St John’s wort versus placebo in obsessive–compulsive disorder: results from a double-blind study

Kenneth A. Kobak, Leslie V. H. Taylor, Alexander Bystritsky,
Cary J. Kohlenberg, John H. Greist, Phebe Tucker, Gemma Warner,
Rise Futterer and Tanya Vapnik

Introduction

- >42% of US population report using an alternative therapy. (Eisenberg et al., 1993, 1998)

- Herbal medicines are one of the most common types of alternative treatments, comprising 15% to 33% of alternative therapies used. (Brevoort, 1998; Eisenberg et al., 1998)

- Only about 39% of alternative treatments are discussed with their physician. (Eisenberg et al., 1998)
St John’s Wort (Hypericum perforatum) is one of the most widely used herbal medicines, and is licensed in Germany for the treatment of anxiety and depressive disorders.

Lot of studies have been done on St John’s wort (SJW) for depression. To date, no placebo-controlled trials of SJW have been conducted in OCD even though it is widely used in this group of patients.

There is pharmacokinetic evidence for the serotonergic (Perovic and Muller, 1995), dopaminergic (Muller et al., 1997) and GABAergic (Cott, 1997; Wonnemann et al., 2000) activity of hypericum.
**Structure**

**Active components:**
- Hypericin
- Pseudohypericin
- Hyperforin

[Image of Hypericin structure]
The aim of the current study was to examine the efficacy of St John’s Wort for the treatment of OCD.
Method and Study Design

- NCCAM (NIH) Funded.

- This was a 12-week, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group study.

- Sixty subjects were randomized to either St John’s Wort (LI 160, 300 mg) (n=30) or matching placebo (n=30).

- Following double-blind treatment, subjects were offered 12 weeks of open label treatment with hypericum.
Subjects

- Outpatients aged 18–65 years, diagnosis of OCD of at least 1 year duration. 4 sites: Los Angeles, Milwaukee, Oklahoma City & Madison.

- Exclusions: concurrent behavior therapy, suicide risk, 2 prior failed antidepressant trials for OCD, baseline HAM-D score >15.

- Due to reports that SJW is a potent inducer of hepatic enzymes \{3A4, 1A2…\} (Ernst, 1999), subjects taking theophyline, cyclosporine or warfarin were excluded. Subjects taking indinavir and other protease inhibitors were excluded, due to reports of interactions between SJW and these compounds.
Procedures and Outcome measures

- Subjects were assessed at baseline and after 4, 8 and 12 weeks of treatment. A telephone visit was done at the end of weeks 1, 2, 6 and 10 for safety, efficacy and adverse event monitoring.

- Primary Outcome: change in Y-BOCS (Yale Brown Obsessive Compulsive Scale).

- Secondary Outcome: change in HAM-D and CGI and PGI (Clinical Global Impression and Patient Global Impression) scores.
St John’s wort and Dosing

- St John’s wort extract LI 160 and matching placebo (both supplied by the manufacturer, Lichtwer Pharma, Berlin, Germany).

- The product has been standardized to total hypericin content (hypericin and pseudohypericin) and a range of analytical marker substances.

- Flexible-dose design. Subjects started on 300 mg b.i.d. for 2 wks., with option of increasing the dose to 1800 mg per day depending on response. Min. dose: 300 mg b.i.d.
N=60

**Randomized**

30=Placebo
- 21 completed
- 1 discontinued
- S/E: Confusion
- 13 Open-label

30=SJW
- 22 completed
- 1 discontinued
- S/E: Sinusitis
- 16 Open-label
Results

- Y-BOCS range at baseline: 16–34 (St John’s wort), 16–36 (placebo).

- The mean change from baseline to endpoint on the Y-BOCS total score was significant for both SJW (3.43) and placebo (3.60) \[t(27)=3.418, P=0.002 \text{ and } t(29)=3.987, P=0.001\], respectively.

- However, the mean change with SJW (3.43) was not significantly different than the mean change found with placebo (3.60) \[t(56)=0.127, P=0.899\].
Mean change (YBOCS) from baseline to endpoint, St John’s Wort versus placebo.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean change</th>
<th>SE</th>
<th>SD</th>
<th>95% Confidence interval Lower</th>
<th>95% Confidence interval Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>St John’s wort</td>
<td>28</td>
<td>− 3.43</td>
<td>1.00321</td>
<td>5.30847</td>
<td>− 5.4870</td>
<td>− 1.3702</td>
</tr>
<tr>
<td>Placebo</td>
<td>30</td>
<td>− 3.60</td>
<td>0.90287</td>
<td>4.94522</td>
<td>− 5.4466</td>
<td>− 1.7534</td>
</tr>
<tr>
<td>Difference*</td>
<td>-</td>
<td>− 0.17</td>
<td>1.34632</td>
<td>-</td>
<td>− 2.52557</td>
<td>2.86843</td>
</tr>
</tbody>
</table>

*P = 0.899, t(56) = − 0.127

Y-BOCS, Yale–Brown obsessive–compulsive scale
Contd...

- No significant difference between SJW and placebo on any of the Y-BOCS subscales (obsessions, compulsions, time spent obsessions, time spent compulsions).

- 29 subjects decided to enter the open-label treatment phase (SJW=16, placebo=13).

- No significant difference between SJW and placebo on change in Y-BOCS score from baseline to last extension visit [7.13 versus 6.54, respectively; \( t(27)=0.282, P=0.780 \)], or from end of double-blind to last extension visit [1.50 versus 2.08, respectively; \( t(27)=0.393, P=0.697 \)].
No significant difference between the treatment conditions on % of patients rated as ‘much’ or ‘very much’ improved at endpoint by either clinician ratings (17.9%. St John’s Wort versus 16.7% placebo; chi squared=0.014, d.f.=1, P=0.905), or patient self-ratings (17.9% SJW versus 20.0% placebo; chi squared=0.043, d.f.=1, P=0.835).
Adverse events noted

19 subjects on St John’s wort reported adverse events rated as ‘possibly’ related to study drug compared to 14 subjects on placebo.

<table>
<thead>
<tr>
<th>SJW</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache (n=6)</td>
<td>headache (n=3)</td>
</tr>
<tr>
<td>GI (n=6)</td>
<td>GI (n=4)</td>
</tr>
<tr>
<td>fatigue (n=4)</td>
<td>fatigue (n=2)</td>
</tr>
<tr>
<td>agitation (n=4)*</td>
<td>agitation (n=0)*</td>
</tr>
<tr>
<td>sleep disturbance (n=3)</td>
<td>decreased sex drive (n=2)</td>
</tr>
</tbody>
</table>

*Chi squared=4.603, d.f.=1, P=0.03

71% AE’S were rated mild in the SJW group compared to 43% in the placebo group (chi squared=4.16, d.f.=1, P=0.04), all others were moderate, none were severe.
Discussion

- The results fail to provide support for the efficacy of St John’s Wort in OCD.

- The mean change on the Y-BOCS was 3.43 points, which is considerably less than the average of 6.1 points found in clinical trials of approved antidepressants (Kobak et al., 1998; Taylor and Kobak, 2000).

- The change on placebo was low & consistent with other studies that have found OCD to have one of the lowest placebo response rates of the anxiety disorders (Huppert et al., 2004).
Thus, these findings cannot be attributable to a high placebo response rate, but rather to a small drug response.

The % of SJW patients rated ‘much’ or ‘very much’ improved was 17.9%; compared to rates of 42% in the open-label trial, 38% for fluoxetine, 43% for fluvoxamine (Kobak et al., 1998). The numerically larger response on placebo suggests that the results are not due to a type II error.

The most prominent explanation is simply that the compound is ineffective for OCD, & the open label results were primarily due to a placebo response.


Limitations

- **Formulation:** (LI 160) was different than the formulation used in some open-label studies (Alterra). The compound used in the current study is among the best characterized, and has been used in several efficacy studies, including the large NIMH study in depression.

- **Dosing:** Whether a more aggressive dosing regimen would have improved results is unknown. But a fairly expected range of dosing was used.
Conclusion

In summary, St John’s wort was not found effective for OCD.

Although these results fail to support its efficacy in OCD, it is the first and only trial to explore this question, and thus by itself cannot be used as the basis for drawing firm conclusions.