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File: ■ St. John's Wort (*Hypericum perforatum*)
■ Willis-Ekbom's Disease
■ CYP Enzymes

HC 021454-500

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RE: Restless Legs Syndrome Alleviation by St. John's Wort Extract in Pilot Study

Pereira JC Jr, Pradella-Hallinan M, Alves RC. Saint John's wort, an herbal inducer of the cytochrome P4503A4 isoform, may alleviate symptoms of Willis-Ekbom's disease. *Clinics (Sao Paulo)*. 2013;68(4):469-474.

Willis-Ekbom's disease is also known as restless legs syndrome. It is a neurological disorder characterized by the urge to move the limbs. Many drugs that relieve the symptoms are inducers of the liver enzyme cytochrome P450 3A4 (CYP3A4), and conversely, drugs that worsen symptoms are inhibitors of CYP3A4. St. John's wort (SJW; *Hypericum perforatum*) is a known inducer of CYP3A4. The purpose of this open-label study was to determine whether SJW alleviates the symptoms of Willis-Ekbom's disease.

Patients (n = 21, aged 12-76 years) with Willis-Ekbom's disease participated in this study conducted at the Faculdade de Medicina de Jundiaí; São Paulo, Brazil. Included patients met all 4 criteria for Willis-Ekbom's disease according to the International Restless Legs Syndrome Study Group (IRLSSG) (criteria not detailed), had symptoms ≥ 3x/week, and had an IRLSSG severity score of ≥15. For the first phase of the study, patients took 300 mg SJW (Hipericin®; Herbarium Labóratorios; Curitiba, Paraná, Brazil) 2 or 3 hours before bedtime for 10 days. The IRLSSG severity rating scale was used to evaluate symptoms at baseline and after 10 days of treatment. Patients were interviewed and asked to report the benefits of treatment in terms of percentage of symptom relief and improvement in sleep. SJW was considered effective if symptoms were relieved by ≥ 70%. For the second phase of the study, patients who reported ≥70% symptom relief continued taking 300 mg/day SJW for 3 months as needed to alleviate symptoms. When symptoms occurred, they would take SJW for 3-5 days and then stopped taking it until symptoms reappeared. The IRLSSG severity rating scale was repeated at the end of phase 2.

At the completion of Phase 1, 17 patients (81%) reported >70% subjective improvement in symptoms and better sleep, as compared to before receiving treatment. Four patients reported no improvement during Phase 1. The patients that continued on to Phase 2 reported that they would remain free of symptoms for 2-7 days (median 3 days) before

needing to take SJW again. They used the SJW for an average of 40 days during this 3-month phase. At the end of Phase 2, all 17 patients reported that they wanted to continue taking SJW for their treatment of Willis-Ekbom's disease. The baseline IRLSSG score for these patients was a median of 24 (±5.1) points, but after the 3-month treatment the median score was 4.1 (±1) points ($P < 0.0001$). No adverse effects were reported.

The authors conclude that SJW may be an effective treatment for symptoms of Willis-Ekbom's disease. They speculate that this may be related to influencing the metabolism and bioavailability of thyroid hormone and its balance with the dopaminergic system. They acknowledge that this was a pilot study, and a double-blind, placebo-controlled study is needed to confirm the findings and determine optimal dosing. Xenobiotics are known to induce or inhibit CYP3A4 for a variable period of time after exposure, which explains why SJW was effective for several days after treatment was stopped. These preliminary findings are encouraging. Patients need to be made aware that inducing CYP3A4 with SJW may alter the metabolism of other drugs taken by the patient. The patient should tell their doctor that they are taking SJW so that concomitant medications can be monitored for safety and efficacy, and concurrent or future diseases can be adequately controlled.

—Heather S. Oliff, PhD

Referenced article can be found at http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322013000400469&lng=en&nrm=iso&tlng=en.