

# 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 (MD), is St John's wort (*Hypericum* extract) better than placebo for reducing depressive symptoms?

## Design

Randomised (allocation concealed\*), blinded (clinicians, patients, outcome assessors, and statisticians)†‡, placebo controlled trial with 8 weeks of follow up.

## Setting

11 academic medical centres in the US.

## Patients

200 physically healthy outpatients who were ≥18 years of age (mean age 42.4 y, 64% women); had MD (single episode or recurrent) without psychotic features according to *DSM-IV* for ≥4 weeks; and scored ≥20 on the Hamilton Depression Rating Scale (HDRS). Exclusion criteria included current 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 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) and remission rate (HDRS score ≤7 and CGI-I score of 1 or 2).

## Main results

Analysis was by intention to treat. A random coefficients 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). The remission rate was higher in the St John's wort group than in the placebo group (p<0.02) (table).

## Conclusion

In patients with major depression, St John's wort did not improve depression scores at 8 weeks. Remission rates differed in the intention to treat sample and favoured St John's wort.

\*See glossary.

†Information provided by author.

Sources of funding:  
Pfizer Inc and National  
Institute of Mental  
Health.

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A modified version of  
this abstract and  
commentary appears in  
*Evidence-Based  
Medicine*.

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

Outcomes	SJW	Placebo	RBI (95% CI)	NNT (CI)
Response rate (HDRS ≤12 and CGI-I of 1 or 2)	27%	19%	42% (–15 to 140)	Not significant
Remission (HDRS ≤7 and CGI-I of 1 or 2)	14%	4.9%	191% (14 to 656)	11 (6 to 76)

‡CGI—Clinical Global Impression—Improvement score; HDRS=Hamilton Depression Rating Scale. Other abbreviations defined in glossary; RBI, NNT, and CI calculated from data in article.

## COMMENTARY

The context of the study by Shelton *et al* is the Cochrane review by Linde and Mulrow that reported the efficacy of St John's wort extracts.<sup>1</sup>

The study by Shelton *et al* is rigorous and conforms to every reasonable expectation of how a pharmaceutical study should be done. 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.<sup>1</sup>

It is, however, not quite the ace of studies. The absolute test for inefficacy of an agent is a 3 arm study in which 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 provides maximal evidence that the new agent does not work. If *neither* reference nor new agent differs from placebo, then the unfortunate study has produced an unlucky result – and an uninformative one. Shelton *et al* cannot be reproached for not running a 3 arm study because given the conclusions of Linde *et al*,<sup>2</sup> this trial could be expected to be a confirmatory study.

The muddle surrounding St John's wort leaves the clinician 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, co-administration of St John's wort with prescribed antidepressants is common. Thus it seems reasonable that treating clinicians should have at least nodding acquaintance with 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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1 Linde K, Mulrow CD. St John's wort for depression. *Cochrane Database Syst Rev* 2001;(2):CD000448.

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.