An Open-Label Trial of St. John's Wort (*Hypericum perforatum*) in Obsessive-Compulsive Disorder

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Background: Recent interest in and evidence for the efficacy of St. John's wort (*Hypericum perforatum*) for the treatment of mild-to-moderate depression has led to speculation about its efficacy in other disorders. *Hypericum*'s mechanism of action is postulated to be via inhibition of the synaptosomal uptake of serotonin. As such, there is a suggestion that *Hypericum* may be effective for obsessive-compulsive disorder (OCD).

Method: Twelve subjects were evaluated with a primary DSM-IV diagnosis of OCD of at least 12 months' duration. Treatment lasted for 12 weeks, with a fixed dose of 450 mg of 0.3% hypericin (a psychoactive compound in *Hypericum*) twice daily (extended-release formulation). Weekly evaluations were conducted with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Patient Global Impressions of Improvement Scale, and the Clinical Global Impressions of Improvement scale (CGI) and monthly evaluation with the Hamilton Rating Scale for Depression.

Results: A significant change from baseline to endpoint was found, with a mean Y-BOCS change of 7.4 points ($p = .001$). Significant change occurred at 1 week ($p = .020$) and continued to increase throughout the trial. At endpoint, 5 (42%) of 12 were rated "much" or "very much improved" on the clinician-rated CGI, 6 (50%) were "minimally improved," and 1 (8%) had "no change." The most common side effects reported were diarrhea (N = 3) and restless sleep (N = 2).

Conclusion: Significant improvement was found with *Hypericum*, with a drop-in Y-BOCS score similar to that found in clinical trials. The fact that a significant change was found as early as 1 week into treatment suggests a possible initial placebo response, although improvement grew larger over time. Results warrant a placebo-controlled study of *Hypericum* in OCD.

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Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 1.2% to 2.4%.[1] Both cognitive-behavioral therapies and medications have proved to be effective treatments.[2] The realization that clomipramine, a potent serotonin reuptake inhibitor (SRI) tricyclic antidepressant (TCA), is an effective treatment for OCD while less serotonergic TCAs are not has contributed to the serotonin hypothesis of OCD.[3] Further support for the importance of serotonin in OCD comes from the double-blind, placebo-controlled trials of fluoxetine, fluvoxamine, paroxetine, and sertraline that found each to be effective treatments for OCD.[2,4] Unfortunately, even with adequate dose and duration of medications, nonresponse or partial response is the rule.[5] In addition, the likelihood of side effects with clomipramine and with the selective serotonin reuptake inhibitors (SSRIs) prompts the search for better-tolerated compounds (e.g., dropout rates in the multicenter trials of fluoxetine, fluvoxamine, sertraline, and paroxetine were 23%, 24%, 27%, and 20%, respectively).[2,4]

Recently, there has been considerable worldwide interest in St. John's wort (*Hypericum perforatum*) as a treatment for mild-to-moderate depression. To date, 23 randomized trials suggest that *Hypericum* is more effective than placebo for the treatment of outpatients with mild-to-moderate depression.[6] In addition, *Hypericum* is very well tolerated, with mild side effects observed in only 2.5% of cases in a large (3250 patients) drug monitoring study.[7]

Hypericum's postulated mechanisms of action have been many and have varied over time, with the most recent being via inhibition of the synaptosomal uptake of serotonin. In a study by Müller and colleagues,[8] *Hypericum* extract weakly inhibited the activities of A and B monoamine oxidases, but strongly inhibited serotonin, dopamine, and norepinephrine reuptake into the synapse (approximately 2 μg/mL). Subchronic treatment of rats

led to a significant down-regulation of β-receptors and a significant up-regulation of serotonin-2 ($5\text{-}HT_2$) receptors in the frontal cortex. Perovic and Müller[9] found a 50% inhibition (IC_{50} value) of serotonin uptake by rat synaptosomes at a concentration of 6.2 μg/mL. Because of the potential for serotonin uptake inhibition, *Hypericum* may be effective for OCD.

To date, there have been no open or controlled trials of *Hypericum* in OCD. However, one case report[10] describes a patient with "significant obsessional (worry) and compulsive (cleaning) who started on St. John's wort, 300 mg of 3% *Hypericum* twice daily, and reported significant improvement." In addition, questions regarding the use of *Hypericum* in OCD have been raised by numerous patients with OCD and their families (Maggie Baudhuin, M.S., oral communication, Obsessive Compulsive Information Centers, Dec. 10, 1997). The current study examined the safety and efficacy of a standard preparation of *Hypericum perforatum* in the treatment of OCD.

METHOD

This was a 12-week, open-label study. Thirteen subjects (4 men, 9 women) with a primary DSM-IV diagnosis of OCD of at least 12 months' duration were recruited. The mean ± SD age was 39.5 ± 12.7 years (range, 21.3–64.3 years). Subjects needed a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale[11,12] (Y-BOCS) to participate and were excluded if their Hamilton Rating Scale for Depression[13] (HAM-D) score was greater than 13. Subjects were also excluded if they had a primary diagnosis of major depression, dysthymia, panic disorder, social phobia, schizophrenia, schizoaffective disorder, bipolar disorder, posttraumatic stress disorder, alcohol or other substance abuse or dependence in the previous 6 months, vascular dementia, primary degenerative dementia of the Alzheimer's type, or personality disorder likely to interfere with participation in the study. None of the subjects had any of these disorders as a current secondary diagnosis, but 3 patients had a prior history of major depression. Subjects with a serious or unstable medical illness were also excluded. Subjects were required to have discontinued monoamine oxidase inhibitors (MAOIs), TCAs, SSRIs, venlafaxine, nefazodone, and bupropion a minimum of 14 days prior to entering this study; those taking fluoxetine required a 5-week washout period. Five of 12 subjects had previously failed to respond to a trial with an SSRI (3 with fluvoxamine [300 mg/day, 8 weeks], 1 with sertraline [100 mg/day, 4 weeks], 1 with fluoxetine [60 mg/day, 12 weeks]). All subjects signed informed consent documents after study procedures were explained.

Treatment lasted for 12 weeks, with a fixed dose of 450 mg of 0.3% hypericin (a psychoactive compound in *Hypericum*) twice daily (extended-release formulation).

Table 1. Weekly Yale-Brown Obsessive Compulsive Scale (Y-BOCS) Scores and Change From Baseline (mean ± SD)

	Y-BOCS Score		Change From Baseline		
Week	Mean	SD	Mean	SD	p Value
Baseline	21.42	4.10			
1	18.91	5.82	2.09	2.51	.020
2	17.83	5.92	3.58	2.81	.001
3	16.91	6.30	4.18	4.12	.007
4	17.91	6.80	4.00	4.36	.012
5	15.11	5.04	4.56	4.03	.010
6	16.18	7.80	5.18	5.34	.009
7	13.80	7.05	6.80	4.18	.001
8	15.18	7.01	5.82	4.45	.001
9	13.60	7.37	6.60	5.78	.006
10	12.88	9.03	8.50	5.58	.004
11	12.60	8.02	8.00	5.64	.002
12	13.27	7.46	7.73	5.73	.001
Endpoint[a]	14.00	7.54	7.42	5.57	.001

[a]Last postbaseline observation carried forward.

Weekly evaluations were conducted with the Y-BOCS, Patient and Clinical Global Impressions of Improvement (PGI; CGI),[14] CGI-Severity (CGI-S[14]; range from 1 "normal" to 7 "among the most severely ill"), and monthly evaluation was conducted with the HAM-D. An intent-to-treat analysis was utilized, with the last available evaluation carried forward as endpoint. All patients with at least one postbaseline efficacy evaluation were included in the analysis.[15]

RESULTS

One patient discontinued after baseline owing to rash (undocumented) and was lost to follow-up, leaving 12 evaluable patients for analyses. The mean weekly Y-BOCS scores are presented in Table 1. A significant change (7.42 points) was found from baseline to endpoint in Y-BOCS scores, ($t = 4.62$, $p = .001$). The mean change from baseline was significant beginning at the end of 1 week of treatment (mean = 2.09 points, $p = .020$) and continued to grow larger over time. The mean effect size was 1.33.

At endpoint, 5 (42%) of 12 patients rated themselves "much" or "very much improved" on the PGI, 6 (50%) were "minimally improved," and 1 (8%) reported "no change." Using the clinician-rated CGI, 5 (42%) were rated "much" or "very much improved" at endpoint, 6 (50%) were rated "minimally improved," and 1 (8%) was rated "no change." Mean CGI-S score changed from 4.09 at baseline to 2.91 at endpoint ($t = 4.49$, $p = .001$). The mean HAM-D score, while subclinical at baseline (6.09 points), changed significantly with treatment (1.91 at endpoint, $t = 3.32$, $p = .008$). The most common side effects reported were diarrhea (N = 3) and restless sleep (N = 2).

Given that 6 of the patients reported a failure to respond to previous treatment with an SSRI, we examined the change for this subgroup separately. Those patients who had previously failed to respond to an SSRI had a

mean Y-BOCS change of 4.33 points, whereas those who did not report previous treatment failure had a Y-BOCS score change of 10.50 points ($t = 2.24$, $p = .049$). These represent effect sizes of 0.86 and 2.32, respectively. The fact that a subgroup of patients accounted for a large percentage of the overall change accounts for the apparent discrepancy between the large overall change in mean Y-BOCS score and the relatively smaller percentage (42%) rated "much" or "very much" improved.

DISCUSSION

Results of the current study found a significant improvement with *Hypericum*, with a drop in Y-BOCS score similar to that found in clinical trials of SSRIs. The effect size of 1.33 denotes a large treatment effect. To put this in the context of the current treatment literature, a recent meta-analysis found the mean effect size (controlling for methodological variables) for the SSRIs as a group to be 0.82; for clinician behavior therapy, 0.99; and for clomipramine, 1.09.[2] The large effect size in the current study is, to some extent, an artifact of an open trial, where the effect size does not factor out the effect of placebo. However, the absolute value of the change (7.42 points) compares favorably with that found in clinical trials (6.01 points).[2] The percentage of patients rated "much" or "very much" improved by clinician on the CGI (42%) was also similar to that found in the multicenter clinical trials for the SSRIs, i.e., fluoxetine, 38%; fluvoxamine, 43%; sertraline, 39%.[4] It appears that those patients who failed to respond to previous treatment with an SSRI did not do as well with *Hypericum* as those who had responded.

The fact that a significant response was found as early as week 1 suggests a possible placebo response. However, improvement grew larger over time, with endpoint change more than 3 times as large as the change at week 1. This response pattern is unlike the typical placebo response pattern found in clinical trials, in which a large initial placebo response is less likely to persist.[16]

The use of alternative therapies in general and herbal medicines in particular is widespread and growing. In a 1998 national survey published in *JAMA*, Eisenberg and colleagues[17] found that the probability of seeing a practitioner of alternative medicine was 46.3%, and 15% had specifically seen a provider of herbal medicine. Other surveys found about a third of all Americans use herbal medicines in a given year.[18,19] Depression and anxiety are among the most common reasons cited for seeking alternative treatments,[17,20] with patients often consulting psychiatrists while still taking herbal compounds,[21] or adding them to conventional therapies unbeknownst to their physicians. Thus, it is important that the safety and efficacy of these compounds be scientifically examined. Issues such as how to standardize herbal medications, contraindications, and drug interactions need to be empirically examined as well. In this regard, neither the primary active component of *Hypericum* nor the exact mechanism of action has been conclusively identifed.[22] Even though hypericin is not the only active compound in *Hypericum perforatum*, hypericin is purported to be the compound related to its psychoactive properties and is the compound upon which it is standardized in Europe. Perovic and Müller[9] provide strong evidence for the inhibition of the reuptake of serotonin, although Müller and colleagues[8] found that *Hypericum* inhibited the reuptake of serotonin, dopamine, and norepinephrine with about equal affinity. The fact that clomipramine, the least selective SRI with regard to blocking serotonin over reuptake norepinephrine, has been found in several meta-analyses to have a larger effect size than the other SRIs,[2,4,23–25] whose mechanisms of action are more selective for serotonin, leads to speculation that more than a single neurotransmitter system is involved in the pathophysiology of OCD.[4,26] Similarly, it could be that several neurotransmitter systems in combination with serotonin contribute to the efficacy of St. John's wort in OCD.

Unlike other forms of alternative treatments, the research methodology used to demonstrate efficacy in herbal medicine is the same as that of conventional medicine, i.e., randomized, placebo-controlled trials.[27] The positive results of this study warrant further investigation of *Hypericum* in OCD. A randomized, placebo-controlled trial would serve to both replicate our findings and determine the extent to which the findings can be attributable to placebo response. Along those lines, we have designed and submitted to the National Institutes of Health a placebo-controlled pilot study to determine the sample size necessary to conduct a larger multicenter trial that would more definitively answer this question.

Drug names: bupropion (Wellbutrin), clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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