

# Review: St John's wort superior to placebo and similar to antidepressants for major depression but with fewer side effects

## QUESTION

**Question:** Is St John's wort (hypericum) an effective treatment for major depression?

**Outcomes:** Proportion of responders at end of treatment or at study endpoint if treatment was longer than 6 weeks (based on score improvements on Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impression index (CGI), rating as at least "much improved" on global improvement subscale, Depression Scale von Zerssen (DS) or any other clinical response measure); safety (proportion of dropouts due to adverse events).

## METHODS

**Design:** Systematic review with meta-analysis.

**Data sources:** Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group (search to July 2007), Cochrane Field for Complementary Medicine database, MEDLINE (1983–2008), EMBASE (1989–2008), PsycLIT and PsycINDEX (1987–1997), Phytodok (private database, Munich), hand search of bibliographies.

**Study selection and analysis:** Two reviewers assessed studies. Inclusion criteria: randomised, controlled, double blind trials of hypericum extracts versus placebo or versus standard antidepressants in people with major depression (DSM-IV or ICD-10). Exclusion criteria: people aged under 16 years, studies of hypericum in combination with other herbs, trials measuring physiological parameters only. Rate ratios and 95% confidence intervals (CIs) were used for dichotomous measures of response. WMDs were used for continuous scores on HAM-D and DS. Response rate ratios were pooled through random effects meta-analysis. Odds ratios (OR) were used to assess adverse events. Heterogeneity was assessed using the  $\chi^2$  test and the  $I^2$  statistic. Subgroup analyses were performed for per protocol data, stratified by country, studies using HAM-D only and studies using CGI only. Random effects meta-regression was used to explore heterogeneity.

## MAIN RESULTS

Twenty-nine double blind studies (n = 5489) met inclusion criteria; 18 compared hypericum extract with placebo and 17 compared hypericum with standard antidepressants. Depression was mild to moderate in 19 studies and moderate to severe in nine. The majority of trials used 500–1200 mg hypericum daily. Trials with antidepressant comparators used fluoxetine (six studies), sertraline (four studies), imipramine (three studies), citalopram (one study), paroxetine (one study), maprotiline (one study) and amitriptyline (one study). The majority of studies assessed response on the HAM-D scale. Hypericum extracts increased response rate (any dichotomous measure) compared with placebo although there was significant heterogeneity in trials (18 randomised controlled trials (RCTs), 3064 people: relative risk (RR) 1.48, 95% CI 1.23 to 1.77;  $I^2 = 79%$ ). Six studies found that hypericum extracts increased remission compared with placebo (six RCTs, 1236 people; RR 2.77, 95% CI 1.80 to 4.26;  $I^2 = 29%$ ). The following were significantly associated with effect sizes: country of origin ( $p = 0.002$ ), precision ( $p = 0.032$ ) and baseline values ( $p = 0.048$ ). There was no difference in numbers dropping out due to adverse events between hypericum extracts and placebo (16 RCTs, 2784 people: OR 0.92, 95% CI 0.45 to 1.88;  $I^2 = 0%$ ) or in response rate between hypericum extracts and standard antidepressants (17 RCTs, 2810 people: RR 1.01, 95% CI 0.93 to 1.09,  $I^2 = 17%$ ). Subgroup analyses with older antidepressants and with selective serotonin reuptake inhibitors (SSRIs) found similar results (older antidepressants: RR 1.02, 95% CI 0.90 to 1.15;  $I^2 = 0$ ; SSRIs: RR 1.00, 95% CI 0.90 to 1.12;  $I^2 = 29%$ ). Hypericum seemed safer than antidepressants, with fewer dropouts due to adverse events (16 RCTs, 2785 people: RR 0.41, 95% CI 0.29 to 0.60;  $I^2 = 0%$ ).

## CONCLUSIONS

Hypericum (St John's wort) extracts are more effective than placebo in people with major depression. They are similarly effective to standard antidepressants but with fewer side effects.

## ABSTRACTED FROM

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The fact that extracts from St John's wort are effective antidepressants has been known for some time.<sup>1</sup> Over the years, this evidence has been getting stronger and stronger. Even though not all trials were positive, most suggested that it is better than placebo in alleviating depression. While most experts now accept that this is the case for mild to moderate depression, doubts have remained regarding major depression.

This meta-analysis shows that St John's wort extracts are also effective for major depression. It demonstrates superiority over placebo and suggests equivalence with synthetic antidepressants. In addition, it provides good evidence to assume that the

risks associated with this herbal medicine are significantly less than those of synthetic antidepressants. This conclusion is also supported by data from observational and other non-randomised studies.<sup>2</sup> However, St John's wort extracts are not risk free. We now know that it powerfully interacts with a range of prescription drugs.<sup>3</sup>

The implications of all this are clear. St John's wort extracts are effective antidepressants. Provided herb-drug interactions can be avoided, they are also safer than conventional drugs. Considering the current debate about the value of synthetic antidepressants,<sup>4</sup> one wonders why they are not used more widely.

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**Competing interests:** None.

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