

Brief Reports

Is St. John's Wort (*Hypericum perforatum*) an Effective Antidepressant?

St. John's Wort (SJW), or *Hypericum perforatum*, is a roadside weed that has been used medicinally for millennia. Traditionally used internally for kidney and lung ailments, insomnia and depression, and externally for wound healing, SJW has become increasingly popular both in the United States and Germany for the treatment of depression. Clinicians should be aware of the popularity of this herb and the data available on it.

Is there evidence for its effectiveness? A recent meta-analysis evaluated 23 randomized trials of St. John's wort in a total of 1757 outpatients with mild to moderate severe depression (Linde et al., 1996). Improvement in depressive symptoms (usually measured by the Hamilton Depression or Clinical Global Impression scales) was observed in all groups. In 15 placebo-controlled trials, SJW was found to be significantly better than placebo (odds ratio 2.67; Linde et al., 1996). In eight treatment-controlled trials, clinical improvement in those receiving SJW did not differ significantly from those receiving standard antidepressants. Side effects were reported less often with SJW: 19.8% of those on SJW reported symptoms, compared with 52.8% of those on standard antidepressants.

Because most of the studies on SJW have been performed in Germany, it bears noting that there are several differences between depression trials performed in Germany and those performed in the U.S. Diagnostic criteria for depression differ: most German trials utilized ICD-9 diagnostic criteria whereas in the U.S., DSM-IV is the standard. The investigator to patient ratio is very different in the two countries. In the U.S., it is common for a small number of investigators to recruit a relatively large number of patients, often through advertising. In Germany, most studies are performed by a relatively large number of primary care physicians, each recruiting a relatively small number of patients from within their practices. Thus, the study populations differ: in the U.S., patients are generally targeted by advertising, are self-selected, may or may not be receiving medical care, and are willing to be treated by strangers. In Germany, patients are already within the medical system and are being recruited and tested by a practitioner with whom they have a continuing relationship. It is unclear what effect this might have on study results. Another major difference between the two countries is the choice of treatment controls. Serotonin reuptake inhibitors (SRI) became popular in the U.S. years before Germany, which until very recently treated depression with small doses of tricyclic antidepressants, often 75 mg/day of imipramine or amitriptyline. This difference in standard therapies has resulted in an absence of clinical trials comparing SJW with SRI.

These differences, however, do not change the fact that SJW clearly has a significant therapeutic effect on depression

and achieves this effect with fewer side effects than tricyclic antidepressants. Whether SJW compares favorably to SRI in terms of either therapeutic benefit or side effect profile remains to be determined.

Mechanism

If SJW shares a mechanism with currently used antidepressants, this is not apparent so far. SJW appears to affect multiple neurotransmitters without fitting easily into known antidepressant categories. Although SJW demonstrates monoamine oxidase inhibition *in vitro*, this effect has not been demonstrated *in vivo*, nor have there been any reported cases of monoamine oxidase inhibitor-associated hypertensive crises in humans using SJW (Cott, 1997).

Other proposed mechanisms involve effects on monoamine uptake. *In vitro*, SJW inhibits not only serotonin but also norepinephrine and dopamine (with IC_{50} of 2.4, 4.5, and 0.9 μ g/ml, respectively; Müller et al., 1997). However, the concentrations required to attain these effects are quite high, and the chances of attaining blood concentrations necessary for these effects are remote. The most potent effect thus far reported is for the GABA receptors, with effects shown at IC_{50} approximately 75 ng/ml for GABA_A and 6 ng/ml for GABA_B (Cott, 1997). Pharmacokinetic studies have been performed with the standardized SJW extract, LI 160 (Jarsin® 300). The only components analyzed thus far are hypericin and pseudohypericin, however, which attain peak concentrations of less than 10 ng/ml at steady state (Staffeldt et al., 1994).

Adverse Effects

Side effects reported for SJW are generally mild and include gastrointestinal symptoms and fatigue (Linde et al., 1996). Photosensitization may develop, especially in fair-skinned people (Wichtl, 1994). An effect first noted in cows who grazed on SJW, photosensitization has been demonstrated in a controlled clinical trial involving metered doses of hypericin and exposure to ultraviolet (UVA) and UVB irradiation (Roots et al., 1996). Using LI 160, a standardized extract from Lichtwer Pharma, Germany, these authors found a measurable increase in erythema in light-sensitive volunteers receiving 600 mg three times daily for 15 days with UVA. These subjects had blood levels of hypericin and pseudohypericin twice that seen during normal use for the treatment of depression. It is believed that the photoactivated hypericins are responsible for this effect, which has also been seen in humans taking high doses of synthetic hypericin (Gulick et al., 1992). Photosensitization is generally mild and transient, disappearing within a few days of drug discontinuation. However, patients using SJW should be warned to avoid sunbathing and to use sunscreen for normal sun exposure. No other adverse effects were seen in the high-dose studies.

SJW is not intrinsically a dangerous plant. However, its status as an over-the-counter antidepressant brings up an indirect risk. Until now, antidepressants (with the possible exception of chocolate) have not been readily available on drugstore shelves. What are the implications of an over-the-counter antidepressant? On the positive side, mildly depressed patients who might not otherwise receive treatment have access to a therapeutic agent. On the negative side, severely depressed patients may attempt to self-treat a life-threatening condition when they should be under the care of a mental health professional.

Toxicology

The toxicity associated with SJW appears to be related to the photoactivated hypericin and similar compounds. A study in which SJW was administered to rats as 5% of their diet for 119 days found no adverse effects on the liver or any significant tissue lesions (Garrett et al., 1982). Hepatic enzymes were induced, an effect which could theoretically increase metabolism and decrease bioavailability of drugs metabolized by those hepatic enzymes.

Formal toxicology studies (Leuschner, 1996) performed with LI 160 reported the no-effect single dose as greater than 5000 mg/kg in mice and rats. In chronic toxicity studies in rats and in dogs (up to 900 mg/kg), only nonspecific symptoms of toxicity were seen including reduced body weight, slight pathological changes in liver and kidneys (most likely due to increased metabolic load), and some histopathologic changes in the adrenals. No effects were seen on fertility or reproduction at doses of up to 300 mg/kg. No teratogenic or mutagenic potential was evident. Long-term (2 year) carcinogenicity studies are currently ongoing.

Summary

SJW is a remarkably safe antidepressant with an apparently unique mode of action. Although it has demonstrated efficacy in mild and moderate depression when compared with placebo or tricyclic antidepressants, several research areas beg to be explored. Its effects should be compared with serotonin reuptake inhibitors. Studies in severely depressed patients are lacking, as are studies on its utility as a therapeutic adjunct to standard antidepressants.

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Jerry M. Cott, Ph.D.¹

Adriane Fugh-Berman, M.D.²

¹ Adult Psychopharmacology Program, National Institute of Mental Health, 5600 Fishers Lane, Room 10-75, Rockville, Maryland 20857. Send reprint requests to Dr. Cott.

² National Women's Health Network, 514 10th St., N.W. #400, Washington, D.C. 20004.

Auditory Hallucinations in Bilingual Immigrants

Hallucinations are false perceptions, which are not sensory distortions or misinterpretations, but which occur at the same time as real perceptions (Jaspers, quoted in Fish, 1967, p. 19). Among the hallucinations, the auditory kind is particularly common among patients with schizophrenia (APA, 1994, p. 275). Auditory hallucinations may be elementary in the forms of noises, partly organized as rhythmic sounds, or fully organized usually as voices or more rarely as music. In schizophrenia, auditory voices are particularly prominent (APA, 1994).

Our interest in hallucinatory voices was prompted by the reports of our bilingual patients regarding their auditory hallucinations. Some of them would report hearing voices only in one language, others in both. To more fully understand this phenomenon, we searched the literature on the experience of auditory hallucinations in bilingual or polylingual patients. We could find only one report. Hemphill (1971) described a study of auditory hallucinations in white and "colored" South African schizophrenic patients who could speak, understand, and think in both English and Afrikaans ("polyglots"). He found that schizophrenic polyglots heard hallucinatory voices in one language only, and it was invariably in their first (*i.e.*, native) language, regardless of what language they now preferred to use. Furthermore, he found some patients to demonstrate psychotic features only in their native language and to be nonpsychotic when conversing in their second language. In one report, he described a 50-year-old Jewish immigrant in New York City who heard American voices threatening to arrest him and take his shop but was completely normal when examined in Yiddish (native language). Hemphill suggested that refugees and immigrants were not polyglots. Finally, he found that patients with organic brain disorders would hear multilingual audi-