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NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Questions and Answers: A Trial of St. John's Wort (*Hypericum perforatum*) for the Treatment of Major Depression

Background on St. John's Wort and Depression

1. What is St. John's wort?

St. John's wort (*Hypericum perforatum* in Latin) is a long-living, wild-growing plant with yellow flowers. Extracts of the plant have been used for centuries in efforts to treat mental disorders as well as nerve pain. In ancient times, doctors and herbalists (specialists in herbs) wrote about its use as a sedative and treatment for malaria as well as a balm for wounds, burns, and insect bites. Today, St. John's wort is used for treating mild to moderate depression, anxiety, or sleep disorders. St. John's wort remains among the top-selling botanical products in the United States and many brands are now available and sold over the counter as dietary supplements.

2. Does St. John's wort have side effects or interact with prescription medications?

The most common side effects of St. John's wort include dry mouth, dizziness, gastrointestinal symptoms, increased sensitivity to sunlight, and fatigue. Research from the National Institutes of Health (NIH) reveals that St. John's wort may reduce the effectiveness of several drugs by speeding up activity in a key pathway responsible for their breakdown. The end result is that blood levels of these drugs decrease because the body breaks them down faster making the drugs less effective. St. John's wort especially affects indinavir, a protease inhibitor used to treat HIV infection. It may also affect cyclosporine, a drug used to help prevent organ transplant rejection, and other drugs that work through this same pathway in the body, such as birth control pills and medications for heart disease and depression. The U.S. Food and Drug Administration (FDA) issued a Public Health Advisory on February 10, 2000, warning physicians of these potential adverse interactions and advising them to alert their patients (see www.fda.gov/cder/drug/advisory/stjwort.htm).

3. What was the St. John's wort extract used in this trial?

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The St. John's wort extract used in this study was LI-160, manufactured by Lichtwer Pharma, AG (Berlin, Germany). It was selected because it is a well-characterized and

well-studied extract of St. John's wort that had published literature supporting its possible efficacy in treating depression. The entire supply of St. John's wort extract used in the study came from one batch and was standardized to between 0.12 and 0.28 percent hypericin. Hypericin is thought to be one of the primary active ingredients in St. John's wort.

4. What is major depression?

Major depressive disorder, also known as major depression, is the most common type of depressive illness. Symptoms usually develop over days, weeks, or months. They can cause distress and/or interfere with the ability to work, study, sleep, eat, and enjoy once-pleasurable activities. The description of a person experiencing a major depressive episode, as found in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, is that of someone who may feel sad, irritable, hopeless, discouraged, tired, worthless, or guilty much of the time. The person also often cannot think clearly, concentrate, or make decisions. This depressed mood lasts most of the day nearly every day for a period of at least 2 weeks. Untreated, the depression can last for 6 months or longer. Other than depressed mood and/or loss of interest or pleasure, symptoms include at least four of the following:

- Significant weight gain or loss
- Disturbance of normal sleeping patterns (insomnia, hypersomnia)
- Agitation or unusual slowness
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide

Major depression can vary in degree from **mild** to **moderate** to **severe**. In mild cases, there may be some significant distress or interference with daily activities at work, at home, and in social life. In moderate depression, problems and impairments in these areas are more pronounced. If the depression is severe, the person may lose completely the ability to function.

5. Are there proven treatments for major depression?

Fortunately, major depression can be successfully treated. Treatments that have been scientifically proven include a variety of antidepressant medications approved by the FDA and certain psychotherapies, such as cognitive-behavioral therapy and interpersonal therapy. A first step toward getting treatment for depression is a complete physical examination and evaluation by a doctor. The physician can rule out medical conditions, such as a viral infection or thyroid disorder, that can cause the same symptoms as depression.

6. Why did NIH fund a trial of St. John's wort?

There is considerable public interest in the possibility that St. John's wort may be an effective treatment for depression. These claims are based on findings from research studies conducted in

Europe; however, these studies had several limitations. According to the researchers who led this NIH study, important issues have been raised regarding the existing studies, including: limited information about the use of St. John's wort in clinically defined major depression; lack of placebo-controlled trials that have included a separate, selective serotonin reuptake inhibitor (SSRI) antidepressant arm; and absence of data regarding long-term use of the extract. In addition, there were concerns that many of the studies had smaller numbers of participants.

Because of the growth in Americans' use of St. John's wort in recent years and the need to answer important remaining questions about the herb's efficacy and long-term use for depression, NIH launched a large study of St. John's wort in 1997. This 4-year, $6 million study was sponsored by the National Center for Complementary and Alternative Medicine (NCCAM), the National Institute of Mental Health (NIMH), and the NIH Office of Dietary Supplements (ODS). The main purpose of the trial was to determine whether a well-standardized extract of St. John's wort is effective in the treatment of adults suffering from major depression of moderate severity.

About the Trial

7. How many people participated in the trial, and what were their characteristics?

There were 340 participants in the trial. The average age of participants entering the study was approximately 42 years. Nearly two-thirds were female (65.9 percent). The ethnic composition of the group was approximately 76 percent White, 10 percent Black/African American, 8 percent Hispanic, and 6 percent "other."

8. How were participants selected?

Eligible participants were men and women ages 18 and older with depression who were confirmed prior to entering the study as having a diagnosis of major depressive disorder as defined by the *DSM-IV*. In addition, to be eligible, participants had to have at least a moderate level of depressive symptoms as measured by the Hamilton Depression Scale (HAM-D), and at least a moderate level of functional impairment from depression on the Global Assessment of Functioning Scale (GAF) of the *DSM-IV*. Individuals with severe symptoms who were in need of hospitalization, at high risk for suicide, or having any signs of psychosis (such as hallucinations or delusions) were excluded. These eligibility criteria provided a well-defined group of participants that would represent adults with major depression whose symptoms were significant, though not completely incapacitating.

9. What are some of the primary characteristics of this trial?

This trial had three treatment arms. Participants were assigned at random to one of three treatments for an initial 8 weeks: St. John's wort, an SSRI antidepressant medication—sertraline (Zoloft), or placebo (inactive pills that looked exactly like St. John's wort or sertraline tablets). This was a double-blind study, meaning neither the participants nor the clinical staff knew which treatments were being assigned. Participants who responded well to their assigned treatment could continue on it for an additional 4 months during the trial's second, or continuation, phase. This

phase allowed researchers to gather additional data on the safety and longer-term effects of the treatments. This was the first trial to include a long-term followup phase studying the use of St. John's wort. Participants had regular followup visits to monitor symptoms and any side effects. If participants experienced significant worsening of depression, suicidality, or psychosis, they were withdrawn from the study; offered FDA-approved treatment with at least three followup visits, based on need; and referred to a psychiatrist not involved in the study for care.

To determine the efficacy of St. John's wort for major depression, the group of participants assigned to St. John's wort was compared to the group assigned to placebo during the first 8 weeks of treatment. Two primary outcomes were measured:

- Improvements in the HAM-D total score, indicated by a reduction to normal levels in score
- Complete response to treatment, the percentage of participants essentially free of symptoms of depression, also called "in remission"

A complete response was determined by both a reduction in the HAM-D score and the clinician's overall estimate of improvement, as measured by the Clinical Global Impressions–Improvement Scale (CGI-I). In addition to the tests already mentioned, several secondary measures of efficacy were used, including clinician-rated and patient-self-administered scales.

10. What are the main results of this trial?

The trial found no statistically significant difference between St. John's wort and placebo on improvement in HAM-D scores or percentage of complete responses. The percentage of participants in remission from major depression at the end of the 8-week initial treatment phase was approximately 24 percent for St. John's wort and about 32 percent for placebo. Overall, the percentage of participants who improved either partially or completely was about 38 percent for St. John's wort and 43 percent for placebo. These findings suggest that St. John's wort is not effective for the treatment of major depression in adults with a moderate level of symptoms. This conclusion is supported by another recently reported placebo-controlled study (Shelton et al., 2001).

The study also found no significant difference between sertraline and placebo on either primary outcome, with about 25 percent of the participants on sertraline reaching remission as compared to about 32 percent on placebo. The rate of response overall was about 49 percent for sertraline and 43 percent for placebo, but this difference was not statistically significant. At the same time, additional planned analyses of the data did show that sertraline was superior to placebo on other secondary tests of efficacy, such as the CGI-I alone. The results of the sertraline versus placebo comparison indicate that the sensitivity of this study to antidepressant effects was limited. In other words, even two treatments (sertraline and placebo) previously proven to differ in efficacy for major depression were found not to differ on the primary measures used in this study.

11. Why did sertraline have no greater effect than placebo?

The authors offer possible explanations as to why sertraline was not superior to placebo overall in this study. First, it is known that 35 percent of studies of approved, active antidepressants do not

show greater efficacy of the antidepressant over placebo. Second, it is possible that the dose range for sertraline of 50 to 100 milligrams (mg) per day during the first 8 weeks, chosen to ensure effective treatment while minimizing side effects, may not have been adequate despite extensive discussions among study designers to find the best possible dose range.

12. What is sertraline?

Sertraline is an FDA-approved antidepressant of the type known as a selective serotonin reuptake inhibitor (SSRI). Serotonin is a neurotransmitter, a chemical messenger in the brain, that is thought to be in low supply in individuals suffering from depression. An SSRI, such as sertraline, works by blocking the reuptake of serotonin in the nerve cells in the brain, thus making more serotonin available for proper brain function.

13. Why was sertraline used in the trial?

Sertraline was included in this trial to provide a third "active" control arm to aid in assessing the trial's overall validity. That is, whether the study measured antidepressant effects and not the impact of unrelated factors, such as the effect of a patient withdrawing from the study before the treatment could work. By having a third trial arm with sertraline and comparing it to placebo, the researchers could also measure how sensitive the trial was to detecting any antidepressant effects of St. John's wort. If sertraline would prove superior to placebo in this study, as expected, then the study's ability to detect antidepressant effects would be confirmed. In addition, the researchers chose to use an SSRI because there is a lack of placebo-controlled trials of St. John's wort that included an SSRI arm.

14. Who provided the extracts and drugs used in the trial?

Lichtwer Pharma donated the St. John's wort extract in tablet form together with matched placebo. Pfizer Inc. donated the supply of sertraline and its matching placebo.

15. What dose of St. John's wort was used in the NIH study?

The starting dose of St. John's wort was 900 mg per day (given in 300 mg tablets, three times a day). That dose could be increased up to 1,500 mg per day in the first 6 weeks of the study until the end of the first phase of the trial at 8 weeks. During the second phase of the trial, after 8 weeks, the dose could be increased to 1,800 mg per day. The average dose of St. John's wort in the initial 8 weeks of the study was about 1,300 mg per day.

16. What dose of sertraline was used in the NIH study?

The average dose of sertraline in this study was 75 mg per day. The starting dose was 50 mg per day and could be increased to 100 mg per day in the first phase of the study. During the second, or continuation, phase of the trial the dose could be increased to 150 mg per day. The range of dosages was comparable to that used in clinical practice.

17. What were the most common side effects for St. John's wort or sertraline in the study?

St. John's wort was generally well tolerated. However, people who were taking the extract did experience more sexual dysfunction, general swelling, and urinary frequency than those taking placebo. Side effects for those taking sertraline included sexual dysfunction, sweating, nausea, and diarrhea.

18. Who conducted the study?

The principal investigator for this study was Jonathan R.T. Davidson, M.D., professor of psychiatry and director of the Anxiety and Traumatic Stress Program at Duke University Medical Center, Durham, North Carolina. Dr. Davidson is an expert in clinical research on conventional as well as complementary and alternative medical treatments for mood and anxiety disorders. Dr. Davidson and his collaborators in the Department of Psychiatry and Behavioral Sciences, the Duke Clinical Research Institute, and the Research Triangle Institute, coordinated the entire study.

19. Who else was involved in the NIH St. John's wort trial?

The scientific aspects of the study were monitored by NIMH and NCCAM staff with the input of an independent group of advisors who were consulted regularly on the protocol and study progress before and during the course of the project. This group included the following: four professors of psychiatry at different universities with specific expertise in the treatment of depression; a professor of pharmacology with expertise in clinical research, pharmacokinetics, and metabolism; a professor of statistics; an expert in botanical medicinal products; and an advocate for people with depression. The study's safety and data quality were monitored on a quarterly basis by the NIMH Data and Safety Monitoring Board, a group including experts in clinical studies and patient representatives. In addition, this study was monitored by the FDA under an Investigational New Drug application filed by Lichtwer Pharma.

20. Where did the study take place?

The study took place in 12 community and academic psychiatric research centers across the United States. The sites and lead investigators were as follows:

- Dean Foundation, Middleton, Wisconsin (Leslie Taylor, M.D.)
- Duke Medical Center, Durham, North Carolina (Murali P. Doraiswamy, M.D. and Richard Weisler, M.D.)
- Eastside Medical Center, New York, New York (Ram K. Shrivastava, M.D.)
- Emory University, Atlanta, Georgia (Charles B. Nemeroff, M.D., Ph.D. and Jeffrey Kelsey, M.D., Ph.D.)
- Harbor-UCLA Medical Center, Torrance, California (Khae-Ming Lin, M.D.)
- Feighner Research Institute, San Diego, California (John P. Feighner, M.D.)
- McLean Hospital, Belmont, Massachusetts (Jonathan O. Cole, M.D.)
- Seattle Clinical Research Center, Seattle, Washington (Peter D. Londborg, M.D.)

- Stanford University, Palo Alto, California (Alan F. Schatzberg, M.D. and Charles Debattista, M.D.)
- University of Cincinnati, Cincinnati, Ohio (Paul Keck, M.D.)
- University of South Florida, Tampa, Florida (David V. Sheehan, M.D.)
- University of Texas Southwestern Medical Center, Dallas, Texas (Madhukar H. Trivedi, M.D.)

21. How long did it take to complete the trial?

Recruitment of participants took place from December 1998 to June 2000. Analysis of results was completed in 2001, and the paper was submitted for publication in late 2001.

Conclusion and Future Research

22. Should St. John's wort be used for major depression?

At this time, it is not known what role St. John's wort should play in the management of depression. The results of this study indicate that St. John's wort is not effective in treating major depression of moderate severity.

23. Will NIH conduct more research on St. John's wort?

NCCAM, NIMH, and ODS are planning to conduct a study of the efficacy and safety of St. John's wort for the treatment of minor depression.

For Additional Reading

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

Shelton RC, Keller MB, Gelenberg AJ, et al. Effectiveness of St. John's wort in major depression. *JAMA*, 2001; 285:1978–86.

Linde K, Ramirez G, Mulrow CD, et al. St. John's wort for depression—an overview and meta-analysis of randomized clinical trials. *Br. Med J*, 1996; 313:253–8.

American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV)*. Washington, DC: American Psychiatric Press, 1994.

NCCAM, St. John's Wort Fact Sheet, available online at nccam.nih.gov, updated April 2002.

NIMH depression information available at www.nimh.nih.gov/publicat/depressionmenu.cfm.

The Coordinating Center for the St. John's wort trial was led by Dr. Davidson and his colleagues at the Duke University Medical Center Department of Psychiatry and Behavioral Sciences, the

Duke Clinical Research Institute, and the Research Triangle Institute. For more Duke University Medical Center news visit www.dukemednews.duke.edu.

NCCAM is dedicated to exploring complementary and alternative healing practices in the context of rigorous science, training complementary and alternative medicine (CAM) researchers, and disseminating authoritative information to the public and professionals. For additional information on CAM, contact the NCCAM Clearinghouse:

Toll-free in the U.S.: 1–888–644–6226
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TTY (for deaf and hard-of-hearing callers): 1–866–464–3615

E-mail: info@nccam.nih.gov
NCCAM Web site: nccam.nih.gov
Address: NCCAM Clearinghouse, P.O. Box 7923, Gaithersburg, MD 20898–7923

Fax: 1–866–464–3616

The NCCAM Clearinghouse provides information about CAM, including St. John's wort, and about NCCAM.

The National Institute of Mental Health is committed to reducing the burden of mental illness through research on mental disorders and the underlying basic science of brain and behavior. For more information about depression or other mental health disorders visit www.nimh.nih.gov.

The Office of Dietary Supplements, whose mission is to explore the potential role of dietary supplements to improve health care, promotes the scientific study of dietary supplements through conducting and coordinating scientific research and compiling and disseminating research results. For more information visit dietary-supplements.info.nih.gov.

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