

Review: St John's wort is more effective than placebo for treating depressive disorders

Linde K, Mulrow CD. *St John's wort for depression*. (Cochrane Review, latest version 09 Jul 1998). In: *Cochrane Library*. Oxford: Update Software.

Question

Are extracts of St John's wort (*Hypericum perforatum*) effective and safe compared with placebo and standard antidepressants in patients with depressive disorders?

Data sources

Studies were identified by searching Medline (from 1983), PsycLIT (1987–97), EMBASE/Excerpta Medica (from 1989), the clinical trial registry of the Cochrane Depression, Anxiety, and Neurosis Group, the Cochrane Complementary Medicine Field, and the private database Phytodok (Munich); by scanning bibliographies of relevant articles; and by contacting authors and pharmaceutical companies.

Study selection

Studies were selected if they were randomised controlled trials (RCTs) that compared St John's wort with placebo or other antidepressants in patients with depressive disorders. Studies with physiological outcome measures only were excluded.

Data extraction

2 reviewers extracted study characteristics and results and assessed the quality of each study. Missing or additional data were obtained from authors or sponsors.

Main results

27 of 45 studies involving 2291 patients met the inclusion criteria. 17 trials were placebo controlled. Follow up ranged from 2 to 12 weeks in 26 studies (mean 5.5 wks)*, and 1 study's length of follow up was unknown. More patients responded to St John's wort than to placebo (14 studies, { $p < 0.001$ }*; heterogeneity

existed among these trials (table). No differences in responder rate occurred for St John's wort compared with low dose antidepressants (5 studies, { $p = 0.79$ }*) (table). Side effects were fewer with St John's wort than with low dose antidepressants {28% v 45%, $p = 0.002$ }*.

Conclusions

St John's wort is more effective than placebo for treating patients with depression. Responder rates do not differ between St John's wort and low dose antidepressants. Fewer side effects occurred with St John's wort than with low dose antidepressants.

*Numbers calculated from data in article.

Responder rates for St John's wort (SJ) v control in depressive disorders†

Comparison at a mean follow up of 5.1 weeks	Weighted event rates		RBI (95% CI)	NNT (CI)
	SJ	Control		
SJ v placebo‡	56%	25%	140% (70 to 239)	4 (3 to 6)

Comparison at a mean follow up of 5.6 weeks	RBR (CI)		NNH
	SJ	antidepressants	
SJ v antidepressants	51%	52%	3% (-12 to 16) NS

†NS = not significant; RBR = relative benefit reduction. Other abbreviations defined in glossary; RBI, RBR, NNT, NNH, and CI calculated from data in article. ‡Heterogeneity existed among trials.

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Abstract also published in ACP Journal Club with a modified version of this commentary and in Evidence-Based Nursing.

Commentary

Many doctors are sceptical of "alternative" remedies and respond to claims made by their advocates with calls for more evidence—specifically from RCTs. This review by Linde and Mulrow reports the result of 27 such trials comparing St John's wort with either placebo or active treatments. It suggests that St John's wort is more effective than placebo and is as effective as low dose tricyclic antidepressants (TCAs) in the treatment of depression. The mechanism of action appears to be similar to that of conventional antidepressants, which is an inhibition of reuptake of monoamines.¹

The authors of the review point to the small sample sizes, brief duration of trials, and inadequate doses of conventional antidepressants used in many (but not all) trials. How seriously should such concerns be taken? It is instructive to compare the St John's wort trials with those comparing more conventional antidepressants: TCAs and selective serotonin reuptake inhibitors (SSRIs). In a

previous review we found that the median sample size of SSRI-TCA trials is 64 patients.² For the equivalent trials comparing St John's wort with active treatment, the median sample size was 101 patients. This suggests that these trials may be of higher quality than those of more conventional treatment. This point should reassure readers who may be concerned that many of the trials are published in unfamiliar German journals. Similarly, although low doses of TCAs were often used in the St John's wort RCTs, 25% of trials comparing SSRIs and TCAs also used low doses. Further work suggests that the necessity of prescribing high dose TCAs may have been exaggerated.³ Hence, although bigger and better trials would be welcome, it would be unfair to condemn St John's wort on the basis of this evidence.

Although this review gives some support for St John's wort, some questions remain unanswered. There appears to be considerable uncertainty about dosage,

with big differences in prescribed doses in these trials. Herbal remedies are often poorly regulated and tend not to be subject to the same surveillance after marketing as conventional treatments. Thus relatively little may be known of possible rare adverse effects. Most clinicians will probably stick to prescribing familiar antidepressants, but St John's wort may be useful for patients who have previously not tolerated conventional antidepressants or who prefer a "natural" alternative.

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- 2 Hotopf M, Lewis G, Normand C. Putting trials on trial—the costs and consequences of small trials in depression: a systematic review of methodology. *J Epidemiol Community Health* 1997;51:354–8.
- 3 Trindade E, Menon D. *Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part I: evaluation of the clinical literature*. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1997 Aug. Report 3E.