consistent with reported effect sizes for standard antidepressants,21,22 while on the CGI-I, it was 0.41. These findings can also be observed in the context of 3 other sertraline studies23-25 that yielded effect sizes of 0.31, 0.33, and 0.45 for the drug relative to placebo on the HAM-D change from baseline to last observation in all study patients.

Adverse effects for sertraline were consistent with its profile, while for hypericum, more frequent anorgasmia, swelling, and urination were noted relative to placebo, although these were mild and the multiple comparisons may have produced spurious associations.

When a new treatment cannot be distinguished from placebo, it is important to determine whether a drug of known efficacy would have been proven effective in that sample. Failure of established antidepressants to show such superiority occurs in up to 35% of trials,26,27 which illustrates the difficulties plaguing randomized placebo-controlled trials in this population. We should, therefore, consider some of the factors that might have contributed to our results. One concern is a high placebo response rate, but this was not unusually high in our sample and is therefore an unlikely explanation.

Addressing specific issues relevant to sertraline, we note the following. Although a dose-effect relationship within the therapeutic range (30-200 mg/d) has not been demonstrated,28-30 one may wonder whether the study dose limitation (up to 100 mg/d in the 8-week trial)
was too restrictive and whether even the highest prescribed dose was administered for an inadequate duration. The protocol dose regimen was chosen on the basis of extensive discussion by all parties concerned in the study design and oversight as the best compromise for ensuring effective treatment while minimizing the incidence of dose-related adverse events. In fact, only 36% of sertraline patients had their dose maximized to 100 mg/d compared with 54% for hypericum or placebo. There were more partial responders to sertraline (23.9%) than to hypericum (14.2%) or placebo (11.2%; \( P = .03 \)). Analyses of the sertraline patients eligible for a dose increase revealed no association between lack of dose increase and presence of adverse events. Thus, it appears that, in this trial, clinicians tended not to increase the sertraline dose for patients with partial response, electing instead to allow more time with the same dose. On the matter of dosing, if any protocol bias existed at all, it would favor hypericum, which could be dosed to the maximum of its permissible range, whereas the maximum permitted dose of sertraline was only 50% of its highest recommended amount.

The study was adequately powered to detect moderate effect sizes (ie, at least 0.40). The observed sertraline effect size was small (0.24) on the HAM-D total score and moderate (0.41) on the CGI-I; hence, the lack of statistical significance on the primary outcome measure.

For hypericum, 2 issues are relevant. Although the hyperforin content of this batch was 3.1%, the formulation was not standardized to hyperforin, which has been suggested by some as an important active ingredient. \(^{31,32} \) Hypericum may be most effective in less severe major depression (eg, HAM-D scores <20), but further study of this possibility needs to be conducted according to the standard diagnostic criteria.

From a methodological point of view, this study can be considered an example of the importance of including inactive and active comparators in trials testing the possible antidepressant effects of medications. In fact, without a placebo, hypericum could easily have been considered as effective as sertraline, as some studies have done with respect to active antidepressants. \(^2,3 \) On the other hand, without sertraline as an active comparator, the results would have been interpreted as evidence for the lack of efficacy of hypericum, without consideration of the possibility that a low assay sensitivity of the trial might have contributed to the finding.

An increasing number of studies have failed to show a difference between active antidepressants and placebo. \(^33,34 \) Many of the presumed factors underlying this phenomenon were carefully attended to in this study, eg, adherence to quality control by rater training, treatment adherence monitoring, inclusion of experienced investigators, and carefully defined entry criteria. Despite all of this, sertraline failed to separate from placebo on the 2 primary outcome measures.

Besides the limitations already discussed, our study tested one particular hypericum extract, although many are marketed. Because the active ingredient of hypericum is unclear, it is difficult to extrapolate clinical data from one extract to other products. The extract we tested is among the best characterized, however, and is the one for which the most efficacy data are available. Thus, we believe that the results can be considered relevant to other hypericum-standardized hypericum extracts.

Because hypericum is widely available, it is likely to be used for milder depression, but its use in this population cannot be supported until trials show clear evidence of efficacy. According to available data, hypericum should not be substituted for standard clinical care of proven efficacy, including antidepressant medications and specific psychotherapies, for the treatment of major depression of moderate severity.

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