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St. John's Wort for Depression

By Carmen Tamayo, MD

DEPRESSION IS A SERIOUS MEDICAL ILLNESS THAT AFFECTS A PERson's mood, thoughts, physical health, and behavior.[1] Depressive disorders, including major depression and dysthymia, are disabling illnesses and affect nearly 19 million Americans each year. In the United States, it is estimated that one in five individuals is affected by a mood disorder in his or her lifetime.[2] The World Health Organization estimates that worldwide 9.5% of women and 5.8% of men will experience a depressive episode in any given year.[3] The lifetime risk for major depressive disorders (MDD) ranges from 10% to 25% for women and from 5% to 12% for men.

History

St. John's wort (*Hypericum perforatum*), a bushy, low-growing plant covered with yellow flowers, has a 2,000-year history of use as a medicinal herb. St. John's wort (SJW) is used widely in the treatment of mild-to-moderate depression in Europe and has become increasingly popular in the United States.

Mechanism of Action

SJW's mechanism of action is not understood fully. The plant contains many biologically active components including hyperforin and adhyperforin (phloroglucinols); hypericin and pseudohypericin (naphthodianthrones); flavonoids; xanthones; oligomeric procyanidines; and amino acids.[4] Treatment with SJW seems to disinhibit the hypothalamus-pituitary-adrenocortical-system in healthy subjects and patients with depression. Furthermore, it decreases intracerebral corticosteroids, which may have an effect in associated depression symptoms. This effect has been proved in studies of patients with atypical depressive features, somatization, and fatigue and for whom SJW appears to be especially effective.[5]

Clinical Trials

In recent years, SJW has undergone extensive scientific investigation.[6,7] Its effectiveness has been shown in studies comparing it with placebo and common antidepressants. However, it is not clear if SJW is as effective as newly developed standard antidepressive agents. In the past 20 years, a number of clinical trials, meta-analyses, and systematic reviews with both positive and negative

results have been published in the literature. Table 1 summarizes systematic reviews and meta-analyses of SJW for depression published between 2000 and 2004. A recent review article found SJW to be more effective than placebo and equally as effective as tricyclic antidepressants in the short-term management (1-3 months) of mild-to-moderate depression.[8]

Clinical trials of SJW conducted in the past five years have shown contentious results. It is important to note that there are major differences in the methodology of these trials (e.g., patient selection, endpoints, SJW doses, and selection of control group). It also is important to note that depression studies typically have a significant placebo response. In fact, failure of established antidepressants to show superiority against placebo occurs in up to 35% of trials.[9] Many factors seem to contribute to this such as: failure in rating the degree of depression at the initiation of the study, short disease duration, lack of established inclusion criteria, lack of patient compliance with the treatment, lack of experienced investigators, use of concomitant medications, and short study duration.

Two of the most recently published trials have been the object of controversy[10,11] because of methodological issues and publication bias. The first study, sponsored by the National Institutes of Health, compared SJW with a placebo in 200 outpatients from 11 U.S. academic centers.[12] Participants completed a one-week, single-blind run-in of placebo, then were randomly assigned to receive either SJW extract (n = 98; 900 mg/d for four weeks, increased to 1,200 mg/d in the absence of an adequate response thereafter) or placebo (n = 102) for eight weeks. Although the study was rigorous and met reasonable expectations for a well-conducted pharmaceutical study, the selected population included only patients with major depression (not mild or moderate). This study did not include a referenced agent or active conventional antidepressant arm. Response was defined as a Hamilton Rating Scale for Depression (HAM-D) score of ≥ 12 and a Clinical Global Impressions (CGI) score of 1 or 2. The rate of change in HAM-D scores over the course of the trial for the intention-to-treat sample revealed no significant difference between treatments (P = 0.16). The number of SJW patients who reached remission (14/98; 14.3%) was significantly higher than placebo (5/102; 4.9%). However, this likely was influenced by very low remission rates in both groups. In a subgroup analysis of patients with less severe initial depression, there was no difference in rate of change in the HAM-D scores between the SJW (n = 60) and placebo groups (n = 50).

The second study, sponsored by Pfizer, compared SJW (LI 160 extract), placebo, and sertraline (Zoloft®, a selective serotonin reuptake inhibitor [SSRI]).[13] This study, which also evaluated patients (n = 340) with severe rather than mild-to-moderate MDD, yielded negative results both for the SSRI and SJW as neither SJW nor sertraline (50-100 mg/d) could be differentiated from placebo. The main outcome measure was change in the HAM-D total score from baseline to eight weeks and rates of full responses. The study may have been too brief, only eight weeks at doses of 900-1,500 mg/d of SJW, and the administered doses too low, as only 54% of patients in the SJW group and 36% in the sertraline group received the maximum permitted dosage to detect full therapeutic effects of SJW or sertraline. In addition, it may not have been powered adequately to detect between-group differences, taking into account the potential improvements in the placebo group.

Several placebo-controlled studies suggest that SJW is more effective than placebo. The largest of these trials treated 375 outpatients with mild-to-moderate depression with SJW (WS 5570) 300 mg tid for six weeks.[14] Median difference in change in HAM-D score between WS 5570 and placebo was 3 points. Percentage of responders was 52.7% in the SJW group vs. 42.3% in the placebo group; the 10.4% difference was statistically significant.

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EDITORIAL GROUP HEAD: Lee Landenberger.

MANAGING EDITOR: Paula L. Cousins.

EDITOR: Leslie G. Coplin.

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Table 1

Systematic reviews and meta-analyses of SJW in the treatment of depression (2000-2004)

Reference	Study Design/ # of trials/# of Subjects/Duration	Intervention	Results
Linde [35] (Cochrane Review 2004)	Meta-analysis 27 RCTs n = 2,291 Follow-up = 5.3 weeks	*Hypericum* vs. placebo and standard antidepressants	Positive. SJW significantly better than placebo. Relative risk (RR) 2.47; 95% confidence interval (CI) 1.69-3.61. Similarly effective as standard antidepressants (single preparations RR 1.01; 95% CI 0.87-1.16, combinations RR 1.52; 95% CI 0.78-2.94).
Shulz[36]	Overview of the studies conducted since 1990 34 RCTs/n = 3,000 Mild-to-moderate forms of depression Follow-up = 4-6 weeks	Comparison of water vs. ethanol extracts; comparison of different doses of SJW with synthetic antidepressants	No major differences in efficacy of the alcoholic extracts. Threshold dose for efficacy about 300 mg/d of extract. Doses of approximately 500-1,000 mg/d of SJW are of comparable efficacy to synthetic antidepressants in their normally prescribed dosages
Whiskey[37]	Systematic review and meta-analysis 22 controlled trials in review 6 controlled trials in meta-analysis n = N/A	SJW vs. placebo and tricyclic antidepressants	Positive. SJW superior to placebo. RR 1.98; 95% CI 1.49-2.62. Not significantly different or comparable in efficacy from tricyclic antidepressants (RR 1.0; 95% CI 0.90-1.11)
Gaster[38]	Systematic review 8 RCTs n = NA	SJW vs. placebo and tricyclic antidepressants	Positive; 23% to 55% absolute increase in response rate for SJW vs. placebo in mild-to-moderate depression; 6% to 18% less effective than tricyclic antidepressants.

In a multicenter study conducted in Germany, 72 similar patients were given 900 mg/d of SJW (WS 5572) or placebo for six weeks.[15] Group differences in favor of SJW were descriptively apparent as early as day 7 of randomized treatment and were statistically significant at days 28 ($P = 0.011$) and 42 ($P < 0.001$). In this study both percentage of responders and > 50% reduction in HAM-D were significantly better for the SJW group. Between baseline and treatment end, the HAM-D total score decreased from 19.7 ± 3.4 to 8.9 ± 4.3 points in the SJW group and from 20.1 ± 2.6 to 14.4 ± 6.8 points in the placebo group (mean ± SD). Good tolerability was observed in both groups with no adverse effects reported. Comparable group differences in favor of WS 5572 were found for von Zerssen's Depression Scale (self-rating), CGI, and a global patient's self-assessment.

A slightly higher dose (up to 1,450 mg/d) was administered to 150 outpatients with moderate depression or dysthymia during a six-week period.[16] This dose was compared with SJW 900 mg/d and placebo. There was a significant reduction in HAM-D score and Beck Depression Inventory (BDI) in all three groups compared to baseline ($P < 0.05$).

A double-blind RCT comparing SJW (900-1,800 mg/d) with sertraline (50-100 mg/d) was conducted in 87 patients who had major depression and had been seen by community-based offices of 12 family physicians.[17] In this study there were no major differences in changes of HAM-D and BDI but significantly more side effects were observed in the sertraline group.

In a seven-week pilot study, SJW (LI 160) was administered to 30 patients with major single or recurrent depression.[18] Both SJW and sertraline were administered in escalating doses (600 mg/d of SJW for one week, followed by 900 mg/d for six weeks) vs. sertraline (50 mg/d for one week, followed by 75 mg/d for six weeks). Results suggested that both treatments were therapeutically equivalent (HAM-D scores for patients on both therapies significantly improved [$P < 0.05$]). However, clinical response (> 50% reduction in HAM-D) did not differ between the two groups.

Comparisons of SJW with fluoxetine hydrocloride (Prozac) and tricyclic antidepressants (imipramine) suggest that SJW is therapeutically equivalent to these widely used drugs. A study of 240 patients with mild-to-moderate depression compared 500 mg/d of SJW (ZE 117) vs. fluoxetine 20-40 mg/d.[19] The mean HAM-D at endpoint decreased to 11.54 for those taking SJW and to 12.20 for fluoxetine ($P < 0.09$). Mean CGI (severity) was significantly ($P < 0.03$) superior for SJW, as was the responder rate ($P = 0.005$) More adverse events were observed for fluoxetine (23%) than SJW (8%), so the main difference between the two treatments was safety.

In a later study, Behnke et al treated 72 patients with mild-to-moderate depression for six weeks with SJW (Calmigen extract) or fluoxetine. Significant decreases ($P < 0.001$) were observed in the HAM-D score (50% in the SJW group, 58% in the fluoxetine group) as well as von Zerssen's Depression Scale (42% in the SJW group, 52% in the fluoxetine group).[20]Assessments by

physicians and patients indicated considerable improvement with no differences between treatments. Again in this study SJW was better tolerated than fluoxetine. The authors concluded that the SJW used in this study is therapeutically equivalent to fluoxetine and therefore is a rational alternative to synthetic antidepressants.

One study that included 324 patients with mild or moderate single or recurrent depressive disorder found SJW (ZE 117, 500 mg/d) to have a better safety profile when compared to imipramine (75 mg bid).[21] However, no significant difference between the two groups on HAM-D or CGI scores was observed. The imipramine group scored significantly better in the anxiety-somatization subscale. Both treatments were equivalent, but SJW was better tolerated.

A randomized, double-blind, crossover safety/efficacy trial, designed and sponsored by the National Institute of Mental Health, the National Center for Complementary and Alternative Medicine, and the Office of Dietary Supplements, currently is being conducted to evaluate the efficacy of SJW and citalopram (Celexa®) compared to placebo in patients with mild-to-moderate depression. For more information, see article on page 80.

Use During Pregnancy and Breastfeeding

There is limited evidence for the efficacy of SJW in pregnant and breastfeeding women. Although no clinical trials evaluating SJW use in pregnancy were found, a recent case report indicated SJW did not have adverse effects in breastfeeding women.[22] In another case report, breast milk samples were obtained from a women with postpartum depression who was taking SJW. No adverse effects on mother or infant were observed.[23] One study in mice found that SJW did not significantly affect cognitive tasks performed by the offspring of mice receiving SJW before and throughout gestation.[24]

In a small safety study, 33 breastfeeding women taking SJW were compared with 101 breastfeeding women who were not taking SJW.[25] Adverse events were observed in both groups and included colicky infants (two in SJW vs. one in the control group), two cases of drowsiness in the SJW group, and one case of lethargy in the SJW group. The differences were not significant. However, the small sample size and possible selection bias of this study prevent one from making definitive conclusions as to whether the adverse events were attributable to SJW.

Safety of SJW

There is concern that adverse effects and safety of herbal medicines are underreported.[26] Nevertheless, safety and tolerability studies have revealed that SJW preparations have better safety and tolerability profiles than synthetic antidepressants[27] and appear to be safe when used in recommended doses and for less than three months. However, it generally takes at least 12 weeks to get a full response from SJW.

The most common observed adverse events in clinical trials and in observational studies have been skin reactions including photosensitization, rash, and itching; gastrointestinal problems; fatigue; restlessness; headaches; dizziness; and dry mouth.[28]

The safety of SJW during pregnancy and breastfeeding has not been established in randomized controlled trials. Very little information on reproductive safety exists; therefore, SJW cannot be recommended as safe therapy for pregnant and breastfeeding women.

SJW Drug Interactions

Interactions of SJW with conventional drugs has become an issue of increased awareness among consumers, health care practitioners, and industry,[29] and more research is needed to determine the nature and severity of the interactions. The U.S. Food and Drug Administration issued a Public Health Advisory on Feb. 10, 2000, stating that SJW appears to affect an important metabolic pathway that is used by many drugs prescribed to treat conditions such as AIDS, heart disease, depression, seizures, certain cancers, and rejection of transplants.[30]

Recent reports indicate that SJW extracts may potentiate the effect of certain enzymes required for the metabolism (absorption and excretion) of drugs such as warfarin, digoxin, theophylline, cyclosporin, and oral contraceptives. This may decrease the serum concentration of these drugs and reduce their therapeutic effects.

In addition, evidence exists that SJW reduces the effect of contraconceptives and that women taking SJW and contraconceptives for an extended period experienced a major incidence of unwanted pregnancies and bleeding.[31]

In general SJW has been shown to lower the plasma concentration (and/or the pharmacological effect) of a number of drugs including alprazolam, amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, irinotecan, methadone, nevirapine, simvastatin, tacrolimus, theophylline, warfarin, phenprocoumon, and oral contraceptives.[32]

HIV-positive or AIDS patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors should use caution when taking SJW.[33] Patients taking photosensitizing drugs and patients with iron deficiencies should avoid SJW because the presence of tannins in SJW may inhibit iron absorption.[34] Several human cases of reversible photosensitivity to SJW have been reported.

Dosage

SJW products are available in a variety of forms (tablets, capsules, liquid extract, tea). Indications and dosage vary according to the manufacturer. Studies suggest that the brands are not interchangeable. Most SJW products are standardized to 3% hypericin extract, but some products are standardized to 2-5% hyperforin. For adults, the most commonly used dose for maintenance therapy is 300-600 mg tid. In clinical trials, dosages varied from 300-1,450 mg/d.

Conclusion

There is an urgent need for better data about the efficacy of newer pharmacotherapies, including SJW, in patients with non-major depression, refractory depression, and other depressive disorders, as well as in a broad array of special populations, including pregnant or breastfeeding women, children, adolescents, and the elderly.

SJW has been reported to be more effective than placebo and as effective as tricyclic antidepressants in the short-term management of mild-to-moderate depression. Overlapping meta-analyses and systematic reviews of multiple trials over the last two decades,[35-38] as well as several more recent short-term randomized trials, support this conclusion. Comparisons of SJW with newly developed SSRIs have provided limited equivalence data to date.

Overall, the evidence supporting the efficacy of SJW in mild-to-moderate major depression remains compelling while the evidence for severe major depression is unclear. In addition, there are ethical concerns with treating major depression with SJW because even if SJW should prove effective in this population, it is much more slow to show clinical effect than standard pharmaceutical options. ❖

Dr. Tamayo is Director, Division of Complementary and Alternative Medicine, Foresight Links Corp., London and Dundas, Ontario, Canada.

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Bone Up on a Healthy Diet

Source: Lin PH, et al. The DASH diet and sodium reduction improve markers of bone turnover and calcium metabolism in adults. *J Nutr* 2003;133:3130-3136.

■ Comments by Mary L. Hardy, MD

OSTEOPOROSIS IS A PREVENTABLE DISEASE THAT increases the risk of fracture for more than 10 million American men and women, causing more than 1.5 million fractures per year.[1] These fractures result in significant morbidity and mortality for populations at risk and represent a large cost (estimated at $14 billion per year) for an already strained health care system.[1] Projections suggest that these numbers only will increase as our baby boomer population ages. An additional 34 million Americans have osteopenia now, and dramatic increases in osteoporosis are anticipated by 2050 due to aging and the cumulative effects of poor diet and lifestyle habits.[1] Current therapy focuses on calcium and vitamin D replacement, along with more aggressive pharmaceutical measures, such as bisphosphonates. Risk factor modification, especially if started early in life, can allow formation of maximum bone mass and reduce the age-related decline in bone density. Increasing weight-bearing exercise, stopping smoking, and decreasing alcohol and caffeine intake commonly are recommended. However, recent literature suggests that dietary modifications, beyond increased calcium intake, may be helpful in maintaining healthy bone mass. Some of these factors may not be immediately obvious to patients or practitioners.

Over the last decade, a number of significant observations have been made regarding diet and bone health. First, there are data suggesting that the acid-base balance of the body may affect the rate of absorption of calcium from bone, as it has been observed that increased acidity increases the rate of calcium loss in the urine. In effect, the large mass of bone acts as a buffer to maintain the acid-base balance of the body. Certain foods, such as meat, grains, and some cheeses, and metabolic states, such as starvation or diabetic ketoacidosis, are felt to increase the acidity of the body. Other dietary constituents besides calcium also have been noted to affect bone density. For example, positive benefits on bone metabolism have been noticed in observational studies of subjects eating a diet high in fruits and vegetables. Increasing fruit and vegetable consumption from 3.6 to 9.5 servings per day decreased urinary calcium excretion by one-third.[2] In addition, high dietary sodium loads have been associated with an increase in urinary calcium loss, especially in postmenopausal women.[3] Even small losses of calcium can have profound effects over a time. It has been calculated that the net loss of 1 mmol/d of calcium could lead to the loss of one-third of the bone mass of a normal adult over two decades, if no other compensatory mechanisms intervened.[4] Thus, even small changes related to dietary interventions could prove very significant in the prevention or modification of osteoporosis.

Lin and colleagues tested the effects of a diet rich in fruits, vegetables, and low-fat dairy products (Dietary Approaches to Stop Hypertension [DASH] diet) in a randomized clinical trial designed to test the diet's effect on blood pressure.[5] Two of the trial sites involved in the larger trial also included measurements designed to examine the effect of the dietary intervention on bone health. The DASH diet differs from the standard American diet in that it is lower in acid load, fats, and cholesterol; is higher in potassium, calcium, and magnesium; and derives more phytochemicals from fruits and vegetables. The trial also included three daily sodium levels: higher (3.5 g), intermediate (2.3 g), or lower (1.1 g). Subjects were adults with mild or borderline elevations in systolic and/or diastolic blood pressure defined as blood pressure greater than 120/80. The group was a little over half women, mainly Hispanic and African-American, who had an average BMI of 29, suggesting that they were overweight, bordering on obese. Subjects were randomly assigned to either the DASH diet or a conventional Western diet for three 30-

day trials at each of the three sodium levels. Subjects were given all of their food and the caloric content was adjusted to maintain their starting weight.

Outcomes included serum measures of bone formation (OC) and resorption (CTX), urinary calcium (UC), and parathyroid hormone (PTH) levels. The DASH diet decreased OC by 11-18% and CTX by 16-18%. Both of these markers of bone resorption were significantly reduced at all three sodium levels. No change was noted in the levels of PTH or UC comparing the DASH diet overall to control. The effect of sodium was more mixed on markers of bone reformation and PTH. However, urine calcium concentrations decreased in a dose-dependent manner with decreasing sodium intake in both control and DASH diet participants. Thus, the DASH diet showed a benefit in reducing the markers of bone turnover. In addition, lowering sodium led to a decrease in urinary calcium loss, another potentially negative factor for bone mass.

Despite the fact that the exact mechanism by which the DASH diet positively affects bone health is unknown, health professionals should be vigorously recommending this style of diet to patients. Besides the bone benefits, additional favorable outcomes for cardiovascular health have been seen with lower blood pressure (both systolic and diastolic in patients with mildly elevated blood pressure), as well as reduced serum homocysteine, total cholesterol, and LDL. There appears to be little downside to this diet and we should make every effort to encourage our patients (and ourselves!) to comply with it.

Information and a patient education handout about this diet are available at the National Heart Lung and Blood Institute's web site.[6] Materials include patient handouts, recipes, and diet diary forms, making it easy for you to educate your patients about this heart- and bone-healthy diet. This diet gives a whole to meaning to the adage: Eat well and be strong. ❖

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5. Lin PH, et al. The DASH diet and sodium reduction improve markers of bone turnover and calcium metabolism in adults. *J Nutr* 133:3130-3136.
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CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients; and
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE / CME Questions

38. According to World Health Organization statistics, what percentage of women experience a major depressive disorder in any given year?

a. 5.8%
b. 9.5%
c. 12.4%

39. What are some common side effects of St. John's wort?

a. Photosensitization
b. Fatigue
c. Headaches
d. All of the above

40. A recent clinical trail found that patients following the DASH diet showed a benefit in reducing the markers of bone turnover.

a. True
b. False

Answers: 38. b, 39. d, 40. a.

Trial Studies St. John's Wort for Minor Depression

Researchers are now recruiting for a clinical trial that examines the use of St. John's wort (SJW), a common herbal supplement, for the treatment of minor depression.

The researchers will randomly assign a total of 300 participants with minor depression to a standardized extract of SJW, citalopram (a standard antidepressant), or placebo in a 12-week double-blind trial. The researchers will assess changes in patients' symptoms, functioning, and quality of life. Those patients who show no improvement will receive the active treatment they had not been assigned before, while patients with improved symptoms will take their assigned treatment for another 14 weeks for a total of 26 weeks.

The three-site study is being funded with more than $4 million from the National Institute of Mental Health, the National Center for Complementary and Alternative Medicine, and the Office of Dietary Supplements. The four-year study began in February 2003.

A number of other studies have examined SJW for major depression, says David Mischoulon, MD, PhD, staff psychiatrist at Massachusetts General Hospital in Boston. He is also the sub-investigator at the Boston site.

"Overall, the body of evidence is encouraging. The overall trend is that SJW is probably good for major depression that is in the mild-to-moderate range of severity and less effective for more severe depression," he says. "That was part of what led us to think about studying SJW for minor depression. We thought that if SJW treats milder illness most effectively, then this particular population might be likely to benefit."

Men and women ages 18-85 who meet diagnostic criteria for minor depression are eligible to participate. They must have experienced depressive symptoms for at least six months but less than two years continuously without meeting criteria for a major depressive episode or dysthymia within the past year. Additional exclusionary criteria include other mental disorders, such as schizophrenia, bipolar disorder, anxiety, and substance use disorders. Individuals with some active physical illnesses, such as cardiovascular, renal, respiratory, endocrine, neurological, or blood diseases also are not eligible for the study.

Depression seems to attack women more frequently than men, at a ratio of about 1.5 to 1, Mischoulon says. He's not sure why that is the case, but women may be more likely to seek help if they are feeling psychological distress. "These studies may need nothing more than a reflection of the willingness of certain people to seek help. It may be possible that depression may be equally common in men."

Many people who take SJW for minor depression probably do so without having had a formal diagnosis by a psychiatrist, especially since the milder symptoms of minor depression make it tricky to diagnose, he says.

The symptoms of minor depression are fewer in number and cause less impairment than those involving a major depressive disorder. These symptoms include either a depressed mood most of the day and nearly every day or a markedly diminished interest or pleasure in daily activities, plus two to four of the following symptoms: significant weight loss or gain, or decrease or increase in appetite; disturbance in sleep pattern; noticeable agitation or slowness; fatigue or loss of energy; inappropriate feelings of worthlessness or guilt; diminished ability to concentrate, indecisiveness; recurrent thoughts of death or suicide.

Recruiting for a study like this can be difficult because a lot of people with minor depression may be reticent to actually get into treatment, Mischoulon says. "Their symptoms aren't severe, and they are functioning more or less normally. It is a challenging study to recruit because it is a disorder in which people are less likely to ask for help."

For more information about the study or recruitment, contact the following study sites:

- Boston, MA, at Massachusetts General Hospital. Principal investigator: Andrew A. Nierenberg, MD; coordinator: Alana Burns at (617) 724-3222.
- Los Angeles, CA, at Cedars-Sinai Medical Center. Principal investigator: Mark Rapaport, MD; coordinator: Christina Kustak at (310) 423-0735.
- Pittsburgh, PA, at the University of Pittsburgh. Principal investigator: Robert Howland, MD; coordinator: Michael Lightfoot at (412) 246-5735. ❖

In Future Issues:

Feverfew for Migraine

Garlic for Cardiovascular Disease