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FILE: ▪St. John's wort (*Hypericum perforatum*)
▪Depression
▪Dysthymia

HC 040561-303

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RE: Trial Examines St. John's Wort for Dysthymia and Depression

Randlov C, Mehlsen J, Thomsen CF, Hedman C, von Fircks H, Winther K. The efficacy of St. John's wort in patients with minor depressive symptoms or dysthymia - a double-blind placebo-controlled study. *Phytomed*. March 2006;13(4):215-221.

Short-term treatment with St John's wort (SJW, *Hypericum perforatum*) is used to treat mild-to-moderate depression. SJW has not been evaluated as a treatment of dysthymia, a type of depression that is characterized by chronic symptoms that are not disabling but keep the person from functioning at full capacity and from feeling well. The purpose of this study was to evaluate a proprietary SJW extract made according to 2 levels of standardization for levels of hypericin, a marker compound to which many leading SJW extracts are standardized for quality control purposes, in the treatment of dysthymia and mild depression.

Two types of patients were recruited via advertisements in local Danish newspapers: patients diagnosed with mild or moderate depressive episodes that last at least 2 weeks and patients diagnosed with dysthymia (depressed mood for most days within the last 2 years). Patients using an antidepressant medication within 4 weeks of study entry were excluded. Patients (n = 150; 113 women, 37 men; mean age of 50.9 years) were randomly allocated to 6 weeks of placebo or either of 2 SJW extracts: 270 mg SJW extract (0.18% hypericin)/tablet taken 3 times daily or 270 mg SJW extract (0.12% hypericin)/tablet taken 3 times daily. The SJW formulation used, PM235, is based on a standardized 60% v/v extract and is manufactured by Cederroth International AB, Sweden. A battery of tests was performed at baseline, at week 3, and at week 6 (study end). Of a total of 150 patients enrolled, 129 patients completed the study.

Fifty-four percent of the patients were diagnosed with dysthymia, 13% had moderate depression, and 33% had mild depression. A clinically significant improvement was defined as a symptom reduction of 50% or more from baseline on the Hamilton Depression rating scale (HAM-D) or a final HAM-D score of less than 7. Neither of the

SJW preparations (i.e., with the 2 levels of hypericin) produced an effect that was significantly different than placebo. However, when doing a subgroup analysis of final HAM-D scores, patients without dysthymia had a tendency toward improvement with the higher level of hypericin (P = 0.057). Likewise, patients without dysthymia had a significant improvement on the Beck Depression Inventory test compared to placebo, with the higher level of hypericin having more responders (P = 0.045). Despite the findings the authors state that there was no statistically significant difference between the hypericin groups so they decided to pool the data from the low and high dose groups. A reanalysis of the data showed that patients without dysthymia had a statistically significant improvement over placebo (P =0.03) on their final HAM-D scores. However, there was no clinically significant difference between the number of placebo-treated and SJW-treated patients who decreased their HAM-D score by more than 50%.

The authors conclude that SJW did not have a significant effect in patients with dysthymia. Also, when pooling the 2 SJW-treated groups together, SJW was significantly superior to placebo in minor depressed patients. They state that the negative findings need to be confirmed in additional studies.

It is commendable that the authors published negative findings in regard to dysthymia. A negative finding is common for antidepressants in dysthymia, a patient group that is commonly considered difficult to treat. However, the group size was rather small, and in fact no significant differences were seen in any of the treated groups compared with placebo. It may be for this reason that the investigators combined the 2 SJW-treated groups into one, resulting in a sample large enough to attain statistical significance. Generally, 100 patients per group are needed in studies of depression in order to attain significant statistical differences.

Nevertheless, the results should not be too surprising to those who are familiar with the clinical and pharmacological literature on SJW, i.e., the difference in dosage levels of hypericin in the 2 preparations should not be expected to produce any clinically measurable effects with respect to measurements of depression. Although most SJW extracts are standardized to hypericin levels, hypericin was initially chosen as a standardization marker by Lichtwer Pharma for its now-famous SJW extract LI 160 a.k.a. Jarsin 300®), the SJW preparation upon which more clinical trials have been published than any other brand of SJW. Lichtwer chose hypericin as a marker for quality control purposes; there is little data to support any contention that it is a primary active compound with antidepressant activity. Unfortunately, however, it appears to be a trend in the marketplace that people will often impute such activity to a naturally-occurring compound like hypericin, which, although biologically active, is not considered to have antidepressant activity.

—Heather S. Oliff, PhD

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