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

HC 100251-292

Date: November 15, 2005

RE: Trial Shows St. John's wort Extract to be More Effective than Fluoxetine in Major Depressive Disorder

Fava M, Alpert J, Nierenberg A, Mischoulon D, Otto M, Zajecka J, et al. A double-blind, randomized trial of St. John's Wort, fluoxetine, and placebo in major depressive disorder. *J Clin Psychopharmacol.* 2005;25:441–447.

St. John's wort (*Hypericum perforatum*), a perennial flowering plant native to Europe and Asia, has been used medicinally for thousands of years. The Greek physicians Hippocrates, Pliny, and Galen prescribed it for various healing purposes, and it continued to be used during the Renaissance and Victorian eras for various ailments including mental disorders. Today it is used primarily for treatment of depression. More than 30 clinical trials have studied the safety and efficacy of St. John's wort for clinical depression, and most determined St. John's wort is superior to placebo and has a safety profile superior to pharmaceutical antidepressants.[1] The current study is a double-blind, randomized, parallel-group, multi-center, clinical trial comparing St. John's wort extract LI-160 (Lichtwer Pharma AG, Berlin, Germany), standardized to contain 0.12% to 0.28% hypericin, to fluoxetine (Prozac®; Eli Lilly Co., Indianapolis, IN, USA) and placebo for major depressive disorder (MDD).

This study, funded by a grant from Lichtwer Pharma AG, contained a 7-day, single-blind, washout period, followed by a double-blind 12-week therapy phase. It was conducted at 2 sites—the Depression Clinical and Research Program of the Massachusetts General Hospital in Boston, MA, and the Department of Psychiatry, Rush-Presbyterian–St. Luke's Medical Center in Chicago, IL. Included in the study were 135 volunteers (57% women; mean age 37.3 ± 11.0 years) with MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-4) lasting at least 2 weeks. A person may be diagnosed with MDD if 5 of the following 9 symptoms are present for 2 or more consecutive weeks, for most of each day, every day: depressed mood in adults or irritable mood in children and adolescents; significant reduction in level of interest or pleasure in most or all activities; loss or gain of weight when not dieting; insomnia (difficulty falling or staying asleep) or

hypersomnia (sleeping more than usual); behavior that is agitated or slowed down; decreased energy or fatigue; thoughts of worthlessness or extreme guilt; reduced ability to think, concentrate or make decisions; thoughts of death or suicide. One of the symptoms must be either depressed mood or loss of interest. Additional inclusion criteria included 18 to 65 years old, a HAMD-17 score ≥ 16, not pregnant, use of adequate contraception for women of child bearing potential, willingness and ability to comply with the study protocol, and written informed consent. HAMD-17 Hamilton Depression Scale (HAMD) score, a 17-question screening tool that assesses the severity of depression based on the presence of a depressed mood, self-depreciation and feelings of guilt, insomnia, agitation, and other symptoms. The mean HAMD-17 score for the 135 study participants was 19.7 ± 3.2).

Volunteers were randomized to receive 300 mg LI-160 three times daily, 20 mg fluoxetine per day, or placebo. Medication and placebo were administered using a double-dummy technique, so that each group received 4 tablets/capsules per day. Therefore, the LI-160 group received 3 LI-160 capsules plus 1 placebo capsule per day, while the fluoxetine group received 1 fluoxetine capsule per day and 3 placebo capsules. The primary outcome measure was the HAMD-17 score after 12 weeks of treatment. Secondary outcome measures were the Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), and the Beck Depression Inventory (BDI). HAMD-17, CGI-S, and CGI-I assessments were made by the researchers at each visit (baseline, then 6 visits over the 12-week treatment phase). The BDI is a self-administered 21 item self-report depression scale. The CGI is 7-point scale completed by the psychologist or psychiatrist that assesses the severity of illness (1 = normal/not at all ill, 7 = among the most extremely ill patients) and global improvement (1 = very much improved, 7 = very much worse). Safety was determined by monitoring vital signs (blood pressure and heart rate) and laboratory assessments (complete blood count, chemistries, and urinalysis) conducted at the pre-baseline screening examination and at after 12 weeks of treatment.

Baseline HAMD-17 score was 19.6 ± 3.5 for LI-160, 19.6 ± 3.1 for fluoxetine and 19.9 ± 2.9 for the placebo group. After treatment, the mean HAMD-17 score was significantly less in the LI-160 group compared to fluoxetine at all visits except visit 5 (week 8). After 12 weeks of treatment (visit 6), the mean HAMD-17 score was significantly less in the St. John's wort extract LI-160 group compared to fluoxetine after 12 weeks of treatment (10.2 ± 6.6 vs. 13.3 ± 7.3, respectively; $P < 0.05$). The LI-160 group showed a trend toward a significant reduction in the HAMD-17 score compared to placebo after 12 weeks of treatment (10.2 ± 6.6 vs. 12.6 ± 6.4, respectively; $P < 0.062$). Fluoxetine was not significantly better than placebo for the primary outcome measure after 12 weeks of treatment. Mean CGI-I significantly decreased with LI-160 treatment compared to fluoxetine (2.4 ± 2.2 vs. 3.0 ± 2.0, respectively; $P < 0.05$).

No volunteers in the LI-160 group dropped out due to adverse events (AEs), while 2 of 47 volunteers (4%) in the fluoxetine group discontinued the study because of AEs. No significant differences in rates of AEs occurred in any group, except for skin rash, which was more common in the placebo group. The most common complaints in the LI-160 group were headache (42%), dry mouth (22%), nausea (20%), gastrointestinal upset (20%), and sleepiness (18%).

This clinical trial adds to the growing body of evidence that specific St. John's wort extracts are at least as effective, if not more effective, than conventional antidepressant medication for the treatment of MDD. A previous equivalence trial of the St. John's wort special extract WS 5570 (Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany), standardized to 3-6% hyperforin and 0.12-0.28% hypericin, compared to paroxetine (Paxil®; GlaxoSmithKline, Philadelphia, PA) for moderate and severe depression showed a significantly greater reduction in HAMD score in the WS 5570 group compared to paroxetine after 7 weeks of treatment.[2] This study used escalating doses of WS 5570 and paroxetine, instead of the set dose in the LI-160 vs. fluoxetine trial. If escalating doses of fluoxetine had been used, a significant reduction in HAMD-17 score may have been detected in the current study, instead of the non-significant reduction seen with 20 mg/day fluoxetine. The authors recognize this limitation in their study design, writing, "data from our group suggest that a significant proportion of patients nonresponding to 20 mg/d may go on to respond when the dose is increased to 40 or 60 mg/d." Similarly, a greater proportion of LI-160 nonresponders may have respond to doses greater than the 900 mg/day LI-160.

A third study sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Mental Health compared 900–1500 mg/day St. John's wort extract LI-160 and 50–100 mg/day sertraline (Zoloft®, Pfizer, New York, NY).[3] The NCCAM trial found that neither LI-160 nor sertraline was significantly different than placebo for the treatment of MDD. However, as the authors of the current LI-160 vs. fluoxetine study note, "negative studies for antidepressant medications are relatively common among agents meeting approval for Food and Drug Administration approval, and all studies on an agent need to be considered when evaluating the true effect size of the agent."

—John Neustadt, ND

References

[1]Miller AL. St. John's Wort (Hypericum perforatum): clinical effects on depression and other conditions. *Alt Med Rev.* 1998;3(1):18-26.

[2]Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. *Bmj.* Mar 5 2005;330(7490):503.

[3]Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA.* April 10, 2002 2002;287(14):1807-1814.

The American Botanical Council has chosen not to reprint the original publication.