The Effectiveness of St. John's Wort in Major Depressive Disorder: A Naturalistic Phase 2 Follow-Up in Which Nonresponders Were Provided Alternate Medication

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Background: A continuation study of an extract of St. John's wort *(Hypericum perforatum)* for depression was performed in follow-up to an acute study that found no significant difference between St. John's wort extract and placebo.

Method: Seventeen subjects with DSM-IV–defined major depressive disorder who responded to St. John's wort extract in the acute-phase study (phase 1) were continued on double-blind treatment with the same preparation for 24 weeks. Ninety-five subjects who did not respond to either St. John's wort or placebo were treated with an antidepressant for 24 weeks.

Results: During antidepressant treatment, mean scores on the Hamilton Rating Scale for Depression for phase 1 nonresponders decreased significantly ($p < .0001$), with no significant difference between St. John's wort nonresponders and placebo nonresponders. Of the 17 subjects continued on treatment with St. John's wort extract, 5 (29.4%) relapsed.

Conclusions: The subjects who did not respond to St. John's wort extract or placebo in phase 1 were, by and large, not resistant to antidepressant treatment. This suggests that the lack of efficacy found by Shelton et al. in the acute-phase study was unlikely to be the result of a high proportion of treatment-resistant subjects.

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St. John's wort *(Hypericum perforatum)* has been used for centuries for various medical conditions, and its effects on depression have been studied extensively in the United States and Europe. It is especially popular in Germany, where alternative therapies are often used in medical practice.[1] One meta-analysis of 23 randomized trials[2] concluded that St. John's wort was superior to placebo and comparable to standard antidepressants for mild to moderate depression. However, that report and other reviews[3,4] note that many of the studies analyzed had serious methodological flaws, such as lack of standardized diagnoses and rating instruments, short duration, inexperienced investigators, small sample sizes, and lack of a placebo control. Recently, a double-blind, placebo-controlled, random-assignment, multicenter study[5] in France of 375 adult outpatients with mild to moderate major depression found a significantly greater reduction in total score on the 17-item Hamilton Rating Scale for Depression (HAM-D) for patients treated with the St. John's wort extract WS 5570 than for those treated

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with placebo. Significantly more patients in the St. John's wort group met criteria for treatment response or remission in this 6-week study.

Two multicenter, random-assignment, double-blind, placebo-controlled trials of St. John's wort extract for depression[1,6] have been conducted recently in the United States. Neither found St. John's wort to be an effective antidepressant. Shelton et al.[1] studied 200 adult outpatients with major depressive disorder (baseline HAM-D score of ≥ 20). Patients received either placebo for 8 weeks or St. John's wort extract, 900 mg/day, for 4 weeks, increased to 1200 mg/day over the next 4 weeks if no response was shown.

At the end of 8 weeks, there were no significant differences between the groups' scores on the HAM-D or the secondary measures: the Beck Depression Inventory, the Hamilton Rating Scale for Anxiety, the Global Assessment of Functioning scale, and the Clinical Global Impressions-Severity of Illness and Clinical Global Impressions-Improvement scales (CGI-S and CGI-I). Response rates in the intention-to-treat (ITT) analysis were 26.5% for St. John's wort and 18.6% for placebo (not statistically significant). (St. John's wort produced a significantly higher but modest remission rate: 14.3% vs. 4.9%). St. John's wort extract was well tolerated: more than 80% of subjects in each group completed the trial, and only 1% discontinued due to adverse effects. Headache was the only adverse effect occurring more frequently with St. John's wort than with placebo. The results from this study do not support significant antidepressant or antianxiety effects for St. John's wort when compared with placebo in depressed outpatients.

The second study[6] involved 340 outpatients with major depression and a baseline score on the HAM-D of ≥ 20. Subjects received the *H perforatum* extract LI-160, 900 to 1500 mg/day; sertraline, 50 to 100 mg/day; or placebo for 8 weeks. One hundred twenty-nine subjects who responded to acute treatment entered a continuation phase in which they continued to receive blinded treatment for another 18 weeks. At 8 weeks, neither sertraline nor *H perforatum* was significantly different from placebo on HAM-D or CGI scores. On average, sertraline-treated subjects showed much improvement in their scores on the secondary CGI-I measure, but there were no trends suggesting efficacy for *H perforatum* on any measure. Participants from each treatment group who entered the continuation phase maintained their improvement equally. These results also fail to support the efficacy of *H perforatum* in moderately severe major depressive disorder.

We conducted a follow-up study of patients in the Shelton et al. study[1] to shed more light on the role of St. John's wort in depression. Subjects who responded to treatment with St. John's wort extract were continued on blinded treatment for 24 weeks. Nonresponders, after a 1-week washout period, were treated with various antidepressants based on clinician's choice.

METHOD

Study Design

The acute phase trial was conducted at 11 different academic medical centers between November 1998 and January 2000. All patients provided written informed consent as approved by the institutional review board for each participating facility. The participants were physically healthy male or female outpatients, at least 18 years of age, with single-episode or recurrent major depressive disorder without psychotic features according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[7] of at least 4 weeks' duration. Participants had a score of ≥ 20 on the HAM-D[8] at baseline, defining a depression of at least moderate severity. Following the screening visit, eligible subjects were given a 1-week placebo run-in, followed by a baseline evaluation and randomization to either a standardized St. John's wort extract (Lichtwer Pharma, LI-160; Berlin, Germany) or placebo for an 8-week, double-blind treatment period.

For the purpose of this analysis, response was defined as a HAM-D score ≤ 12 and a CGI-I score of ≤ 2. (Those with a baseline HAM-D score of ≤ 22 also had to have more than a 50% reduction in the HAM-D score from baseline.) Participants considered to have responded during the first phase of double-blind treatment were told whether they were taking St. John's wort extract or placebo. Those taking St. John's wort extract could choose to continue open-label treatment with St. John's wort for up to 6 months. St. John's wort responders who decided to continue were provided with St. John's wort extract and followed every 2 months until week 24. Any person in this group who relapsed was referred for appropriate follow-up treatment. Acute-phase responders to placebo were informed that they had responded to placebo by a clinician independent from the original study. These persons were referred for treatment as needed and were advised to seek treatment should depressive symptoms recur.

Nonresponders (N = 95) in either treatment group (i.e., patients with a total score of > 12 on the HAM-D and a CGI-I score of > 2) who completed 8 weeks of double-blind treatment were discontinued from study treatment. One week later, at the end of week 9 (i.e., postwashout), those subjects were evaluated and treated openly with a marketed antidepressant of the investigator's choice for 24 weeks. Treatment could be discontinued or changed at any time at the discretion of the investigator in cases of worsening depression or the emergence of suicidal ideation (Tables 1–3 give details on which medications were used).

Statistical Methods

The primary efficacy analysis was a random coefficient regression model that examined differences in linear rate of change in HAM-D total scores over the course

Table 1. Number of Antidepressants Received by Nonresponders to St. John's Wort or Placebo for Depression During Continuation Phase

No. of Medications	N	% of Total Subjects
1	63	70.8
2	19	21.4
3	4	4.5
4	1	1.1
5	2	2.2
NA	6	6.3

Abbreviation: NA = not available.

Table 2. First Medication Received by Nonresponders to St. John's Wort or Placebo for Depression During Continuation Phase

Medication	Receiving as First Medication, N (%)	Dose, mg/day, Mean (SD)	Range, mg/day
Citalopram	11 (12.4)	28.2 (18.9)	10–60
Lorazepam	1 (1.1)	1.0 (NA)	
Fluvoxamine	1 (1.1)	12.0 (NA)	
Nortriptyline	1 (1.1)	75.0 (NA)	
Paroxetine	11 (12.4)	20.9 (8.6)	10–40
Fluoxetine	19 (21.3)	25.0 (12.8)	10–50
Mirtazapine	1 (1.1)	15.0 (NA)	
Nefazodone	2 (2.2)	200.0 (0)	
Trazodone	2 (2.2)	25.0 (0)	
Venlafaxine	4 (4.5)	49.7 (21.9)	37.5–75
Bupropion	7 (7.9)	150.0 (0)	
Zolpidem	1 (1.1)	5.0 (NA)	
Sertraline	28 (31.5)	92.9 (56.9)	50–250

Abbreviation: NA = not applicable.

of the 2nd phase (weeks 9 through 32) between nonresponders who received St. John's wort extract and those who received placebo during phase 1. This model measures each patient's deviation from the population average change over time and includes a random intercept and slope for each subject. For this model, all available data (baseline [week 9] and weeks 10, 12, 16, 20, 24, 28, and 32) were used. The model (performed using SAS Version 6.12, PROC MIXED; SAS Worldwide; Cary, N.C.) estimated fixed effects for treatment and site. Population-averaged estimates for the linear trend over time, as well as the linear trend over time by treatment, were produced by this model. The treatment-by-time interaction tested the linear slope differences between treatment groups. The treatment-by-site interaction was not significant ($F = 1.8$, $df = 6,155$; $p > .10$) and was, therefore, dropped from the model. This evaluation was an ITT analysis that included all patients who were randomly assigned to treatment, even those patients without a postbaseline assessment. We pooled the sites with a low number of patients during phase 2 (all sites with 5 patients or fewer were pooled into 1) and adjusted for site in our analysis, which was in fact significant ($F = 14.1$, $df = 6,155$; $p < .0001$).

Secondary analyses also examined HAM-D score response and remission rates. Response was defined in the same way as it had been defined for phase 1: a HAM-D score of ≤ 12, at least a 50% improvement in HAM-D score from phase 2 baseline, and a CGI-I score of ≤ 2. Remission was defined as a HAM-D score of ≤ 7. Response and remission rates for the completer sample (those with a week 32 assessment) were also calculated. Phase 1 treatment differences in phase 2 response and remission rates were examined using the Cochran-Mantel-Haenszel test (site as stratification variable). Baseline was chosen as both the phase 1 baseline (week 0) and phase 2 baseline (week 9), which results, therefore, in 2 measures of HAM-D score response. Relapse during phase 2 was defined, among those patients who had achieved responder status, as an increase in HAM-D total score to ≥ 14.

Table 3. Second Medication Received by Nonresponders to St. John's Wort or Placebo for Depression During Continuation Phase

Medication	Receiving as Second Medication, N (%)	Dose, mg/day, Mean (SD)	Range, mg/day
Citalopram	2 (7.7)	40.0 (14.1)	30–50
Liothyronine[a]	2 (7.7)	37.5 (17.7)	25–50
Fluvoxamine	1 (3.9)	50.0 (NA)	
Nortriptyline	1 (3.9)	150.0 (NA)	
Paroxetine	1 (3.9)	30.0 (NA)	
Fluoxetine	3 (11.5)	40.0 (38.5)	20–80
Mirtazapine	2 (7.7)	30.0 (0)	
Nefazodone	1 (3.9)	600.0 (NA)	
Trazodone	1 (3.9)	50.0 (NA)	
Venlafaxine	4 (15.3)	74.7 (37.5)	37.5–112.5
Bupropion	4 (15.3)	150.0 (50)	100–200
Sertraline	4 (15.3)	48.8 (36.6)	20–100

[a]Shown as μg/day.
Abbreviation: NA = not applicable.

RESULTS

Phase 2 Sample Characteristics

In the original trial, 200 patients were randomly assigned to either St. John's wort (N = 98) or placebo (N = 102). Of the 200 subjects, 158 (79%) completed phase 1. Forty-one (26%) were classified as responders and 117 (74%) as nonresponders. Of the nonresponders, 98 (84%) were willing to participate in the second phase of the study, and 95 (81%) provided information during phase 2. (Table 4 shows demographic and clinical characteristics of the nonresponders.) Of the 41 responders, 24 (59%) received St. John's wort during phase 1, 17 (71%) of whom provided information during phase 2. (Table 5 shows demographic and clinical characteristics of St. John's wort phase 1 responders at baseline.)

Primary Efficacy Analysis

The random coefficient regression model, examining the rate of change in HAM-D scores for phase 1 nonresponders over the 24 weeks of the phase 2 open-label treatment, revealed a significant time effect ($F = 155.3$, $df = 1,37$; $p < .0001$). This indicates that the patients who

Table 4. Demographic and Clinical Characteristics of Nonresponders to St. John's Wort or Placebo for Depression During Phase 1 Who Were Willing to Participate During Phase 2

Patient Variable	St John's Wort (N = 43)	Placebo (N = 55)	Total (N = 98)
Female, %	60.5	72.7	67.5
Age, mean ± SD, y	40.8 ± 12.4	42.3 ± 14.3	41.6 ± 13.5
Ethnicity, white, %	83.7	85.5	84.7
Marital status, %			
Married or cohabiting	32.6	40.0	36.7
Single	39.5	27.3	32.7
Widowed	0	3.6	2.0
Divorced/separated	27.9	29.1	28.6
Depression diagnosis, %			
Single episode	32.6	37.0	35.0
Recurrent	67.4	63.0	65.0
Melancholic	40.5	46.3	43.8
Age at onset of initial MDE, mean ± SD, y	29.3 ± 14.8	28.6 ± 15.8	28.9 ± 15.3
Duration of current MDE, mean ± SD, y	2.1 ± 3.4	2.9 ± 4.0	2.5 ± 3.8

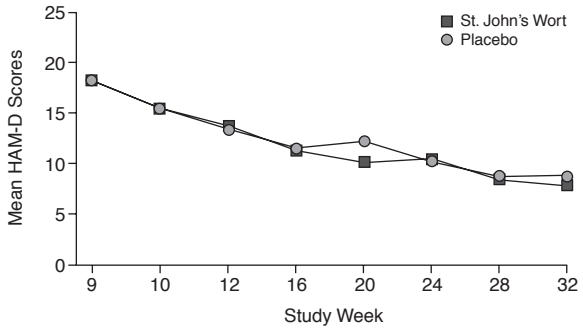
Abbreviations: MDD = major depressive disorder, MDE = major depressive episode.

Table 5. Demographic and Clinical Characteristics of Phase 1 Responders to St. John's Wort at Baseline

Patient Variable	Total (N = 24)
Female, %	66.7
Age, mean ± SD, y	44.4 ± 13.7
Ethnicity, white, %	91.7
Marital status, %	
Married or cohabiting	37.5
Single	41.7
Widowed	4.1
Divorced/separated	16.7
Depression diagnosis, %	
Single episode	29.2
Recurrent	70.8
Melancholic	33.3
Age at onset of initial MDE, mean ± SD, y	32.6 ± 17.3
Duration of current MDE, mean ± SD, y	1.3 ± 1.4

Abbreviations: MDD = major depressive disorder, MDE = major depressive episode.

Figure 1. Hamilton Rating Scale for Depression (HAM-D) Scores During Phase 2 for Phase 1 Nonresponders by Phase 1 Study Group



did not respond to St. John's wort extract or placebo in the initial phase of the study *did* respond when treated with an antidepressant medication afterward. However, whether prior treatment was with St. John's wort or placebo had no effect on the outcome of subsequent antidepressant treatment (Figure 1). The mean (SD) baseline (week 9 of the original study) HAM-D score in nonresponders who had taken St. John's wort extract in phase 1 was 18.3 (5.3) and in nonresponders who had taken placebo in phase 1 was 18.1 (4.5) (Table 6). The mean (SD) endpoint (week 32) score was 7.9 (5.8) in the former and 8.8 (6.2) in the latter group. Therefore, there was no significant effect of prior treatment group ($F = 0.7$, $df = 1,352$; $p = .42$) or a time-by-treatment interaction ($F = 0.04$, $df = 1,37$; $p = .8$).

Secondary Efficacy Analyses

In the ITT sample of nonresponders to phase 1, there was no significant difference in last-observation-carried-forward (LOCF) phase 2 response rates compared with week 0 or week 9 (baseline of phase 2). Of subjects who failed to respond to St. John's wort extract in phase 1, 25 (61.0%) of 41 achieved a response to marketed antidepressant medication in phase 2 relative to week 0, whereas among subjects who failed to respond to placebo in phase 1, 31 (57.4%) of 54 achieved a response to antidepressant medication in phase 2 (Cochran-Mantel-Haenszel $\chi^2 = 0.13$, $df = 1$, $p = .72$). There was no significant difference in LOCF response rates with reduction compared with week 9 (phase 1 St. John's wort: 17/41 [41.5%]; phase 1 placebo: 23/54 [42.6%]) (Cochran-Mantel-Haenszel $\chi^2 = 0.001$, $df = 1$, $p = .97$). Of the 40 phase 2 responders, 5 subsequently relapsed (phase 1 St. John's wort: 4/17 [23.5%]; phase 1 placebo: 1/23 [4.3%]) (Fisher exact test $p = .14$, which indicates no difference between the 2 phase 1 treatment groups).

Among the phase 1 nonresponders, there also was no significant difference in phase 2 LOCF remission rates (phase 1 St. John's wort: 15/41 [36.6%]; phase 1 placebo:

Table 6. Hamilton Rating Scale for Depression Scores During Phase 2 by Phase 1 Study Group for All Phase 1 Nonresponders to St. John's Wort or Placebo for Depression

	Phase 1					
	St. John's Wort			Placebo		
Week	N	Mean	SD	N	Mean	SD
9	36	18.3	5.3	50	18.1	4.5
10	35	15.5	5.3	46	15.3	5.7
12	35	13.8	6.5	49	13.3	6.7
16	33	11.2	5.9	43	11.5	6.5
20	26	10.2	6.4	34	12.2	6.6
24	24	10.5	6.9	35	10.2	5.9
28	17	8.5	4.4	24	8.6	6.4
32	28	7.9	5.8	38	8.8	6.2

24/54 [44.4%]) (Cochran-Mantel-Haenszel $\chi^2 = 0.38$, df = 1, p = .54). Pooled response rate compared with week 0 was 56/95 (59.0%). Overall pooled response rate compared with week 9 was 40/95 (42.1%), and pooled remission rate was 39/95 (41.1%).

In the completer sample, there was no significant difference in week 32 response rates with reduction compared with week 0: phase 1 St. John's wort: 22/28 (78.6%); phase 1 placebo: 27/38 (71.1%) (Cochran-Mantel-Haenszel $\chi^2 = 0.73$, df = 1, p = .39). There was not a significant difference in week 32 response rates with reduction compared with week 9: phase 1 St. John's wort: 15/28 (53.6%); phase 1 placebo: 21/38 (55.3%) (Cochran-Mantel-Haenszel $\chi^2 = 0.001$, df = 1, p = .97). There was not a significant difference in week 32 remission rates: phase 1 St. John's wort: 13/28 (46.4%); phase 1 placebo: 21/38 (55.3%) (Cochran-Mantel-Haenszel $\chi^2 = 0.41$, df = 1, p = .52). Pooled response rate for completers compared with week 0 was 49/66 (74.2%), whereas the pooled response rate compared with week 9 was 36/66 (54.6%). Pooled remission rate versus week 9 was 34/66 (51.5%).

Of the 17 patients who experienced response with St. John's wort extract during phase 1 and who continued into phase 2 follow-up, 5 (29.4%) experienced a relapse during phase 2, and 3 patients (17.6%) experienced adverse events during phase 2. These included 2 occurrences of diarrhea, 1 occurrence of weight loss, 1 occurrence of dry skin, and 1 occurrence of intermittent bruxism.

DISCUSSION

Both groups—the nonresponders to placebo during phase 1 and the nonresponders to St. John's wort extract—had a statistically significant increase in response during the continuation phase of treatment. This suggests, therefore, that the Shelton et al. study[1] did not contain a disproportionate treatment-resistant population. The secondary analyses confirm the primary analysis: There was no difference in the second phase between patients originally assigned to St. John's wort and those who took placebo.

From our acute-phase data, we found little "signal" of therapeutic efficacy for St. John's wort in depression. Results from our naturalistic follow-up, that most nonresponder subjects responded to marketed antidepressants, support the null finding of our previous study by showing the lack of treatment resistance. To be sure, 12 (71%) of 17 patients who responded to St. John's wort in phase 1 continued to respond to the herb for the 24 weeks of continuation treatment. This finding might suggest that a subpopulation among patients with major depressive disorder will achieve and maintain response to St. John's wort, although a placebo response cannot be ruled out.

This study is limited by its naturalistic follow-up design and by the relatively few patients who continued on St. John's wort treatment. Also, the homogeneity of the sample limits the generalizability of our findings. The participants were outpatients from tertiary care clinics in academic medical centers and were not necessarily seeking treatment with herbal products. Patients who are from other health care environments, are less severely ill, or are interested in alternative treatments might respond differently.

The literature on St. John's wort continues to be confusing, but there has been a recent trend from large, rigorous trials toward negative results, particularly in outpatients with moderate to severe depression. The role of St. John's wort in treating depression remains a subject of controversy.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), liothyronine (Triostat and Cytomel), mirtazapine (Remeron), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

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