St. John's wort was not better than placebo for reducing depression scores

Shelton RC, Keller MB, Gelenberg A, et al. **Effectiveness of St John's wort in major depression. A randomized controlled trial.** JAMA. 2001 Apr 18;285:1978-86.

QUESTION

In patients with major depression, is St. John's wort (*Hypericum* extract) better than placebo for reducing depressive symptoms?

DESIGN

Randomized (allocation concealed*), blinded {clinicians, patients, outcome assessors, and statisticians}†,* placebo-controlled trial with 8-week follow-up.

SETTING

11 academic medical centers in the United States.

PATIENTS

200 physically healthy outpatients who were ≥ 18 years of age (mean age 42.4 y, 64% women); had major depression (single episode or recurrent) without psychotic features according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* for ≥ 4 weeks; and scored ≥ 20 on the Hamilton Depression Rating Scale (HDRS). Exclusion criteria included having cognitive, post-traumatic stress, eating, or substance use disorders in the past 6 months; panic disorder in the past year; and bipolar, psychotic, or primary personality disorders. Patients who improved during the 1-week placebo run-in period were also excluded. 84% of patients completed the study.

INTERVENTION

Patients were allocated to St. John's wort, one 300-mg tablet 3 times daily (n = 98) or to placebo (n = 102) for 8 weeks. The dose was increased to 4 tablets (1200 mg) daily for those who had not sufficiently improved by week 4 (mean daily dose 3.7 tablets [1110 mg] for St. John's wort, 3.6 tablets for placebo).

MAIN OUTCOME MEASURES

Rate of change in HDRS scores. Secondary outcomes included response rate (HDRS score ≤ 15 and Clinical Global Impression-Improvement [CGI-I] score of 1 or 2).

MAIN RESULTS

Analysis was by intention to treat. A random coefficient regression model showed that both groups improved over time ($P < 0.001$), but the groups did not differ for change in HDRS scores or response rates (Table). At 8 weeks, the mean HDRS score was 14.2 for St. John's wort and 14.9 for placebo ($P > 0.2$).

CONCLUSION

In patients with major depression, St. John's wort did not improve depression scores at 8 weeks.

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*See Glossary.

†Information provided by author.

St. John's wort (SJW) vs placebo for major depression at 8 weeks‡

Outcome	SJW	Placebo	RBI (95% CI)	NNT (CI)
Response rate	27%	19%	42% (–15 to 140)	Not significant

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article. Response = Hamilton Depression Rating Scale score ≤ 12 and Clinical Global Impression–Improvement score of 1 or 2.

COMMENTARY

The context for the study by Shelton and colleagues is the Cochrane review by Linde and Mulrow showing that St. John's wort extract is efficacious (1). The study by Shelton and colleagues is rigorous and meets every reasonable expectation for a well-conducted pharmaceutical study. Although the result was negative, many will see this as the gold-standard study, carrying far more qualitative weight than many studies cited in Linde and Mulrow (1).

It is, however, not quite the ace of studies. The absolute test for inefficacy of an agent is a 3-arm study in which a new agent, placebo, and reference agent of known efficacy are compared. If the reference agent differs from placebo but the new agent does not, then this finding provides maximal evidence that the new agent does not work. If neither reference nor new agent differs from placebo, then the study has produced an unlucky result—and an uninformative one. Shelton and colleagues cannot be reproached for not running a 3-arm study because, given the conclusions of Linde and colleagues (2), this trial could have been expected to be a confirmatory study.

The muddle surrounding St. John's wort leaves clinicians in an "anything goes" situation. Enough positive data exist that it would be reasonable for a clinician to recommend St. John's wort, or as is often the case, to acquiesce to patient wishes. Alternatively, sufficient uncertainty exists that it would be equally reasonable for the clinician not to engage in explicit or implicit endorsements of St. John's wort.

Many patients are going to request St. John's wort or self-administer it with or without the clinician's approval. Anecdotally, coadministration of St. John's wort with prescribed antidepressants is common. Thus, it seems reasonable that treating clinicians should have at least a nodding acquaintance with the pharmacology and safety data regarding St. John's wort, analogous to having a working knowledge of the effects of, say, alcohol or nicotine.

Unravelling the uncertainties surrounding St. John's wort will take years to achieve. Meanwhile, we should remember that prescribed antidepressants have efficacy, tolerability, and safety data.

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References

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2. **Linde K, Ramirez G, Mulrow CD, et al.** St John's wort for depression—an overview and meta-analysis of randomised clinical trials. BMJ. 1996; 313:253-8.

