Hypericum extract was better than placebo and equivalent to imipramine for moderate depression


**QUESTION:** In patients with moderate depression, how effective and safe is hypericum extract (St John’s wort) compared with imipramine and placebo?

**Design**
8 week randomised (unclear allocation concealment†),‡ blinded (clinicians and patients),§ placebo controlled trial.

**Setting**
18 general practitioners’ practices in Germany.

**Patients**
263 patients who were 18–65 years of age (mean age 47 y; 75% women) and had a diagnosis of moderate depression; score of ≥18 on the Hamilton Depression Rating Scale (HDRS); clinical global impression rating of moderate, marked, or severe; and depression lasting ≥4 weeks and ≤2 years. Exclusion criteria included bipolar disorders, alcohol or drug dependence, or suicidal risk. 230 patients (87%) completed the study; 251 (95%) were included in an intention to treat analysis.

**Intervention**
Patients were allocated to hypericum extract (STEI 300, Steiner Arzneimittel, Berlin, Germany), 1050 mg/day (n = 106); imipramine, 50 mg/day titrated to 100 mg/day by day 5 (n = 110); or placebo (n = 47).

**Main outcome measures**
The primary endpoint was change from baseline in HDRS score. Hypericum was compared with placebo at 6 weeks; hypericum with imipramine at 8 weeks.

**Main results**
Greater improvement from baseline occurred with hypericum extract than with placebo at 6 weeks (mean decrease in HDRS score of 13.4 v 10.3, 95% CI for the 3.1 difference 1.5 to 5.4). Hypericum extract and imipramine had similar changes in score from baseline at 8 weeks (mean decrease of 15.4 v 14.2, CI for the 1.2 difference −0.6 to 2.6). More patients who received hypericum extract had ≥50% improvement in HDRS scores than did patients who received placebo (p = 0.027†); the proportions did not differ between hypericum and imipramine (p = 0.14‡) (table). Fewer patients in the hypericum group than the imipramine group reported adverse effects (p < 0.001‡) (table).

**Conclusion**
In patients with moderate depression, hypericum extract (St John’s wort) was more effective than placebo and as effective and safe as imipramine.

**Hypericum extract (HE) vs placebo at 6 weeks and HE vs imipramine (Imi) at 8 weeks for moderate depression§**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Comparison</th>
<th>Event rates</th>
<th>RBI (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% improvement in HDRS score</td>
<td>HE v placebo</td>
<td>67% v 48%</td>
<td>40% (3.5 to 101)</td>
<td>6 (3 to 50)</td>
</tr>
<tr>
<td></td>
<td>HE v Imi</td>
<td>76% v 67%</td>
<td>14% (−4.3 to 37)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

**RRR (CI) | NNT (CI)**

| Adverse effects | HE v Imi | 22% v 46% | 53% (30 to 69) | 4 (3 to 9) |

§HDRS = Hamilton Depression Rating Scale. Other abbreviations defined in glossary; RBI, RRR, NNT, and CI calculated from data provided by the author.

**COMMENTARY**

The trial by Philipp et al confirms previous trials showing that short term treatment with high doses of some hypericum preparations are as effective for depressive symptoms as low doses of tricyclic antidepressants in mild to moderate depressive episodes. The dose of tricyclic antidepressant used in this trial (100 mg/d of imipramine) was lower than the dose some have considered necessary for treatment to be effective (>100 mg/d or equivalent)1. The evidence in support of this dosing recommendation has not been robust. To help address this question, acute, continuation, and maintenance phase trials comparing hypericum with standard doses of tricyclic or selective serotonin reuptake inhibitor antidepressants and placebo are needed. Furthermore, clinicians remain uncertain about the potential of hypericum to achieve remission, and some preparations may even be ineffective in the treatment of depression.2

As in previous trials, Philipp et al report reduced side effects of hypericum compared with tricyclic antidepressants. The clinical importance of such reduced side effects is unknown given that none of the side effects in patients receiving imipramine led to discontinuation of the drug and the side effects of imipramine tend to wear off over time.3 Furthermore, concerns exist about the interactions between hypericum and commonly prescribed drugs as warfarin and theophylline, and the increased risk of photosensitivity and skin cancer with long term use of hypericum.4

At present, insufficient evidence exists to recommend hypericum as a short term treatment alternative to other types of antidepressants for depressive episodes. Health consumers should know that St John’s wort preparations bought in health food shops are often no more effective than placebo in depression, and their use, especially given the potential for adverse interactions with other drugs, may have safety concerns.

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