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FILE: ▪St. John's Wort (*Hypericum perforatum*)
▪Major Depression

HC 110581-365

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RE: Cochrane Review of St. John's Wort for Major Depression

Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD000448. DOI: 10.1002/14651858.CD000448.pub3.

Depression is typically treated with antidepressant medications. Although newer antidepressants (SSRIs, serotonin selective reuptake inhibitors) are better tolerated than older drugs, they still have many unwanted side effects. Extracts of St John's wort (SJW, *Hypericum perforatum*) are prescribed in Germany to treat depression. The purpose of this systematic review was to investigate whether extracts of SJW are more effective than placebo and as effective as standard antidepressants in the treatment of major depression; and whether they have fewer adverse effects than standard antidepressant drugs. Similar reviews have been published in the past. This review is an update, including the latest published studies.

Only randomized, double-blind studies were included in this review. Patients were required to have major depression (meeting DSM-IV or ICD-10 criteria). Trials in children (< 16 years) were not eligible. Studies evaluating combination products were excluded. Trials using inappropriate synthetic drugs (e.g. benzodiazepines) or a dosage of an antidepressant below the lower thresholds recommended in current guidelines were excluded. Experimental and control treatments had to be administered for a duration of at least four weeks. Trials that only measured physiological parameters were excluded. Electronic databases were searched through July 8, 2008. Reference lists were also searched. The methodological quality of each trial was assessed by at least two independent reviewers using Jadad scales. The report contains a table listing all of the included trials and their Jadad scores. Data were extracted from the reports and a meta-analysis was conducted. The main outcome measure for assessing effectiveness was the response rate according to the HAMD, MADRS, or CGI scales. The main outcome measure for adverse effects was the number of patients who dropped out due to adverse effects.

A total of 79 relevant studies were identified and 29 trials (with 5489 patients) met the inclusion criteria, including 18 placebo-controlled studies and 17 active-controlled studies. The report includes a large table that describes all of the included studies. The severity of depression was described as mild to moderate in 19 trials, and moderate to severe in nine trials (one trial did not classify severity). Eighteen trials were from German-speaking countries, four from the US, two from the UK, and one each from Brazil, Canada, Denmark, France and Sweden. Many different SJW preparations were used in the trials. The range of daily doses varied between 240 and 1800 mg, but most trials used 200-500 mg. The active comparators were fluoxetine (6 trials, dosage 20-40 mg), sertraline (4 trials, 50-100 mg), imipramine (3 trials, dosage 100-150 mg), citalopram (1 trial, 20 mg), paroxetine (1 trial, 20-40 mg), maprotiline (1 trial, 75 mg), and amitriptyline (1 trial, 75 mg). Treatment duration lasted four weeks (1 trial), six weeks (19 trials), seven weeks (1 trial), eight weeks (5 trials) or 12 weeks (4 trials). The majority of studies were of high quality (Jadad score of 5 out of 5).

Efficacy
In the placebo-controlled studies, patients receiving SJW were significantly more likely to be treatment responders (responder rate ratio = 1.48; 95% CI: 1.23 – 1.77), but study results were highly heterogeneous. Variables affecting the heterogeneity were baseline values (higher values had smaller effect size), precision of the study (more precise studies had smaller effect size), and country of origin (trials from German-speaking countries reported more positive findings). Remission rates (HAMD score < 8 or < 7) were significantly higher in patients receiving SJW than in those receiving placebo (ratio = 2.77; 95% CI: 1.80 – 4.26).

In comparator trials, the results were statistically homogeneous. An analysis based on the Hamilton Rating Scale for Depression (HAM-D) revealed no statistical differences between the groups (RR = 1.01; 95% CI: 0.93 – 1.09). Analysis based on the Clinical Global Impression Index (CGI) also found no relevant differences (RR = 1.01; 95%CI: 0.94 – 1.09). Studies from German-speaking countries reported findings that were slightly more favorable to SJW. However, in the multivariable meta-regression analysis, trials with higher HAM-D baseline values had less favorable results (P = 0.010), while country of origin and precision had no significant influence in comparator trials.

Safety
The number of patients dropping out for adverse effects (AEs) was similar among patients receiving SJW and placebo (OR = 0.92; 95%CI: 0.45 – 1.88). Patients treated with SJW were less likely to drop out of the study due to AEs than patients treated with either older or newer (SSRIs) pharmaceuticals. More patients treated with older pharmaceuticals had AEs than those taking SSRIs.

Overall the findings support the use of SJW for treatment of major depression. It appears that SJW is effective and safe.

The authors of this 147 page report conclude:

"Patients suffering from depressive symptoms who wish to use a St. John's wort product should consult a health professional. Using a St. John's wort extract might be justified, but important issues should be taken into account: St. John's wort products available on the market vary to a great extent. The results of this review apply only to the preparations tested in the studies included, and possibly to extracts with similar characteristics. Side effects of St. John's wort extracts are usually minor and uncommon. However, the effects of other drugs might be significantly compromised."

In previous versions of this Cochrane review (published in 1998 and 2005), included trials were not restricted to patients with major depression, whereas the inclusion criteria of the present study were restricted to patients with major depression. This is not to say that SJW is ineffective in depressed patients who are not classified as having major depression. Rather, this restriction helped to decrease variability in the analysis.

A limitation of this report is that the authors concluded that the results only pertain to the preparations evaluated in the report. The authors state in a table that the following preparations were used: Hypericum extract LI160, HYP611, Calmigen, STW3-1, STW3-IV, STW3-VI, LoHyp-57, WS5572, WS5573, WS5570, Iperisan, STEI 300, ZE117, D-0496, and Psychotonin forte. A table summarizing the design of each study provides the SJW preparation that was used, together with the manufacturer.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.