St. John’s wort (SJW) is a common plant that has become popular in Europe and the US for treatment of mild-to-moderate depression. Research has shown it is effective in alleviating symptoms of depression with minimal side effects and is also useful in premenstrual syndrome. It has an excellent safety profile, although some known drug interactions. Confusion has arisen recently regarding the appropriate use of SJW and this review provides clear guidelines. General considerations for the use of herbs in mental health, as well as a useful summary, are also provided.

ST. JOHN’S WORT AS AN HERBAL TREATMENT FOR DEPRESSION AND GENERAL CONSIDERATIONS FOR THE USE OF HERBS IN MENTAL HEALTH

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INTRODUCTION

St. John’s wort (SJW) is a common roadside plant that has gained increasing popularity in the Europe and the United States as an effective alternative to pharmaceutical antidepressants. Research in treating patients with depression has shown that it relieves symptoms of sadness, helplessness, hopelessness, anxiety, headache, and exhaustion, all with minimal side effects. It is also useful in seasonal affective disorder and premenstrual syndrome. It has an excellent safety profile, but with some drug interactions mentioned below. More information is needed on its long-term efficacy and safety through studies, although it has been historically used by many depressed patients in Europe for years with no observed ill effects.

A metaanalysis published in the British Medical Journal in 1996
increased awareness and was associated with an increase in its popularity in the United States. The analysis evaluated 23 randomized trials (20 were double-blind) of SJW in a total of 1,757 outpatients with mild to moderate depression.1 Most trials were 4-8 weeks in duration. All groups showed improvement in depressive symptoms [usually measured by the Hamilton Depression (HAM-D) or Clinical Global Impressions (CGI) scales]. In 15 placebo-controlled trials, SJW was found to be significantly better than placebo. In 8 trials comparing SJW to tricyclic antidepressants, clinical improvement was similar, but with fewer and milder side effects. Of those on SJW, 19.8% reported symptoms compared with 52.8% of those on tricyclic antidepressants.

The National Center for Complementary and Alternative Medicine and the National Institute of Mental Health funded a multicenter study comparing SJW to sertraline (Zoloft) and placebo in patients diagnosed with major depression. While the vast majority of these studies have demonstrated that SJW extract is superior to placebo for depression, there were notable exceptions with two studies published in the Journal of the American Medical Association. The first of these negative trials was published in 2001. A randomized, double blind, placebo-controlled clinical trial was conducted with 200 patients diagnosed with major depression and a baseline HAM-D score of at least 20. After a 1-week, single blind run-in of placebo, participants were randomized to receive either 900 mg/d SJW extract (0.3% hypericin) or placebo for 4 weeks. The dose could be increased to 1,200 mg/d for the remainder of the 8-week study if there was not an adequate treatment response. Response rates in the intention-to-treat analysis were not significantly different between the two groups: 26.5% for St John’s wort vs 18.6% for placebo. The number of participants reaching remission of illness was significantly higher with SJW than with placebo ($P = 0.02$), but the rates were low in the full intention-to-treat analysis (14.3 vs 4.9%, respectively). The authors conclude, “These results do not support significant antidepressant or antianxiety effects for St John’s wort when contrasted with placebo in a clinical sample of depressed patients.”2 The study was challenged due to the very low placebo response, an uncommon finding in antidepressant trials for which placebo response is generally 25-30%.

The NIH-sponsored study is the longest and the most rigorous SJW study conducted thus far.3 Three hundred forty moderate to severely depressed patients were randomly assigned to receive SJW extract, placebo, or sertraline for 8 weeks. Based on clinical response, the daily dose of SJW extract could range from 900 to 1,500 mg and sertraline from 50 to 100 mg. Patients who responded at week 8 could continue on their blinded treatment for an additional 18 weeks. The two primary outcomes were change in the HAM-D score from baseline to 8 weeks and rates of full response (as determined by change in HAM-D and CGI scores). For change in HAM-D score, neither sertraline nor SJW extract was statistically significantly different from placebo. Full response occurred in 31.9% of the placebo-treated patients vs 23.9% of the SJW extract-treated patients ($P = 0.21$) and 24.8% of sertraline-treated patients ($P = 0.26$). Neither sertraline nor SJW extract performed as well as placebo in this primary outcome. Sertraline was better than placebo on the CGI improvement scale ($P = 0.02$), which was used as secondary measure in this study.

The media reports, based on this trial, that SJW is ineffective for the treatment of major depressive disorder, do not provide an entirely accurate picture. In studies of antidepressants, the tested drug often fails to do better than placebo. This is due to both the high subjectivity of the scales used and the typically large placebo response. A review was conducted of clinical trial data from the nine antidepressants approved by the U.S. Food and Drug Administration (FDA) between 1985 and 2000 and included 10,030 patients with depression who participated in 52 antidepressant clinical trials evaluating 93 treatment arms. The researchers found that fewer than half (48%, 45/93) of the antidepressant treatment arms showed superiority to placebo.4 To avoid a false-negative result (type II error), antidepressant trials would have to study 300 or more patients per arm, or more sensitive research designs must be developed.5 The appropriate conclusion from this trial is that it wasn’t sensitive enough to detect the effectiveness of either sertraline or SJW extract or that this was primarily a group of “nonresponders” that were not otherwise characterized biochemically.

**MECHANISM OF ACTION**

SJW has been reported to work by enhancing the quantity of the antidepressant neurotransmitters serotonin, norepinephrine, and dopamine.
in vitro. In reality, though, the concentrations may be too low for these actions to be significant. SJW’s most potent effect may be on the receptors for the inhibitory neurotransmitter GABA_A and GABA_B.

SJW was well reviewed in a monograph that includes information about analytical methods for active constituents, as well as a review of the pharmacology and toxicology.

DOSE AND ADMINISTRATION

The recommended dose of SJW is 300 mg three times per day of a standardized extract of 0.3% hypericin, for a total of 900 mg daily. Higher doses of 1,200 to 1,800 mg have been used successfully in more seriously depressed patients, with no increase in side effects. If there is any gastrointestinal discomfort from the herb, it can be taken with food. The 900 mg can also be taken 450 mg twice per day, or all at once, in the morning for those who find it stimulating (to keep it from interfering with sleep) or in the evening for those who find it to be sedating. A small percentage of patients may become anxious on SJW. They should lower their dose, or discontinue the herb altogether, and may change to other natural antidepressant supplements, including specific amino acids and essential fatty acids.

Many patients report positive effects almost immediately, with a sensation of “a weight being lifted,” decreased anxiety, and an enhanced ability to concentrate. As with most antidepressants, though, it may take 3 or 4 weeks before one notices significant effects.

There are generally no withdrawal effects from St. John’s wort, so one can stop and restart as needed. After a few months, rather than stopping all at once, it’s a good idea to taper off gradually, to assess continued need and dose level. SJW remains a safe, effective alternative to prescription antidepressants, with the appropriate cautions.

CHANGING FROM CONVENTIONAL ANTIDEPRESSANTS TO ST. JOHN’S WORT

Changing from conventional antidepressants to St. John’s wort can be done safely in mild depression by using a withdrawal protocol appropriate to the specific drug and adding in one 300 mg dose of SJW each time the drug dose is lowered, usually every few days. By the end of 1-4 weeks, the patient can discontinue the antidepressant completely. In more serious depression, maintain the antidepressant at half strength for a month while increasing the St. John’s wort to full dose and then reevaluate. Taper off the medication as the full antidepressant effect of the herb takes effect.

This protocol is generally well tolerated. No reports have been published of serotonin syndrome or any other significant adverse effects using these combinations. While there is no evidence of danger, caution is indicated in changing from an monoamine oxidase (MAO) inhibitor to SJW as with other antidepressants. Conservatively, one should observe a 2- to 4-week washout period between stopping the drug and starting the herb.

There are those who do best remaining on a low dose of antidepressant in combination with SJW. The latter can potentiate the drug, and the lower dose has fewer drug side effects.

ADVANTAGES OF ST. JOHN’S WORT COMPARED TO ANTIDEPRESSANT DRUGS

- Side effects are generally mild and infrequent
- Drug side effects include headaches, nausea, sexual dysfunction, insomnia, sedation, “drugged” feeling, agitation, heart arrhythmias, weight changes, short-term memory loss, and rashes
- St. John’s wort is nonhabituating, nonaddictive, and with no withdrawal symptoms upon discontinuing use
- Does not interfere with REM sleep; most often enhances sleep and dreaming
- No adverse effects when mixed with alcohol or most drugs
- Far less likely to cause drowsiness or agitation
- There has not been a single reported death from an overdose of St. John’s wort versus one report of an annual rate of 30.1 deaths by overdose per one million prescriptions of antidepressant.
SOURCES AND QUALITY

There is wide variation in the quality and content of commercially available SJW preparations. Such variability can affect clinical response as well as the results of clinical studies. Patients may do well taking one brand, then, upon changing to another brand, experience a decrease in effectiveness, and vice versa. Side effects may vary also. Similarly, some patients may experience side effects such as gastrointestinal irritation from lower quality brands, while tolerating higher quality brands.

SIDE EFFECTS

Although SJW was reputed to have some MAO inhibition activity in vitro, this effect has not been demonstrated in vivo in either animals or humans nor are there any reported cases of MAOI-associated hypertensive crises in individuals using SJW. Thus there is no need to restrict tyramine-containing foods such as cheese and red wine.

Side effects reported for SJW are generally mild, including gastrointestinal symptoms and fatigue. Extreme sun sensitivity or "photosensitization" may also occur, especially in fair-skinned people.

Kasper and Schulz reviewed efficacy and safety from 20 controlled clinical trials, including a total of 1,787 patients. They concluded that the effective dosage is 600 to 900 mg/day, of 0.3% extract, and that the risk of photosensitization is insignificant.

Animal studies show low toxicity for SJW. Rats fed SJW as 5% of their diet for 119 days experienced no adverse effects. In chronic toxicity studies in rats and in dogs, only nonspecific symptoms of toxicity were seen, with no effects on fertility or reproduction, and no birth defects in offspring.

COMBINATIONS WITH OTHER HERBS

SJW has been combined with other herbs and nutrients, such as kava and ginkgo. While SJW may take as long as 2-6 weeks to reach its full effect, kava's rapid onset has been a historically useful addition, acting immediately on any anxiety or insomnia component. Recent concerns about the potential adverse effects of kava on the liver have placed clinical applications on hold and will be addressed in a future issue of *Seminars in Integrative Medicine*. In the elderly, ginkgo may be an especially useful adjunct.

DRUG INTERACTIONS

Herbal products contain a number of pharmacologically active ingredients, some of which may potentially participate in herb–drug interactions.

A proposed mechanism for herb–drug interactions has been through induction of the CYP 450 enzyme system, a family of enzymes concentrated in the liver and intestinal mucosa, and on P-glycoprotein (Pgp), an ATP-dependent pump that moves substrates out of cells. These can be affected by a range of naturally occurring compounds, such as grapefruit juice and cruciferous vegetables as well as by certain drugs. Other reports of interaction are only theoretical or are solely based on in vitro studies.

Lists of substrates, inducers, and inhibitors of the various enzymes systems are regularly updated and can be found on the internet at: http://www.georgetown.edu/departments/pharmacology/cliniclist.html.

There has been some media attention paid to SJW interactions, from its reputed actions as an MAO inhibitor (which it is not), to its reducing the efficacy of a number of drugs. These include cyclosporine (immunosuppressant for organ transplant patients); digoxin; the protease inhibitors Indivar (used in HIV/AIDS); warfarin; theophylline (asthma), and oral contraceptives.

The last two merit further discussion, since they affect a larger population and have less evidence to support the claims.

Theophylline

Several authors have cited interaction between the asthma medication theophylline and SJW. However the published report referred to is a discussion of a single case of a 42-year-old woman, smoking half a pack of cigarettes daily (tobacco induces liver enzymes) also taking 11 other prescription medications, who had been taking SJW for 2 months. On cessation of SJW, her plasma theophylline levels rose within 7 days. The case obviously is hard to evaluate and does not constitute definitive evidence of a SJW–theophylline interaction.
Oral Contraceptives

Despite popular press articles, there are as yet no reports of unwanted pregnancy caused by oral contraceptive failure due to SJW consumption. A letter to The Lancet by The Swedish Medical Products Agency reported eight cases of irregular or breakthrough menstrual bleeding in women aged 23-31 years who had been taking long-term oral contraceptives and had begun taking SJW. Such reports have also been received from patients, whose symptoms cleared upon stopping the herb. The interaction is unclear and may reflect a lowering of concentration of the oral contraceptive. If unwanted pregnancy is a concern, one should err on the side of caution regarding this combination.

GENERAL GUIDELINES FOR THE USE OF HERBAL MEDICINES

- The clinician should take a careful history of the patient’s use of herbs and other supplements
- An accurate medical diagnosis must be made before using herbs for symptomatic treatment
- Natural is not necessarily safe: Attention should be paid to quality of product, dosage, and potential adverse effects, including interactions
- Herbal treatments should, for the most part, be avoided in pregnancy (and contemplated pregnancy) and lactation
- Herbal usage in children should be done with care, using the appropriate dosage based on weight
- Adverse effects should be recorded, and dosage reduced, or the product discontinued. It can be carefully restarted to ascertain whether it is the source of the problem

GENERAL CONSIDERATIONS FOR THE USE OF HERBS

Changes in the practice of medicine are causing a shift to increasing self-care with more benign, less invasive treatments. As such, it is critical that practicing clinicians (and, in turn, patients) be made aware of the indications, actions, and drug interactions of herbal remedies.

The World Health Organization estimates that 80% of the world’s population relies on herbal medicine. Meanwhile, the use of herbs in the United States is expanding rapidly, to the point at which herbal products are readily found in most pharmacies and supermarkets. From 1990 to 1997, as the use of complementary/alternative medicine rose from 34 to 42%, herbal use quadrupled from 3 to 12%.20

It is worth remembering that these rapid changes have come by popular demand. The public has discovered that natural medicines often provide a safe, effective, and economical alternative, and research is increasingly validating this finding. Many of those who use herbal and high-dose vitamin products fail to tell their physicians. Either they assume “natural” products are harmless and not worth mentioning or they fear telling health professionals who may be skeptical about their use. Health professionals, however, are beginning to familiarize themselves with the subject. Aside from some advantages of natural products, herb–drug interactions are a growing concern: almost one in five prescription drug users are also using supplements.20

In Europe, there is a less of a problem since herbs are classified with other pharmaceutical products and routinely prescribed by doctors. In fact, in Germany prescriptions of SJW outnumber those for all other antidepressants. Most of the research to date is European, since industry has had financial incentive to do the necessary research. The United States has recently joined in these efforts and the NIH National Center for Complementary and Alternative Medicine and the NIMH completed a $4.3 million joint clinical trial to determine the efficacy of SJW in major depression. Herbal studies are now in progress at a number of America’s major medical universities.

HEALTH AND HERBS FOR MENTAL HEALTH

In the Eisenberg survey,20 two of the top five conditions for which consumers sought alternative treatment were anxiety and depression. Besides SJW, there are other herbs with popularity for these and related problems: kava for relief of
stress and anxiety (until recent concerns about potential effects on the liver), ginkgo biloba for senile dementia or benign forgetfulness, and valerian for sleep. A $20 million NIH trial comparing ginkgo to placebo in the development of dementia in older Americans began in 2000.

**SAFETY**

Side effects of psychiatric drugs can be serious, the worst being death by overdose. According to one report, overdoses yielded an annual rate of 30.1 deaths per one million prescriptions of antidepressant. On the other hand, to quote Norman Farnsworth, PhD, Professor of Pharmacognosy at the University of Illinois, Chicago: “Based on published reports, side effects or toxic reactions associated with herbal medicines in any form are rare...In fact, of all classes of substances ...to cause toxicities of sufficient magnitude to be reported in the United States, plants are the least problematic.” It is important to caution patients that if they feel any ill-effects from an herbal product, they should inform the prescribing doctor. Then, depending on the severity, the patient should either reduce the dose or stop taking the herb altogether. Unlike pharmaceuticals, withdrawal reactions are rarely an issue.

It is essential to obtain a complete drug and herbal history. There are contraindicated combinations, which will be covered individually. On the other hand, there are many combinations that work well together. For example, individuals taking a drug that is metabolized by the liver can be protected by the liver-supporting herb, milk thistle (*Silybum marianum*).

**PREGNANCY, BREASTFEEDING, AND CHILDREN**

Many herbs have not been approved for use by pregnant and nursing women in the guidelines of the German Commission E, the equivalent of the FDA. Now available in English translation, the German Commission E has published a collection of reports based on safety and efficacy data on over 200 herbs.

Herbs may often be a treatment of choice for children. Despite lack of modern research, centuries of use have shown many products to be safe when dosed appropriately by weight.

**AGING**

Considering the phenomenon of polypharmacy in the elderly and problems of impaired metabolism and clearance, herbs may offer an alternative to drugs. On the other hand, we also must be aware of herb–drug interactions. SJW can be very useful for depression in the elderly, ginkgo for...
cognitive decline, and kava, for sedation (but see above), without the adverse effects of the benzodiazepines. These herbs can be used in combination with each other as well.

**Selection and Use of Herbs**

**Standardized Extracts**

For those new to the medicinal use of herbs, dose selection can be confusing. As discussed above, unlike synthetic drugs containing a single compound, herbs often have a number of different active ingredients. Even these will vary in proportion, based on many factors, including where the plant was grown and when (season or even the time of day) it was harvested. The manufacturer may adjust the mixture to help account for these variations.

In order to standardize the product, that is, to have a consistent, measured amount of product per unit dose, one ingredient is selected as the marker, usually the presumed active ingredient. Though research may reveal different or additional active ingredients, for convenience the designated constituent will usually remain the accepted marker. This situation is demonstrated in the example of SJW.

SJW is standardized to hypericin, the long-accepted active antidepressant ingredient. Further research has found hyperforin to be a likely active ingredient. Some SJW products are actually standardized for both. In any case, all compounds (even as-yet-undiscovered contributors) remain distributed throughout the plant, alongside the hypericin. As a result, the standardization of hypericin serves as a useful guidepost for the strength of all the (active) ingredients.

Hypericin content is listed on the label, with most products using a 0.3% concentration, so that a 300-mg capsule contains 0.9 mg (0.3 × 300 mg) of hypericin. In kava, the marker is kavalactones, and in ginkgo, flavone glycosides.

**Herbal Preparations and Dosing**

Herbs can be purchased as teas, tinctures, tablets, and capsules. Teas and tinctures, being liquid, are absorbed more rapidly and with a shorter duration of action. Tinctures are made by soaking one part herbal material with 5 or 10 parts by weight of alcohol, making a 1:5 or 1:10 concentration. To remove the alcohol taste, the tincture can be placed in warm water or tea for a few minutes to let the alcohol evaporate. Glycerin may also be used instead of alcohol, but the resulting extract is weaker.

Capsules and tablets are the most common delivery system. Gelatin- or vegetable-based capsules are filled with powdered dried herb, while tablets are powdered herbs, compressed into a solid pill, often with a variety of inert ingredients as fillers.

They are supplied in a variety of sizes and strengths, so it is important to read the label carefully. The label will also usually give an average suggested dose as a guideline, based on research and clinical use. It is recommend to start at the low end, watch for a response, including unwanted effects, and adjust the dose accordingly.

For example, patients may do well on 300 mg of SJW once per day, while others need four times that dose. Most will fall in the middle, with the recommended 300 mg three times daily. Some herbs such as kava take effect immediately, while others take days, weeks (SJW, ginkgo), or even months to do so, with individual variation.

**Regulatory Issues**

Most herbal products are regulated as “dietary supplements.” In 1994, the U.S. Dietary Supplement Health and Education Act (known as DSHEA) set new guidelines with regard to quality, labeling, packaging, and marketing of supplements. It also sparked a surge of interest in herbal products. DSHEA allows manufacturers to make “statements of nutritional support for conventional vitamins and minerals.” Since herbs aren’t nutritional in the conventional sense, DSHEA allows them to make only what they call “structure and function claims,” but no therapeutic or prevention claims. Thus, a SJW label can claim that it “optimizes mood,” but cannot say “natural antidepressant,” which would be a therapeutic claim.

Since the labels (by law) give insufficient information, it is particularly important for the health practitioner to be well educated in this area. Ideally, supplements would be labeled so that the purchaser would know exact indications and possible side effects, as with over-the-counter medicines.

Quality control is essential, with assurance that the product contains the ingredients and quantities as labeled and without such contaminants as bacteria, molds, or pesticides. There are trade and
professional organizations, such as the American Herbal Products Association, that are setting standards called “Good Manufacturing Practices” for the herbal industry. In general, we recommend buying herbal products from a recognized manufacturer.

There are a number of excellent websites on the subject listed below.

**WEBSITES**

Alternative Medicine Foundation, Inc: HerbMed.org

**RESOURCES**


**REFERENCES**

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