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St. John's Wort for the Treatment of Depression: An Update

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When last reviewed in this newsletter,[1] two large negative studies had recently examined St. John's wort (SJW), an herbal therapy for depression, casting doubt on its efficacy in the treatment of depression. Literature on efficacy, adverse effects, and particularly drug interactions of SJW continues to grow, as does controversy regarding its use.

History and Botany

St. John's wort (*Hypericum perforatum*) is a perennial herb native to Europe, North Africa, and western Asia. It is now naturalized in Australia and the Americas where its bright yellow star-shaped flowers are often recognized along roads and fields. SJW is so named due to its coincident blooming in late June, when John the Baptist is said to have been born.

Its medical use dates back to the ancient Greeks, documented by Hippocrates, Dioscorides, and Galen. Thirteenth century medical texts listed SJW as *Herba demonis fuga*, "the herb that chases away the devil."[2] The Swiss physician Paracelsus reportedly used SJW to treat psychiatric disorders including depression and melancholy in the 16th century, while American Eclectic physicians prescribed it for treating "hysteria and nervous affections with depression."[3] In Europe, SJW remains among the most commonly used antidepressants, being prescribed in Germany nearly twice as commonly as all other antidepressants. Demand has led to large-scale cultivation in Europe, North and South America, Australia, and China.[3]

Mechanism of Action

St. John's wort flowers, and to a lesser extent its leaves, yield multiple active constituents. The mechanism of action is not fully understood, but biologically active components include hyperforin, adhyperforin, hypericin, pseudohypericin, flavonoids, xanthones, and others.[4] The two most relevant constituents appear to be hyperforin

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and adhyperforin. Because hypericin was formerly considered the active ingredient and products were standardized to its content, hyperforin and adhyperforin content probably varied significantly between products leading some to hypothesize this as an explanation for differences seen in the trials. Both hyperforin and adhyperforin appear to modulate the effects of serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid (GABA).[5] Inhibition of interleukin-6 and increased cortisol production have also been reported.[6] Clinical effects may be the result of a combined contribution of multiple mechanisms, each individually too weak to account for the action.[7]

Clinical Evidence

Numerous trials have demonstrated that SJW is more effective than placebo and perhaps the equal of pharmaceutical antidepressants in the treatment of mild-to-moderate depression. Recent American trials, however, shed doubt on its effectiveness in more severe forms of depression.

Important Trials

Two large U.S. trials failed to show a benefit of SJW over placebo; this received significant media attention and piqued the interest of the medical community. The National Institutes of Health-sponsored Shelton et al trial compared SJW (Jarson 300 mg tid) to placebo for eight weeks in 200 outpatient subjects at 11 U.S. academic medical centers.[8] After a one-week, single-blind run-in of placebo, participants were randomized to receive placebo (n = 102) or SJW (n = 98) 900 mg/d for four weeks. Initial non-responders' doses were increased to 1,200 mg/d. There was significant improvement over eight weeks in both arms, and SJW was not superior to placebo in primary outcomes. SJW did produce a statistically significant greater remission rate than placebo (14.35% vs. 4.9%, respectively).

This was a rigorous and well-conducted trial but has been criticized for various reasons. The study enrolled subjects with chronic depression (average of more than two years). The study did, however, exclude those with a history of failing to respond to an antidepressant in the current episode or failing more than one trial of antidepressants in the past. This study also lacked an active control. A non-blinded follow-up study by this research group found that nonresponders openly treated with marketed antidepressants of the investigator's choice for 24 weeks responded to treatment. The authors suggest this indicates their initial study did not contain a disproportionate treatment-resistant population, thus supporting lack of efficacy of SJW in the prior trial.[9]

Another U.S. trial sponsored by Pfizer and conducted at Duke University compared SJW (LI160 300 mg tid titrated up to 1,500 mg/d), sertraline (50-100 mg/d), and placebo in 340 patients with severe major depression over eight weeks.[10] In the primary analysis (reduction of Hamilton-Depression scale [HAM-D] score), neither SJW nor sertraline improved depression scores more than placebo. On a secondary endpoint (Clinical Global Impressions Scale [CGIS]), sertraline was better than placebo.

The largest European double-blind, placebo-controlled, randomized, multicenter trial demonstrated that SJW (WS5570 300 mg tid for six weeks) was more effective than placebo (n = 375) at reducing HAM-D scores in outpatients with mild-to-moderate depression.[11]

Controversy remains about why the U.S. trials contradict the mostly positive European trials. Barrette points out in the last *Alternative Medicine Alert* update on SJW that the U.S. trials were performed at academic sites while the German studies generally used community physician practices. Most German trials enrolled patients with mild-to-moderate depression but few used DSM-IV criteria. The U.S. trials trained all raters extensively and tested for reliability (e.g., scoring videotaped vignettes). The U.S. trials used a higher cut-off for the

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depression scores, potentially enrolling more severely depressed subjects. However, two more recent European trials, by Philipp et al and Szegedi et al, demonstrated a benefit of SJW over placebo and at least an equal benefit of SJW to paroxetine, respectively. Each of these trials enrolled subjects with a similar baseline HAM-D score to the U.S. trials.[12-14] Disparities may be the result of an overestimation of effect in the older smaller studies as well as variable efficacy of SJW in different patient populations.[15]

Systematic reviews published between 1996 and 2000 concluded SJW is more effective than older antidepressants in the management of mild-to-moderate depression.[16-18] Earlier trials have been criticized for faulty methodology, including poorly defined entry criteria resulting in heterogeneous populations, small enrollment, inadequate blinding, use of nonstandard outcome scores, use of combination products or low doses of SJW and/ or standard antidepressants, and short duration of follow-up. Because a variety of commercial products have been used, the generalizability of these studies to other preparations of SJW is uncertain.[1]

Linde et al published the most recent and methodologically sophisticated meta-analysis (listed in the Cochrane database) addressing such limitations in 2005.[15] They included 37 trials, including 26 comparisons with placebo (n = 3,320 patients) and 14 comparisons with synthetic standard antidepressants (n = 2,283 patient). This review only included randomized, double-blind studies that dealt with depressive disorders, used appropriate clinical outcomes for assessing depressive symptoms, and compared extracts of St. John's wort with placebo or standard antidepressants. Of note, among the 30 trials excluded from this analysis were seven that had been included in previous versions of their own reviews.

Results of the placebo-controlled trials demonstrated significant heterogeneity. In trials restricted to patients with major depression, the combined response rate ratio (RR) for hypericum extracts compared with placebo from six large trials showed a small benefit 1.15 (95% confidence interval [CI] 1.02-1.29) and from six smaller trials a larger benefit 2.06 (95% CI 1.65-2.59). In trials not restricted to patients with major depression, the RR from six large trials was 1.71 (95% CI 1.40-2.09) and from five smaller trials was 6.13 (95% CI 3.63-10.38).

Trials comparing hypericum extracts and standard antidepressants were statistically homogeneous. Compared with selective serotonin reuptake inhibitors (SSRIs) and tri- or tetracyclic antidepressants, respectively, RRs were 0.98 (95% CI 0.85-1.12; six trials) and 1.03 (95% CI 0.93-1.14; seven trials).

Patients given hypericum extracts dropped out of trials due to adverse effects less frequently than those given older antidepressants (odds ratio [OR] 0.25; 95% CI 0.14-0.45). The same observation was noted, although it was not statistically significant, between hypericum extracts and newer antidepressants (OR 0.60, 95% CI 0.31-1.15).

The more recent placebo-controlled trials suggest that hypericum extracts have minimal side effects and that the effects are similar to standard antidepressants. Linde et al concluded that current evidence regarding hypericum extracts is "inconsistent and confusing."[19]

Recent Trials

Since the publication of the most recent meta-analysis by Linde et al, there have been two trials comparing extracts of SJW and SSRIs.

Szegedi et al published a trial designed to test whether SJW (hypericum extract WS5570) works as well as paroxetine in moderate-to-severe major depression.[14] The study was a randomized, double-blind, double-dummy, reference-controlled, multicenter, non-inferiority trial. Included were 251 adult outpatients with acute major depression (total score 22 on the 17-item HAM-D scale) drawn from 21 psychiatric primary care practices in Germany. Each received 900 mg/d hypericum extract WS5570 divided three times a day or 20 mg paroxetine once a day for six weeks. After two weeks, initial nonresponders' doses were increased to 1,800 mg/d hypericum or 40 mg/d paroxetine. The primary outcome measure was change in score on HAM-D from baseline to day 42. Secondary measures included change in scores on the Montgomery-Åsberg Depression Rating Scale (MADRS), CGIS, and Beck Depression Inventory. HAM-D scores decreased by 14.4 (SD 8.8) points, corresponding to 56.6% (SD 34.3%) of the baseline value in the hypericum group and by 11.4 (SD 8.6) points, or 44.8% (SD 33.5%) of baseline value, in the paroxetine group. Intention-to-treat analysis and per protocol analysis showed statistical superiority of hypericum over paroxetine. The incidence of adverse events was 0.035 events per day of exposure for hypericum and 0.060 for paroxetine. The authors concluded that hypericum extract WS5570 was at least as effective as paroxetine and better tolerated in the treatment of moderate-to-severe major depression.

Bjerkenstedt et al compared SJW extract with fluoxetine and placebo in a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter, outpatient trial funded by Lichtwer Pharma, makers of LI160.[20] Included were 163 adult outpatients with major depression (total score > 21 on the 21-item HAM-D

scale) drawn from general practices in Sweden. Each received SJW extract LI160 300 mg tid, fluoxetine 20 mg qd, or placebo for six weeks. The primary outcome measure was change in score on HAM-D from baseline to week 4 (SJW vs. placebo) and to week 6 (hypericum vs. fluoxetine). Secondary endpoints included remission (HAM-D total score < 8) at week 4, MADRS, and CGI. HAM-D scores were reduced 35-40% during the four-week double-blind treatment without any significant between-group differences. At six weeks a total reduction of 48% was observed for both SJW and fluoxetine, but this portion of the trial was not placebo-controlled. Remission was the only secondary outcome measure for both hypericum (24%) and fluoxetine (28%) that was significantly superior to placebo (7%). The authors conclude that both active treatments failed to prove superiority over placebo in primary outcome measures, but that they both improved remission rates. SJW and placebo were significantly better tolerated than fluoxetine.

Adverse Effects

Systematic reviews of adverse effects of SJW were published in 2003 and 2004.[21,22] In randomized trials, SJW was tolerated as well as placebo, significantly better than older antidepressants, and perhaps slightly better than SSRIs when taken as recommended. The most common side effects are mild gastrointestinal symptoms, skin reactions, fatigue, sedation, restlessness, dizziness, headache, and dry mouth.[22] Observational studies suggest adverse events occur in 1-3% of patients. In a 2001 review of 8 million people taking recommended doses of SJW extracts, 95 adverse events were documented.[23]

Photosensitivity has been seen in animals grazing on SJW and several human cases of reversible photosensitivity to SJW have been reported. Hypericin has been confirmed as the cause of photosensitivity in a Phase I study of pure hypericin in HIV-positive adults, with severe phototoxicity occurring in 11 of 23 subjects.[24] Other studies have not demonstrated phototoxic reactions in patients administered oral LI160.[25]

One case of reversible subacute polyneuropathy occurred on sun-exposed areas after four weeks of hypericum.[26]

Induction of hypomania and mania are known complications of antidepressant therapy, and cases of hypericum precipitating hypomania and mania have been reported.[12,27-30]

Rare cases of hypertension and tachycardia have been reported.[31] However, blood pressure and heart rate were equivalent in 200 patients enrolled in a six-week study comparing SJW (1,800 mg/d) to imipramine (150 mg/d).[32] One report describes a cardiovascular collapse during anesthesia in a healthy 23-year-old woman who had been taking SJW for six months.[33]

Anorgasmia has been reported in 25% of subjects taking 900-1,500 mg/d of SJW for eight weeks compared to 16% taking placebo and 32% taking sertraline.[11] Reduced sperm motility has been reported in vitro with the use of SJW.[34]

Table

Drugs reported to interact with St. John's wort

Amitriptyline	Oral contraceptives
Cyclosporine	Paroxetine
Digoxin	Sertraline
Indinavir	Simvastatin
Irinotecan	Tacrolimus
Midazolam	Theophylline
Nefazodone	Trazodone
Neveripine	Warfarin
Nifedipine	General Anesthesia

Drug Interactions

A broad range of drug interactions has been described but the clinical relevance of many of these remains unclear *(see Table)*. Perhaps the most clinically relevant interactions occur with cyclosporine (lowering serum cyclosporine concentration), other antidepressants, particularly the SSRIs (serotonin syndrome), antiretroviral therapy (reducing the concentration of protease inhibitors in HIV-infected patients), and coumadin-type anticoagulants (decreasing anticoagulation). There is concern that SJW may interfere with the efficacy of oral contraceptives (OCs).

SJW induces CYP 3A/3A4 apparently through upregulation of this enzyme by hyperforin.[35,36] Thus, most interactions with SJW result in a lowered concentration of the second drug. In addition, evidence suggests that SJW also induces the intestinal transport protein P-glycoprotein, which may further lower plasma levels of drugs.

Cyclosporin is metabolized largely by CYP 3A4 and there are multiple case reports of kidney, heart, and liver transplant rejections and reduced cyclosporine serum levels in patients who received concomitant SJW. An observational study found that 30 kidney transplant recipients taking SJW had significant decreases in cyclosporine levels. These levels increased when SJW was discontinued.[37]

OCs are also metabolized in part by CYP 3A4 and

there have been multiple case reports of breakthrough bleeding in women who use these and SJW.[38] Several reports also describe unwanted pregnancies in women taking OCs and SJW.[39] A randomized controlled trial, however, involving 18 healthy females (ages 18-35 years) treated with a low-dose OC (0.02 mg ethinylestradiol, 0.150 mg desogestrel) alone or combined with SJW extract (Jarsin LI160 300 mg bid) failed to demonstrate evidence of ovulation during combination treatment, but did show increased intracyclic bleeding episodes.[40]

Protease inhibitors and nonnucleoside reverse transcriptase inhibitors are also metabolized by CYP 3A4 and SJW has been demonstrated to decrease their serum concentrations probably by this mechanism, and perhaps through inducing drug pump P-glycoprotein.[41-43]

There is one report of a 42-year-old woman with decreased serum theophylline levels after concomitant ingestion of SJW 300 mg qd. Theophylline is metabolized by CYP 1A2. The woman was taking several other medications and smoking tobacco. However, upon discontinuing SJW her theophylline levels rose.[44]

Reductions in concentration of nifedipine and midazolam, which are metabolized by CYP 3A4, were reported in a human study.[45]

Warfarin is metabolized by CYP 2C9 and there are at least seven cases of lowered international normalized ratio (INR) in patients felt to be stable with concomitant use of SJW. Increases in warfarin dose or discontinuation of SJW led to INR returning to target values.[38] It is believed this interaction may be due to induction of drug pump P-glycoprotein.[41]

One case report of cardiovascular collapse during anesthesia in a 23-year-old female taking SJW and one of delayed emergence from anesthesia in a 21-year-old female taking SJW have been published.[46,47]

Tricyclic antidepressant concentrations were reduced significantly in a 14-day open study of 12 depressed patients.[48] These drugs are metabolized by multiple CYP enzymes.

Consistent with serotonin syndrome, anxiety, confusion, irritability, restlessness, dizziness, nausea, vomiting, and headache were reported in a case series of five elderly patients who started SJW while on stable doses of sertraline (four patients) and nefazodone (one patient).[49] A similar interaction was reported in a 61-year-old woman and a 50-year-old woman taking paroxetine.[50,51] A single case report described severe hypertension in a patient taking SJW who consumed aged cheese and red wine.[52]

Digoxin levels were reduced by about 25% in a 10-day controlled trial in patients concomitantly treated with SJW.[53] It is felt this may be due to induction of the P-glycoprotein drug transporter.

Dosage and Formulation

Most studies used 300 mg given three times a day but doses have ranged from 500 mg to 1,800 mg daily. Several standardized ethanol and methanol extracts exist. Most products were formulated to contain 0.3% hypericin providing 2.7 mg/d hypericin when 900 mg hypericum is taken. Recently some manufacturers have begun standardizing to hyperforin (usually 2-5%). The continuing problem of standardization and purity was seen in a study of eight SJW products purchased in Germany (two are available in the United States).[54] The products were found to contain "widely differing amounts" of hypericin and hyperforin. Some even demonstrated pronounced batch-to-batch variability. A review by an independent laboratory reported that among the 10 products selected for testing (two were immediately dropped from further testing because they lacked information about the part of the SJW used, an FDA labeling requirement), three failed testing for cadmium contamination, exceeding the cadmium limit established for medicinal plants by the World Health Organization by 100-1,000%. One of these also had lead contamination above the limit established by the state of California. A fourth product failed for suggesting a dose that was likely to be too low to be effective—less than one-quarter of the standard dose.[55]

Conclusion

The most stringent reviews of the literature on SJW continue to suggest benefit in the treatment of patients with mild-to-moderate depression and those with depressive symptoms not necessarily rising to the level of major depressive disorder (MDD). In more severe forms of MDD the evidence is unclear, and suggests only minor benefit at best. Numerous herb-drug interactions, some with significant clinical relevance, continue to be reported. Although adverse events have been reported, SJW appears to be better tolerated than older antidepressants and at least as well tolerated as SSRIs. Longer studies comparing SJW with newer antidepressants are warranted.

Recommendation

SJW may be a reasonable choice for short-term treatment of patients with mild-to-moderate depression and those with depressive symptoms not necessarily rising to the level of MDD who prefer to use a "natural" therapy. Although it has not demonstrated clear superiority over other antidepressants, SJW is relatively inexpensive and

well-tolerated. Prescribers should familiarize themselves with the list of drug-herb interactions and carefully avoid any relevant combinations. All patients should be asked about their use of herbal products and dietary supplements. Because there is significant variability between SJW products available, it makes sense to recommend those utilized in positive clinical trials. There is little reliable evidence to support SJW use in moderate-to-severe depression and it should not be a first-line agent in these patients. ❖

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Guided Imagery for Treating Pain

By Dónal P. O'Mathúna, PhD

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PAIN MANAGEMENT HAS RECEIVED DRAMATICALLY increased attention in recent years, as evidenced by the new Joint Commission on Accreditation of Healthcare Organizations (JCAHO) regulations.[1] Pain is now considered "the fifth vital sign," requiring regular assessment and appropriate intervention. In spite of this, misunderstanding about pain and pain management is common and much remains to be understood. This occurs in part because of the subjective nature of pain and individuals' differences in their perception and tolerance of pain.

Many complementary and alternative therapies claim to reduce pain. They are often recommended in an effort to avoid pain medications' side effects, which can include sedation, confusion, falls, and urinary incontinence.[2] Relaxation techniques have become especially popular in the treatment and management of pain, especially chronic pain.[3] Mind-body medicine in general is based on the assumption that the mind can be used to influence physical conditions. Guided imagery is one such technique that can easily be learned by most people.[1] Before recommending it for patients with chronic pain, the evidence for its effectiveness should be reviewed.

Background

The recent practice of guided imagery was developed and refined by Roberto Assagioli in a popular book published in 1980.[4] In its most popular form, people are guided to focus on a favorite place or activity which they find comfortable and enjoyable. The focus can be on

something real or something imagined. The guidance can come in the form of specific instructions from a person or a recording, or more generally in the form of relaxing music.[5] Once in the relaxed setting, people are guided to focus on colors, scents, sounds, or other aspects of the scene which they are imagining to deepen the experience. This form of guided imagery is sometimes referred to as "pleasant imagery" in contrast to "attention imagery."[6] In the latter form of guided imagery, people are guided to visualize and objectify their pain and then to change or discard it.[7]

Mechanism of Action

Guided imagery is based upon the belief that one's thinking and beliefs can powerfully impact one's experience of pain.[5] However, there are divergent opinions on whether it is best to focus on the pain or distract one's attention from the painful stimuli.[6] Adaptation theory suggests that if patients focus on pain it will decrease over time during therapy. On the other hand, hyper-vigilance theory suggests the opposite, that pain is increased as it is focused upon.[6] The differences probably relate to diversity in both types of pain and people's individual coping strategies.

Clinical Studies

Many anecdotal reports claim that guided imagery effectively reduces patients' pain and anxiety.[5] At the same time, little controlled research has been conducted to establish which strategies are objectively effective.[3] A review of controlled studies of guided imagery prior to 1999 found "preliminary evidence" for its effectiveness in reducing pain and some other symptoms.[8] The review also concluded that larger, better designed studies were needed.

One such study of chronic tension headaches enrolled 350 subjects, of which 260 completed the study.[9] New patients at a headache clinic were given individualized headache therapy and assigned to either a guided imagery group or a control group. An audiotape provided guided imagery instructions over soothing music and subjects were instructed to listen to it daily for one month. Headache frequency and severity decreased for both groups, but the guided imagery group experienced significantly greater improvement ($P = 0.004$). Significant differences were also found for vitality and mental health measures in the Medical Outcomes Study Short Form (SF-36).

Another common form of headache pain is migraine. A study of 40 migraine sufferers randomly assigned them to receive guided imagery, biofeedback, both, or neither.[10] The control group was connected to biofeedback equipment and encouraged to relax for the same length of time as the other groups. After six 20-minute sessions, no significant differences were found between any of the groups in frequency or duration of migraines, interference with activities, or analgesic usage. However, patients in the guided imagery group reported a significantly improved ability to cope with their pain ($P < 0.05$).

One controlled study compared the effectiveness of pleasant and attention guided imagery.[6] Fifty-five women diagnosed with fibromyalgia pain were randomly assigned to one of three groups. One group received guidance in pleasant imagery ($n = 17$), another in attention imagery ($n = 21$), and a third received usual treatment ($n = 17$). After four weeks, the group visualizing peaceful and beautiful scenery had significantly improved pain ratings on a visual analog scale (VAS) compared to the control group ($P < 0.005$). The group using guided imagery to focus on pain did not differ from the control group ($P > 0.05$), and had increased pain ratings compared to the pleasant imagery group ($P < 0.005$).

A pilot study randomly assigned 28 older women with osteoarthritis and joint pain to two groups.[11] The intervention consisted of listening for 10-15 minutes twice daily to an audiotape guiding subjects with pleasant imagery and progressive muscle relaxation. The control group consisted of standard care along with journaling, which was also required of the intervention group. After 12 weeks, pain scores and mobility difficulties were significantly reduced in the intervention group (both $P < 0.001$) with no change in the control group.

A controlled trial randomly assigned 44 patients with various forms of chronic pain to two groups.[7] One group did not change their pain management strategies. The other group used a seven-minute guided imagery audiotape three times daily for four days. The instructions encouraged people to relax, to view their pain as an object, and then to change or discard the object. Each day all participants were interviewed about their pain. Their descriptions were classified into six categories: that pain is never-ending, relative, explainable, torment, restrictive, or changeable. Statistical analysis of changes was not carried out. However, clear improvements occurred with guided imagery. The number of people in the treatment group reporting pain as never-ending changed from 11 to 0, while in the control group it went from 10 to 15. Those reporting pain as changeable went from 4 to 11 in the guided imagery group compared with 5 to 2 in the control group. However, reports of pain as restrictive went from 8 to 0 with guided imagery, but

also went from 5 to 1 in the control group. Differences in the other descriptors were less clear-cut.

Most studies of guided imagery for pain have focused on chronic pain. However, a pilot study was conducted with 13 men scheduled for knee or hip replacement surgery.[2] In addition to usual preoperative and postoperative care, all subjects were given an audiotape. The intervention group's tape contained music and guidance on developing pleasant and comfortable images while the control group's tape contained only relaxing music. Participants were instructed to listen to the tape on the evening after surgery and twice daily until discharged. Statistical analysis was not conducted because of the small sample size. Differences were visible between the intervention and control groups in VAS pain scores (2.35 vs. 5.30, respectively), IV morphine use during the first four postoperative days (36.70 vs. 84.87 mg), and length of stay (9.29 vs. 14.83 days).

Conclusion

Most of the studies located by searching PubMed found guided imagery effective for reducing pain. No adverse effects were reported. However, many of the studies enrolled small numbers of subjects or were pilot studies. Some variation in outcomes was reported depending on the particular type of pain. Also, much remains unclear about guided imagery, including the preferred form of guidance, the best type of imagery, individual variation in responses, and the optimal frequency and duration of therapy. For example, in spite of a belief that better outcomes result from prolonged use of guided imagery, a 2004 review found no studies supporting this perceived relationship.[12] The reviewer conducted a meta-analysis of 10 studies of varying duration and found increased effect size over the first 5-7 weeks, but decreased effect size at 18 weeks. Much remains to be understood about the precise way to carry out guided imagery.

Recommendation

Given the lack of adverse effects from guided imagery, and the relative ease and cost-effectiveness of its introduction, guided imagery can be recommended for patients with pain. Patients should be alerted to the variation found in some studies, both with individuals and types of pain, so that they are not led to have unrealistic expectations. Pain perception and management is complicated and should be individualized. The evidence to date warrants larger studies of guided imagery to determine how its outcomes can be optimized. As a nonpharmacological strategy for reducing pain, guided imagery should be included among the strategies made available to patients suffering pain, especially chronic pain. ❖

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CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. 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, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

32. U.S. trials of St. John's wort contradict the mostly positive results of European trials.
a. True
b. False

33. St. John's wort should *not* be a first-line agent in which of the following patients?
a. Patients with mild-to-moderate depression
b. Patients with depressive symptoms not necessarily rising to the level of major depressive disorder who prefer to use a "natural" therapy
c. Patients with moderate-to-severe depression
d. All of the above

34. As a nonpharmacological strategy for reducing pain, guided imagery should be included among the strategies made available to patients suffering pain, especially chronic pain.
a. True
b. False

Answers: 32. a, 33. c, 34. a.

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Echinacea: Another Negative Trial

Source: Turner RB, et al. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N Engl J Med* 2005; 353:341-348.

Goal: To evaluate the effects of different chemical constituents from *E. angustifolia* on rhinovirus infection and symptoms of the common cold in healthy young adults.

Design: Randomized, placebo-controlled, double-blind prospective cohort trial.

Subjects: Volunteers (n = 437) who upon testing were susceptible to rhinovirus type 39 (data available for analysis from 399 subjects).

Methods: Prospective subjects were tested for sensitivity to rhinovirus 39 (serum neutralizing antibody titer ≤ 1:4) and then randomized to prophylaxis (beginning seven days before virus exposure) or treatment (virus exposure to day 5) groups with one of three chemically distinct preparations of *E. angustifolia* root or placebo. There were seven treatment groups: one of three preparations offered during both prophylaxis and treatment phases, or placebo offered during the prophylaxis phase and one of three extracts employed during treatment phase, or the control group that received placebo during both phases. After direct nasal challenge with the rhinovirus, subjects were isolated in individual hotel rooms for five days. Treatment was offered three times daily as 1.5 cc of tincture containing the equivalent of 300 mg echinacea root (900 mg /d). Symptom scores were evaluated every morning and evening, and nasal lavage was performed every morning (to detect unsuspected viral infections, rhinovirus type 39, and to measure interleukin-8 and leukocyte concentrations).

Results: No statistically significant treatment effects were identified for any one of the three *E. angustifolia* extracts.

Conclusions: Specified extracts of *E. angustifolia* root provide no clinically significant benefit with regard to infection with a rhinovirus and the symptoms associated with the common cold.

Study strengths: Methodologically sound trial (save for dosage employed), including antibody testing before virus challenge and isolation after exposure; repeated analyses of study treatments to ensure consistency; compliance.

Study weaknesses: Employed subtherapeutic dosage of echinacea material (critical flaw).

Of note: Conventional medical practice offers no effective antiviral treatment against rhinoviruses; while rhinoviruses cause an estimated 40% of all colds, there are numerous subtypes of rhinovirus (> 100), and other viruses known to cause the common cold include coronaviruses, respiratory syncytial virus, and adenovirus (that stated, the model used in this study has accurately predicted response to treatment in other studies); the various preparations (extracted with supercritical CO_2, 60% or 20% ethanol) came from a single lot of *E. angustifolia* root; the more typical dose of *E. angustifolia* root is close to 3 g daily.

We knew that: Multiple studies on the efficacy of echinacea have been published and have produced conflicting results; at least three different species of echinacea, with different phytochemical characteristics, are used clinically (*E. pallida* var *angustifolia*, *E. purpurea*, and *E. pallida* var *pallida*), with *E. purpurea* being used most commonly in the United States; variability in phytochemical composition has led to efforts to isolate and standardize active participles; polysaccharides, derivatives of caffeic acid, and alkamides present have all been shown to possess biologic activity in vitro and in vivo and are presumed to represent the active participles

in echinacea; extraction procedures, manufacturing techniques, plant parts used, geography, and time of plant harvesting impact the chemical constituents found within an echinacea product; there is a known correlation between cold symptom severity and level of interleukin-8 and polymorphonuclear-leukocyte response.

Clinical import: This study is very well done save for the major complicating factor of the low dosage of material used (again, the typical recommended dosage of echinacea is three times higher than that employed in the trial). The results show that a subtherapeutic dosage of the specified extracts of *E. angustifolia* offer no benefit over placebo in preventing or treating the common cold, adding little to our understanding of echinacea's benefits or lack thereof. The authors rightly state that it will be difficult to conclusively prove that echinacea has no benefit in the treatment of the common cold in light of the wide variety of echinacea preparations available. It is possible that higher doses may be effective, that some people respond to echinacea while others do not, and that other constituents, or the natural milieu of the constituents, play a significant role in the effectiveness of echinacea against the common cold, if there be any. Even against the background of the lack of conventional treatment against the common cold, however, the authors are likewise correct in stating the burden of proof should lie with those advocating the use of echinacea.

Unfortunately, as evidenced in the accompanying editorial by a longtime unapologetic critic of integrative medicine, there are those who would use evidence of ineffectiveness specific to a given therapy as evidence of the lack of efficacy for all of complementary and alternative medicine (CAM). To extrapolate the findings of a single echinacea study to protest against the use of any CAM therapy is as misguided as equating COX-2 inhibitors with all prescription aids. Those promoting themselves as possessors of singular wisdom enabling clear discernment of what is implausible do a disservice to science. A scientist observes an association between intervention and effect, and develops a hypothesis that can then be tested, with results serving to support or refute that hypothesis. Fixed perceptions are often fixed *mis*perceptions, and a knee-jerk dismissal of data (either for or against an intervention) rarely serves the common good let alone the balanced appraisal of evidence, the goal to which this publication aspires. Those putting limits on what is "plausible" would have curtailed previous work that has proven revolutionary in health care, including the discovery of the association between peptic ulcer disease and the microbe *Helicobacter pylori*. Fundamentalism in any form can prove dangerous and has no place in modern health care, nor in the pages of *The New England Journal of Medicine*.

What to do with this article: Remember that you read the abstract. ❖

Heartache and Heart Failure

Source: Ferketich AK, et al. Depressive symptoms and inflammation among heart failure patients. *Am Heart J* 2005;150: 132-136.

Goal: To assess levels of pro-inflammatory cytokines in people with heart failure both with and without increased symptoms of depression.

Study Design: Prospective, cross-sectional study.

Subjects: Fifty adults with heart failure, ischemic or non-ischemic, recruited from an outpatient heart failure clinic (data available for analysis from 32 subjects).

Methods: Depressive symptoms were measured using the Beck Depression Inventory (BDI), with subjects classified as having increased symptoms of depression with scores ≥ 10. A subscale of the BDI (cognitive-affective subscale score) was also employed that permits classification of depressive symptoms attributable to the process of heart failure as opposed to those caused by an intrinsic affective disorder (symptoms shared by both groups may include fatigue, weight loss, and sleep disorders). Blood samples were obtained to determine levels of IL-6, IL-1β, and TNF-α.

Results: No relationship between BDI or BDI subscale scores and IL-6 or IL-1β was found. A significant relationship between BDI and BDI subscale scores and TNF-α, however, was identified. Pro-inflammatory cytokine levels were not significantly correlated.

Conclusion: Depression-specific activation of a pro-inflammatory cytokine, TNF-α, occurs apart from the process of heart failure itself, and may contribute to morbidity and mortality in people with heart failure.

Study strengths: Use of BDI subscale to tease out influence of depressed mood on cardiac function.

Study weaknesses: Not all participants had cytokine measures performed for reasons not adequately explained; technical difficulties experienced with certain cytokine measurements; small sample size.

Of note: Multiple linear regression models were employed that controlled for age, gender, smoking, and antidepressant use; total BDI score may be influenced by both the physical symptoms of heart failure and the presence of an intrinsic cognitive-affective disorder; only one of the three pro-inflammatory cytokines measured (TNF-α) increased in response to elevated symptoms of depression.

We knew that: Depression has been associated with increased risk of heart failure as well as poor prognosis in patients with established heart failure; evidence suggests that pro-inflammatory cytokines are elevated in people with heart failure; pro-inflammatory cytokines exert negative effects on cardiac function including promotion of left ventricular remodeling, induction of contractile dysfunction, and uncoupling of myocardial beta-adrenergic receptors; elevated levels of IL-6, IL-1β, and TNF-α have been associated with major depressive disorder (MDD) as well as

depression in the absence of MDD.

Comments: This interesting, yet underpowered, trial suggests an association between depressed mood state and increased levels of pro-inflammatory cytokines in people with heart failure. The notion that anxiety, depression, or inadequately managed stress may contribute to systemic activation of the inflammatory cascade has long been considered and has not been lost on researchers, yet to this day continues to escape many clinicians. Inflammation represents the pathophysiologic process central to some of the most troubling chronic maladies experienced by patients. Few people with chronic illness are counseled that with proper treatment of depression, or through the use of proven techniques for amelioration of stress, they may be able to control some aspects of their disease and lessen physical symptoms. This trial is flawed in important ways, but it does support an association between mental processes and physiology, between mind and body, that mandates continued study.

What to do with this article: Remember that you read the abstract. ❖

Spilling the Beans (Coffee and Vascular Health)

Source: Vlachopoulos C, et al. Chronic coffee consumption has a detrimental effect on aortic stiffness and wave reflections. *Am J Clin Nutr* 2005;81:1307-1312.

Goal: To assess the effect of chronic coffee ingestion on aortic stiffness and wave reflections.

Study Design: Cross-sectional study performed in Athens, Greece.

Subjects: Two hundred twenty-eight clinically healthy participants (141 men).

Methods: Coffee consumption (all types, including "Greek" and espresso) over the previous year was ascertained using a food-frequency questionnaire and classified in the following manner: low (< 200 mL/d), moderate (200-450 mL/d), and high (> 450 mL/d) intake. Subjects were studied in the morning after fasting overnight. Blood pressure was determined and aortic elastic properties were then assessed by measuring the carotid-femoral pulse wave velocity (PWV), augmented pressure (AP), augmentation index (AIx), and Δt.

Results: Fifty-four percent of participants reported moderate-to-high consumption of coffee, with men consuming more coffee on average than women. A linear significant relationship was established between level of coffee consumption and arterial pressures as well as indices of arterial function, with the high-consumption group having significantly higher arterial pressures, and values for PWV, AIx, AP, and Δt. The difference between aortic and peripheral pulse pressure values relative to coffee intake was also significant, suggesting that coffee consumption has a greater effect on aortic pulse pressure, but this latter finding was also associated with variables such as smoking habits, body mass index, and blood lipids.

Conclusion: Chronic coffee consumption has a detrimental effect on aortic stiffness in healthy subjects, which may increase the risk for cardiovascular disease (CVD).

Study strengths: Multiple linear regression analysis for numerous variables.

Study weaknesses: Limitations associated with food-frequency questionnaire/recall; only assessed otherwise healthy individuals.

Of note: One cup of coffee (150 mL) was held to contain 80 mg of caffeine; consumption of decaffeinated coffee, tea, caffeine-containing soft drinks, and chocolate were included in the analysis; none of the subjects reportedly used medications that contained caffeine; carotid-femoral PWV is an established index of aortic stiffness; the waveform generated within an artery is the sum of the forward traveling waveform (generated by pump action) and the backward traveling "echo" reflected at a peripheral site (the merging of incident and reflected waves appears as an inflection point where early and late systole divide); AP represents the maximum systolic pressure minus the pressure at the inflection point; high AIx values can indicate increased wave reflection due to increased arterial stiffness; Δt represents the time from the beginning of the waveform to the inflection point, and also reflects arterial stiffness; the more coffee participants ingested on average the more likely there was to be a significant history of smoking; the majority of participants were at least slightly overweight.

We knew that: Large artery stiffness and wave reflections are independent predictors of CVD risk (determine left ventricular function and coronary blood flow); the pulse wave travels at higher speed in a stiff blood vessel; the pathophysiologic manifestations of increased aortic stiffness and wave reflections include elevated systolic blood pressure, increased pulse pressure, and decreased diastolic blood pressure; data on the effects of coffee intake on CVD risk remain contradictory, but caffeine has previously been shown to acutely increase aortic stiffness and wave reflection, and to acutely increase blood pressure; chronic coffee ingestion has been associated with higher levels of inflammatory markers.

Comments: This paper lends additional evidence to that of other studies addressing the potential downside of coffee/caffeine ingestion that have appeared in this newsletter. Far be it for the editors of this periodical to assault one's right to wake up to the smell of fresh coffee (more likely to wake up as a result of fresh coffee!), but the amount of data pointing to potential consequences of both acute and chronic caffeine ingestion are compelling. Additionally, patients with high intakes of coffee/caffeine appear more likely to have other factors that place them at higher risk for CVD, including tobacco use, dyslipidemia, and being overweight. It may well be time for all of us to go to sleep earlier rather than make up for sleep deprivation with a stop at the local coffee shop before work.

What to do with this article: Keep a copy of the abstract on your computer (to review with your morning green tea). ❖

Supplement to *Alternative Medicine Alert*
September 2005

ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

St. John's Wort and Depression Patient Handout: Question & Answer

THE NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE (NCCAM) HAS developed this fact sheet on the use of St. John's wort (SJW) for depression. It is part of a series intended to help consumers make informed decisions about whether to use complementary and alternative medicine (CAM) for a disease or medical condition.

Key Points

St. John's wort is an herb that has been used for centuries for medicinal purposes, including to treat depression. The composition of SJW and how it works are not well understood.

There is some scientific evidence that SJW is useful for treating mild-to-moderate depression. However, recent studies suggest that SJW is of no benefit in treating major depression of moderate severity. More research is required to help us know whether SJW has value in treating other forms of depression.

SJW interacts with certain drugs, and these interactions can be dangerous. It is important to inform all of your health care providers about any therapy that you are currently using or considering, including any dietary supplements. This is to help ensure a safe and coordinated course of care.

1. What is St. John's wort?

St. John's wort (*Hypericum perforatum* in Latin) is a long-living plant with yellow flowers. It contains many chemical compounds. Some are believed to be the active ingredients that produce the herb's effects, including the compounds hypericin and hyperforin. How these compounds actually work in the body is not yet known, but several theories have been suggested. Preliminary studies suggest that SJW might work by preventing nerve cells in the brain from reabsorbing the chemical messenger serotonin, or by reducing levels of a protein involved in the body's immune system functioning.

2. For what medicinal purposes has SJW been used?

SJW has been used for centuries to treat mental disorders as well as nerve pain. In ancient times, doctors and herbalists wrote about its use as a sedative and treatment for malaria as well as a balm for wounds, burns, and insect bites. Today, SJW is used by some people to treat mild-to-moderate depression, anxiety, or sleep disorders.

3. What is depression?

Depression is a medical condition that affects nearly 19 million Americans each year. A person's mood, thoughts, physical health, and behavior all may be affected. Symptoms commonly include:

- Ongoing sad mood
- Loss of interest or pleasure in activities that the person once enjoyed
- Significant change in appetite or weight

- Oversleeping or difficulty sleeping
- Agitation or unusual slowness
- Loss of energy
- Feelings of worthlessness or guilt
- Difficulty "thinking," such as concentrating or making decisions
- Recurrent thoughts of death or suicide

The three major forms of depressive illness are described below. Each can vary from person to person in terms of symptoms experienced and the severity of depression.

In major depression, people experience a sad mood or loss of interest or pleasure in activities for at least two weeks. In addition, they have at least four other symptoms of depression. Major depression can be mild, moderate, or severe. If it is not treated, it can last for six months or more.

In minor depression, people experience the same symptoms as major depression, but they are fewer in number and are less disabling. Symptoms last at least six months but less than two years continuously.

In dysthymia, a milder, but more chronic form of depression, people experience a depressed mood for at least two years (one year for children), accompanied by at least two other symptoms of depression.

In bipolar disorder, also called manic depression, a person has periods of depressive symptoms that alternate with periods of mania. Symptoms of mania include an abnormally high level of excitement and energy, racing thoughts, and behavior that is impulsive and inappropriate.

4. Why is SJW used as an alternative therapy for depression?

Some patients who take antidepressant drugs do not experience relief from their depression. Other patients have reported unpleasant side effects from their prescription medication, such as a dry mouth, nausea, headache, or effects on sexual function or sleep.

Sometimes people turn to herbal preparations because they believe "natural" products are better for them than prescription medications, or that natural products are always safe. Neither of these statements is true.

Finally, cost can be a reason. SJW costs less than many antidepressant medications, and it is sold without a prescription (over the counter).

5. Does SJW work as a treatment for depression?

There has been scientific research to try to answer this question. In Europe, results from a number of scientific studies have supported the effectiveness of certain SJW extracts for depression. An overview of 23 clinical studies found that the herb might be useful in cases of mild-to-moderate depression. The studies, which included 1,757 outpatients, reported that SJW was more effective than a placebo and appeared to produce fewer side effects than some standard antidepressants (Linde et al. *British Medical Journal*, 1996).

Other studies conducted recently have found no benefit from the use of SJW for certain types of depression. For example, the results of a study funded by Pfizer Inc., a pharmaceutical company, found that SJW, when compared with placebo, was not effective for treating major depression (Shelton et al. *JAMA*, 2001).

In addition, several components of the National Institutes of Health (NIH) funded a large, carefully designed research study to find out whether SJW extract benefits people with major depression of moderate severity. This clinical trial (a research study in people) found that SJW was no more effective for treating major depression of moderate severity than placebo (Hypericum Depression Trial Study Group. *JAMA*, 2002).

6. Are there any risks to taking SJW for depression?

Yes, there are risks in taking SJW for depression.

Many so-called "natural" substances can have harmful effects—especially if they are taken in too large a quantity or if they interact with something else the person is taking.

Research from NIH has shown that SJW interacts with some drugs—including certain drugs used to control HIV infection (such as indinavir). Other research shows that SJW can interact with chemotherapeutic, or anticancer, drugs (such as irinotecan). The herb may also interact with drugs that help prevent the body from rejecting transplanted organs (such as cyclosporine). Using SJW limits these drugs' effectiveness.

Also, SJW is not a proven therapy for depression. If depression is not adequately treated, it can become severe and, in some cases, may be associated with suicide. Consult a health care practitioner if you or someone you care about may be experiencing depression.

People can experience side effects from taking SJW. The most common side effects include dry mouth, dizziness, diarrhea, nausea, increased sensitivity to sunlight, and fatigue.

Source: National Center for Complementary and Alternative Medicine. Available at: http://nccam.nih.gov/health/stjohnswort/. Accessed Aug. 19, 2005.