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St. John's Wort: A Review of Selected Literature

By

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Abstract

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In the last decade, alternative medicine, such as the use of herbal and dietary supplements, has increased its presence within western mainstream medicine. Many individuals who have chronic health conditions use these treatments first or in conjunction with mainstream medicine. Depression is one of the most common disorders treated in health care settings and affects millions of adults each year in the United States. St. John’s Wort (SJW) has become one of the most popular alternative medicines for the treatment of depression.

Many individuals pursue the use of this alternative medicine for various reasons. However, in an individuals’ pursuit to feel better and the ease of obtaining lay literature, their choice may not be well informed which leads to unsafe use of the product. Practitioners are aware of the popularity of alternative treatment but do not always elicit this information from their patient. Practitioners need to educate themselves and elicit alternative medicine information from their patient to avoid interventions that could lead to harming their patient.

Since SJW is the most popular alternative medicine its important for practitioners to review the literature on its efficacy, tolerability and safety compared to the more popular mainstream antidepressants used in the United States in treating mild, moderate and severe major depression.
St. John’s Wort: A Review of Selected Literature

Introduction

Alternative and complementary medicines are terms used interchangeably when referring to a variety of therapies that are outside the domain of mainstream western medicine. Eisenberg et al. (1998) revealed that alternative medicine use and expenditures increased substantially between 1990 and 1997. These authors reported total spending for alternative treatments in the United States rose from $14.6 billion in 1990 to $21.2 billion in 1997. This included herbs, dietary supplements, and other interventions such as acupuncture, chiropractic, hypnosis, homeopathy, and energy healing. This same survey found that visits to alternative practitioners rose from 427 million in 1990 to 629 million in 1997, while visits to primary care physicians during the same period actually declined slightly from about 388 million to 386 million (Eisenberg et al., 1998).

National Institute of Mental Health (NIMH) (2001) reported the use of herbal remedies increased 380 percent from 1990 to 1997. Eisenberg et al. (1998) found most alternative therapies are used for chronic conditions including back pain, anxiety, depression, insomnia and headaches. Consumers choosing alternative medicine receive their information mostly from lay literature and do not always make what health care professionals would consider “informed decisions” or “choices”. One explanation is that access to alternative treatment information is easily obtained. People who want to feel better may seek these treatments and yet not use them safely if this choice is not fully informed.

Alternative Treatments and Depression

Depression is one of the most common disorders treated in primary care settings and affects more than 19 million adults in the United States each year (NIMH, 2001). Depression costs the
nation $44 billion in treatment, disability, and lost productivity (National Institutes of Health, 1997). There are barriers to treating depression successfully. Two barriers seem to be the adverse effects of antidepressants and their high cost. This may be a reason for St John’s Wort (SJW) becoming such a widely used herbal medicine for depression in the United States. Wagner, Jester, LeClair, Taylor, Woodward, & Lambert (1999) found that consumers self-diagnosed their depression and used herbal remedies for treatment because they perceived them safer than prescription drugs. The use of SJW in the United States has risen drastically with annual sales increasing from $20 million to $200 million between 1995 and 1997 (Gaster & Holroyd, 2000).

**Significance to Nursing**

Consumers are increasingly choosing SJW for many reasons, but alarmingly unsafe behaviors are increasing as well. Beckman, Sommi & Switzer (2000) and Wagner et al. (1999) identified some very disturbing, risky behaviors that consumers display when routinely self-treating and self-diagnosing themselves. Consumers will readily self-treat depression without advice or guidance from medical professionals regarding the efficacy, safety and dosing of SJW. Some reasons for treating themselves with SJW included cost, accessibility, lack of response to antidepressants, intolerable side effects of other medications, and perceived safety of natural products (Beckman, Sommi & Switzer, 2000). According to Wagner et al. (1999), the consumers’ accessibility issues stemmed from barriers to and lack of knowledge of healthcare providers, stigma, and the ease of access to SJW’s use and popularity.

Practitioners are aware of the popularity of alternative treatments, yet often fail to elicit this information from their patient. This approach is unsafe and could lead to interventions that will harm the patient. Davidson et al. (1998) found that patients with depressive or anxiety disorders are more likely to seek out alternative treatments for a wide range of medical problems including
their self diagnosed depression or anxiety. Walter, Rey & Harding (2000) found that 80% of herbal remedies and other alternative therapies are playing an increasing role in the treatment of psychiatric disorders.

Crock, Jarjoura, Polen & Rutecki (1999) and Walter, Rey & Harding (2000) found that primary care physicians and psychiatrists are displaying an open and positive attitude towards alternative treatment. Crock et al. discussed the need for practitioners to have access to information and studies on alternative treatments to enhance their knowledge and referral ability. Walter et al. concluded that practitioners are willing to discuss alternative treatments, to help patients make informed decisions about their treatment choices. They also found that familiarity with alternative therapies and the practitioner’s prescribing patterns did not hinder the patient-physician communication. Walter et al. found that only thirty-eight percent (n=327) of the psychiatrists routinely asked patients if they used SJW or other alternative treatments. It is of the utmost importance that practitioners routinely inquire about alternative therapy and have the knowledge and education needed to answer questions posed by patients regarding the use of herbal remedies and other alternative therapies.

Advance Practice Registered Nurses (APRN) have an immediate professional responsibility to educate themselves regarding herbal psychotropics (Glisson, Crawford & Street, 1999). Lack of this knowledge decreases their ability to help patients make safe informed choices. This poses a great disservice to the patient. APRNs need to educate themselves and become more informed about research studies on alternative treatments. With the increasing use of complementary, herbal or homeopathic treatments, APRNs need to take a proactive approach and routinely inquire about a patient’s use of herbal medicine. Eliciting alternative treatment information would allow the APRN to assess the possibility of potential drug interactions, and convey to the
patient the practitioner’s recognition of alternative treatments. This will strengthen the therapeutic alliance and allow the APRN to educate their patient and help them make a safe, well-informed decision about their treatment choices. With effective patient-practitioner communication, potentially serious consequences of misdiagnosis and inappropriate alternative medication use for mental illness can be avoided. If APRNs elicit alternative treatment information and provide comprehensive education to the patient, they would strengthen and fortify the quality of care delivered to the patient.

**Literature Review**

The purpose of this paper is a review of recent selected research literature to explore the efficacy, safety and tolerability of SJW. Studies selected were to compare SJW with placebo, Tricyclic Antidepressants (TCAs), and Selective Serotonin Reuptake Inhibitors (SSRIs) in the treatment of mild, moderate and severe major depression.

Major depressive disorder, also known as major depression, is the most common type of depressive illness. Symptoms usually develop over days, weeks, or months. They can cause distress and/or interfere with the ability to work, study, sleep, eat, and enjoy once-pleasurable activities. The description of a person experiencing a major depressive episode, as found in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, TextRevision (DSM-IV-TR)*, is that of someone who may feel sad, irritable, hopeless, discouraged, tired, worthless, or guilty much of the time. The person also often can not think clearly, concentrate, or make decisions. This depressed mood lasts most of the day nearly every day for a period of at least 2 weeks. Untreated, the depression can last for 6 months or longer. Other than depressed mood and/or loss of interest or pleasure, symptoms include at least four of the following: significant weight gain or loss, disturbance of normal sleeping patterns (insomnia, hypersomnia), agitation
or unusual slowness, fatigue or loss of energy nearly every day, feelings of worthlessness or
guilt, diminished ability to think or concentrate, or recurrent thoughts of death or suicide
(American Psychiatric Association, 2002). Major depression can vary in degree from mild,
moderate or severe. In mild cases, there may be some significant distress or interference with
daily activities at work, at home, and in social life. In moderate depression, problems and
impairments in these areas are more pronounced. If the depression is severe, the person may lose
the complete ability to function.

According to the standards of care from the American Psychiatric Association, the goal of
treatment for major depression is the remission, total absence, of symptoms which can be
achieved with the utilization of appropriate treatment modalities (American Psychiatric
Association, 2002). Remission is induced in the acute phase which lasts a minimum of six to
eight weeks. After remission is reached the patient moves into the continuation phase (lasting 16-
20 weeks) where remission is persevered and relapse prevention begins. Patients who complete
the continuation phase without a relapse proceed to the maintenance phase. The maintenance
phase goal is to protect the patient from reoccurrence and the phase duration varies depending on
the patient.

The majority of these studies used the Hamilton Depression Scale (HAM-D; 17 or 21 items)
as their primary efficacy measurement but occasionally secondary measurement tools were used.
Other measurement tools will not be discussed if significant results were not found. Most of the
studies reviewed used the DSM-IV as the diagnostic criteria for diagnosing mild to moderate or
severe depression. In a few studies, the ICD-10 was used. Since the ICD-10 is usually used in
conjunction with the DSM-IV, although it was not stated as such, the diagnostic criteria used
were assumed to be the DSM-IV. These studies also used the terms SJW and hypericum extracts
interchangeably. For the reader’s convenience highlights of the studies reviewed are in the appendix.

**SJW Overview**

St. John’s Wort (SJW), also known as *Hypericum perforatum*, is a naturally occurring plant found in relatively dry temperate zones of Europe and North America. The name SJW comes from the fact that the plant flowers around St John’s Day (June, 24). Many sources say its red pigment symbolizes the blood of St. John. The word *wort* is an Old English term for plant.

For centuries, SJW has been used for its antidepressant effects. SJW has also been used for its anti-inflammatory, sedative, analgesic, diuretic and wound healing properties (Miller, 1998). Numerous clinical trials have been conducted on SJW in treating varying degrees of depression. Few trials have been conducted on SJW’s other healing properties.

Hypericin is traditionally considered the main active antidepressant component in SJW, but it still remains unclear what substance or substances are actually the active agents (Miller, 1998). It is unknown whether hypericin, hyperforin or hypericum are the antidepressant compounds. The amount of hypericin varies widely in different parts of the plant, under different growth conditions, and at different times of the year (Linde et al. 1996). Most commercial products of SJW are hypericum extracts with 0.3% standardized hypericin present (0.9mg of active constituent), in which 300 to 900 mg are given daily in three divided doses. Staffeldt, Kerb, Brockmoller, Ploch & Roots (1994) found that 600mg hypericin compounds given three times per day was absorbed within two hours and had an average elimination half-life (t½) of 28 hours and the terminal t½ during steady state over fifteen days was 42 hours. This indicates that hypericin could be given in two divided doses but it is usually given in three to maintain a higher steady state of concentration. There are several hypericum preparations that exist and there has
been evidence of comparable efficacy across some preparations (Linde et al. 1996). One of the main hypericum extracts is LI 160 (0.3% standardized hypericin), manufactured by Lichtwer Pharma AG, Berlin, Germany, and is used in Germany’s mainstream medicine for the treatment of anxiety, depression and sleep disorders (Linde et al., 1996). In Europe, SJW is a prescription provided by the practitioner in the United States SJW is found over the counter and available for anyone to use.

Various substances contained in SJW extracts have been found to interact with a number of neurotransmitter systems implicated in depression and other psychiatric illnesses (Rey & Walter, 1998). The mechanism of action remains unclear. The most probable mechanism of action is the inhibition of serotonin reuptake which has been observed with hypericin and hyperforin (Neary & Bu, 1999). SJW has been found to inhibit the uptake of serotonin, norepinephrine and dopamine (Bennet et al., 1998). Studies have shown that high concentrations of hypericin exhibit monoamine oxidase inhibition (MAOI) activity and conclude that this inhibition may be due to the activity of flavonoids and xanthones (Bombardelli, Morrazzoni, 1995). Studies have also shown hypericum to down-regulate B-adrenoreceptor resulting in tricyclic antidepressant effects (Muller, Rolli, Schafer, & Hafner, 1997). It has also been postulated that the antidepressant effect of SJW may be due to it modulating the production of cytokines under stimulation and suppressing interleukin-6 release, which modulates cortisol release and depression (Bennet et al., 1998). Interleukin-6 is a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis via stimulation of corticotropin-releasing hormone (CRH). With depression there is hypersecretion of CRH, hypersensitivity of adrenal cortex to ACTH and increased cortisol levels. Studies propose that the interleukin-6 inhibition may “re-set” the hyperactive HPA axis. Hypericum has also been found to inhibit the binding of benzodiazepines at the benzodiazepine-binding sites at
the GABA receptors (Cott, 1997). Hypericum has many proposed mechanisms of action that
affect a variety of biochemical models of depression including, serotonin, dopamine,
norepinephrine, MAOI, interleukin-6, HPA, B-adrenoreceptor and GABA.

SJW is classified as a dietary supplement by the United States Food and Drug
Administration (FDA), a federal government regulatory agency. FDA requirements for testing
and obtaining approval to sell dietary supplements are less strict than requirements for drugs.
Unlike drugs, dietary supplements can be sold without requiring studies on dosage, safety or
effectiveness.

According to National Center of Complementary and Alternative Medicine (NCCAM)
(2002) and the National Institute news release most SJW studies released are smaller European
ones that suggest SJW is useful in the treatment of mild to moderate major depression. These
studies were reviewed by experts and found to have many limitations and concluded that more
rigorous trials are needed before firm conclusions can be drawn. In response to the growing use
of SJW in the United States, there were two large scale studies launched that are discussed
further in this review. Shelton et al. (2001) was the first large-scale, placebo-controlled study of
SJW conducted in the United States. Davidson et al. (2002) was one of the first large-scale,
multi-site clinical trials of SJW funded by the NCCAM, NIMH, and the Office of Dietary
Supplements (ODS).

*Placebo and SJW*

*Hypericum ZE 117.* The purpose of this study was to evaluate the clinical efficacy and
tolerability of hypericum ZE 117 in patients with mild to moderate major depression. Schrader,
Meier, & Brattstrom (1998) used a prospective, double-blind, randomized, placebo-controlled,
multicenter trial with 162 outpatients from 16 centers. Subjects received either hypericum extract
ZE 117 (250mg tablets twice a day), standardized to 1 mg hypericin, or placebo daily, for six weeks. The instruments used were validated scientific scales. The Hamilton Depression Scale (HAM-D) was used to assess treatment response. A clinical response was determined to be a decrease in the baseline HAM-D by at least 50% or a HAM-D score < 10. Fifty-six percent of patients treated with hypericum ZE 117 were classified as responders compared with 15% of patients on placebo.

Based on the differences in the HAM-D scores (p < 0.001) the authors concluded that hypericum extract ZE 117 was significantly superior to placebo, and was a safe and effective treatment for mild-moderate depressive episodes. The adverse events were few and self-limiting, with the most commonly reported being non-specific gastrointestinal problems in six patients. Schrader et al. (1998) concluded that there were clinically meaningful results because a long treatment period was used with an adequate sample size. They explained the low rate of placebo responders were partly due to reducing the placebo effects in the early phases of treatment by making the first key assessments done at six-weeks.

*Hypericum WS 5572 and WS 5573.* The purpose of this study was to evaluate the efficacy and safety of two different SJW extracts compared to placebo in patients with mild to moderate major depression. Laakmann, Schule, Baghai & Kieser (1998) used a randomized, double-blind, placebo-controlled, parallel group evaluation of two different extracts of SJW and placebo with 147 outpatients from 11 centers. Subjects received three 300 mg doses daily of either hypericum extract WS 5572 containing 5% hyperforin, hypericum extract WS 5573 with 0.5% hyperforin or placebo daily, for six weeks. The hypericum preparations were identical apart from the hyperforin content. The primary efficacy variable was measured by the HAM-D. A clinical
response was determined by a decrease in the baseline HAM-D by at least 50% or a HAM-D score \(< 10\).

Using this criteria the responders respectively were 49% for hypericum WS 5572, 39% for hypericum WS 5573 and 33% for the placebo group. The difference between hypericum WS 5572 and the placebo group was statistically significant (\(p < 0.001\)). This significant relationship suggested that the therapeutic effect of hypericum may have depended on the hyperforin content.

In all groups, two-thirds of the subjects experienced no adverse events. The placebo group actually displayed a higher incidence of adverse events, and there were no adverse events from hypericum WS 5572 or hypericum WS 5573 that did not also appear in the placebo group. The most frequently reported adverse event was headache.

*Hypericum LI 160.* The purpose of the study was to compare the efficacy and safety of the hypericum extract LI 160 (0.3% standardized hypericin) with placebo in patients diagnosed with major depression. Shelton et al. (2001) used a randomized, double-blind, placebo-controlled, multicenter trial with 200 outpatients from 11 centers. Subjects completed a one-week, single-blind run-in of placebo, then were randomly assigned to a treatment group to receive hypericum extract LI 160 (\(n = 98\)), 900mg/day in divided doses for four weeks then increased to 1,200mg/day in the absence of an adequate response for another four weeks. The control group (\(n = 102\)) received a placebo daily for eight weeks. Response and remission rates were calculated for the entire sample as well as for those who completed the full eight weeks of treatment. This report will focus on the sample that completed the study (\(n=75\) SJW, \(n=86\) placebo). Clinical response was defined as a HAM-D score of 12 or less, representing at least a 50% improvement in HAM-D scores from baseline and a Clinical Global Impression (CGI) score of 1 or 2. Remission was defined as a HAM-D score of 7 or less with a CGI score of 1 or 2.
According to the investigators, the response rates in those who completed eight weeks of treatment were not statistically different, with 32.9% for hypericum LI 160 and 20.7% for placebo. The treatment group showed no significant differences in remission rates with 20.3% for hypericum LI 160 and 10.3% for placebo. There was a significant effect for time but not for treatment effect between the two groups. There was also no time-by-treatment interaction. SJW was found to be safe and well tolerated but failed to produce statistically significant differences compared to placebo. Adverse events that occurred in both groups included abdominal discomfort, insomnia and headaches. More significantly, headaches occurred in greater frequency with the hypericum extract LI 160 at 40% than with placebo at 26%.

Summary

Shelton et al. (2001) concluded that SJW was safe and tolerable but was not effective in the treatment of major depression. This was one of the first large-scale, placebo-controlled studies of SJW conducted in the United States. The results do not support significant antidepressant or anti-anxiety effects for SJW when compared to placebo. The authors of this study concluded that patients with significant major depression should not be treated with SJW due to the morbidity and mortality risks of undertreated or inadequately treated major depression. They recognized that patients who have mild depression or who prefer alternative medications may show a different outcome and it would be important to do research on different populations. These researchers called for better designed studies and concluded that, contrary to Schrader et al. (1998) and Laakmann et al. (1998), there was no credible evidence to support the efficacy of SJW for people with depression. This study was funded as an independent research grant to R. C. Shelton by Pfizer Inc., manufactures of antidepressants and SJW extract. The NIMH grant also provided support to Dr. Shelton. No author disclosures were made.
Schrader et al. (1998) and Laakmann et al. (1998) concluded that SJW is superior to placebo with good efficacy and low adverse events in patients with mild-moderate major depression. Schrader et al. used a hypericum extract with hypericin standardized at 1 mg daily, whereas the Laakmann et al. study used hypericum extract with hyperforin standardized at 0.5% and 5%. Laakmann et al. reported that 5% hyperforin extract was superior over placebo concluding that hypericum WS 5572 is an effective antidepressant in treating mild-moderate depression and it had the lowest incidence of adverse events. They concluded that hyperforin content was primarily responsible for the antidepressant effect of SJW preparations while other components appear to be secondary. The authors suggested that to get extracts with comparable antidepressant potency, the hyperforin instead of the hypericin content of SJW preparations should be used (Laakmann et al., 1998).

This is a premature conclusion from only one study. A study comparing hypericin to hyperforin standardized content may be helpful in possibly determining if one or the other makes a difference in the antidepressant effect. The studies do not clearly define the major depression criteria used. Laakman et al. (1998) reported using the DSM-IV (single or recurrent) without giving detail on their exclusion criteria or inclusion criteria. Schrader et al. (1998) used the ICD-10 (F32.0, F32.1) but gave no information of what these criteria consisted of or what the inclusion or exclusion criteria were. The data were only collected over a six week period which is a point where depression spontaneously begins remission.

There is no indication whether participants were included or participated in psychotherapy during these studies. Shelton et al. (2001) indicated and included participants who were in psychotherapy if they had been in therapy three months prior to the study. The adverse events displayed in all three studies were minimal, showing that SJW was adequately tolerated.
Schrader et al. (1998) and Laakman et al. (1998) studies were performed in Europe under European research and clinical practice guidelines which differs from the rigorous Federal Drug Administration research guidelines Shelton et al. (2001) performed under. No author or funding disclosures were mentioned for Schrader et al. (1998) and Laakman et al. (1998).

**TCAs and SJW**

*Amitriptyline and Hypericum LI 160.* The purpose of this study is to evaluate the efficacy and tolerability of hypericum extract LI 160 compared to amitriptyline in patients with mild to moderate major depression. Wheatley (1997) used double-blind, randomized, multicenter study involving 165 outpatients from 16 centers. Subjects were randomized to receive either hypericum LI 160, 900mg/day in divided doses, or amitriptyline, 75mg/day in divided doses, for six weeks. The treatment effect was assessed by the Clinical Global Impression Scale (CGI) and the HAM-D. A clinical response was determined by a decrease in the baseline HAM-D by at least 50% or a HAM-D score < 10. Pre-treatment HAM-D scores ranged from 17 to 24. Differences between response and remission were not delineated in this study.

Sixty percent of the hypericum groups were treatment-responders according to the HAM-D. This was not a statistically significant difference compared to 78% in the amitriptyline group. The CGI scale, assessing drug side effects showed a clear advantage for hypericum LI 160 in terms of tolerability (p < .001 at week 2, p < .05 at week 4 and 6). Wheatley (1997) concluded that hypericum LI 160 showed a comparable efficacy to amitriptyline and had a clear tolerability advantage. Hypericum LI 160 had significantly fewer side effects as compared to amitriptyline, without sedation or cognitive function problems.

*Imipramine and Hypericum LI 160.* The purpose of this study was to evaluate the efficacy and tolerability of hypericum extract LI 160 compared to imipramine in patients with severe
major depression. Vorbach, Arnoldt & Hubner (1997) used a double-blind, randomized, multicenter trial with 209 patients (38 inpatient and 117 outpatients) and 20 centers. Subjects received hypericum LI 160, 1800mg/day in divided doses (higher therapeutic dose), or imipramine, 150mg/day in divided doses, for six weeks. The primary efficacy variable was measured by the HAM-D. A clinical response was determined by a decrease in the baseline HAM-D by at least 50% or a HAM-D score < 10.

In the hypericum group 35% of the patients were responders and 41% for the imipramine group. These findings did not reveal a significant statistical difference. Adverse effects were reported by 23% of subjects receiving hypericum and 41% receiving imipramine, suggesting that hypericum was as effective as, and better tolerated than imipramine.

Summary

Wheatley et al. (1997) and Vorbach et al. (1997) found no significant advantage in terms of the HAM-D response, from hypericum LI 160 compared to amitriptyline and imipramine. Both studies, however, concluded that hypericum had significantly fewer adverse effects than the TCAs. These studies found that hypericum LI 160 had a clear tolerability advantage, and was as effective as imipramine and amitriptyline in treating mild, moderate and severe major depression. These studies used a short six week period, no placebo was used and no statistically meaningful differences were found. No placebo group was used. Such a weak design compromises the strength of efficacy results since the treatment regimes were not tested against a placebo. It could be argued that while a higher therapeutic dosage of 1800mg/day of hypericum LI 160 was used in one study, the TCA’s in both studies were used at subtherapeutic doses skewing the results for determining efficacy. There was no indication whether patients in
psychotherapy were allowed to participate in the study. Both studies were done in Germany and neither revealed author disclosures or who funded the studies.

**SSRIs and SJW**

*Sertraline and Hypericum LI 160.* The purpose of this study was to compare the efficacy and tolerability of hypericum extract LI 160 compared to sertraline in patients with mild-moderate major depression. Brenner, Azbel, Madhusodanan & Pawlowska (2000) used a double-blind, randomized, single center pilot study involving 30 outpatient subjects (n=15 in each group). There were nineteen women and eleven men with an average age of 45 years old. Twenty-one patients had a major depression, recurrent form and nine patients with major depression, single episode. Subjects received hypericum LI 160, 600 mg/day, or sertraline, 50 mg/day, for one week. Subjects then received hypericum LI 160, 900 mg/day, or sertraline 75 mg/day, for six weeks. The treatment effect was measured by the HAM-D. A clinical response was determined by a decrease in the baseline HAM-D by at least 50% or a HAM-D score < 10. Pre-test scores on the HAM-D were > 17.

Clinical response was noted in 47% of the patients in the hypericum group and 40% of the patients in the sertraline group. The difference was not statistically different, and the subjects in both groups had a significant clinical improvement in depression ($p < 0.05$). Few adverse events were reported in either group with headache being the most common.

Brenner et al. (2000) attributed the lack of statistical significance between treatments to the lack of clinical differences rather than to the small sample size. Brenner et al. pointed out that it would be helpful to have larger and more placebo-controlled studies done in comparing the efficacy and safety of hypericum to SSRIs. The authors concluded that this small study showed hypericum was as effective as sertraline and both were well tolerated.
Fluoxetine and Hypericum extract ZE 117. The purpose of this study was to evaluate the efficacy and tolerability of hypericum extract ZE 117 compared to fluoxetine in patients with mild-moderate major depression. Schrader, on behalf of the study group (2000) used a randomized, double-blind, parallel group involving 240 outpatient subjects. Subjects received hypericum ZE 117, 500mg/day in divided doses, or fluoxetine, 20mg/day in daily dosing, for six weeks. Of the 240 patients, 126 were in the hypericum group (52%) and 114 were in the fluoxetine group (48%). Sixty-five percent of the participants were female and the average age was 46.5 years old. HAM-D was used for assessing the success of the treatment. The HAM-D pre-treatment mean was 19.65 for the hypericum group and 19.50 for the fluoxetine group. A clinical response was determined by a decrease in the baseline HAM-D by at least 50% or a HAM-D score < 10. Remission was not delineated in this study.

At the end of six weeks, the mean HAM-D scores decreased to 11.54 in the hypericum group and to 12.20 in the fluoxetine group (p < 0.09). This was not a significant difference. According to the authors, the initial analysis of efficacy rejected the hypothesis of hypericum being inferior to fluoxetine and confirmed them to be equivalent with regard to overall antidepressant effect. However, the hypericum responder rate of 60% was significantly (p = 0.005) greater than fluoxetine at 40%. The secondary analysis revealed a trend in favour of hypericum relative to fluoxetine in improving overall HAM-D scores. Schrader (2000) concluded that the overall tolerability and safety of hypericum was also substantially superior to fluoxetine. The incidences of adverse events were 8% for hypericum and 23% for fluoxetine. The hypericum subjects only reported gastrointestinal symptoms. The fluoxetine subjects reported agitation, gastrointestinal symptoms, dizziness, anxiety and erectile dysfunction.
Schrader (2000) concluded that the treatment of mild to moderate major depression with hypericum was as effective as fluoxetine. The HAM-D results revealed that both treatments were essentially equal in their antidepressant effects, although in this study, significantly more subjects receiving hypericum achieved an antidepressant effect. The authors' interpretation was that the responder rate showed hypericum to be superior with a higher tolerability. Schrader (2000) noted that mild to moderately depressed patients may be less tolerant of side effects compared to severely depressed patients.

**Sertraline, Placebo and Hypericum LI 160.** The purpose of this study was to evaluate the efficacy and safety of hypericum extract LI 160 in moderately severe major depression. Davidson et al. (2002) used a double-blind, randomized, placebo-controlled study involving 340 outpatient subjects in 12 centers. Based on clinical response, subjects received hypericum LI 160, 900-1500mg/day in divided doses, placebo, or sertraline, 50-100mg/day in daily dosing, for eight weeks. Partial or full responders at week eight could continue double blinded treatment for another eighteen weeks. The pre-treatment HAM-D baseline score was at least 20. Efficacy was measured based on the change in HAM-D total scores from baseline to week eight. Full response was defined as a CGI score of 1 or 2 and a HAM-D total score of 8 or less. The main comparison was between the hypericum and placebo groups. Sertraline served as an active comparator to evaluate the study's sensitivity.

On the two primary outcome measures at week eight neither hypericum nor sertraline were significantly different from placebo. Full response occurred in 31.9% of the placebo-treated subjects, 23.9% of the hypericum-treated subjects and 24.8% of sertraline-treated subjects. CGI score at week eight did not differ between hypericum and placebo but sertraline was superior to placebo. In post hoc analysis, sertraline proved superior to hypericum on CGI scale (p = 0.01).
Hypericum and sertraline were associated with more adverse events than placebo. Rates of adverse events in the hypericum and sertraline groups were all higher than in the placebo group. Adverse events with sertraline included forgetfulness, diarrhea, nausea and sweating; with hypericum, frequent urination and swelling, both sertraline and hypericum had events of anorgasmia.

Davidson et al. (2002) concluded that their study failed to support the efficacy of hypericum in the treatment of moderately severe major depression. Hypericum or sertraline could not be differentiated from placebo on the HAM-D. Sertraline showed superiority on the CGI but hypericum showed no efficacy on any measure. They reported a possible limitation and bias; hypericum was dosed at a higher therapeutic range and sertraline was only dosed at 50% of its highest recommended dose. Davidson et al. concluded that until further data are available, hypericum should not be substituted for standard clinical care of proven efficacy, including antidepressant medications and psychotherapy for the treatment of moderately severe major depression.

Summary

Brenner et al. (2000) and Schrader (2000) found that hypericum was just as effective as sertraline and fluoxetine in treating mild to moderate major depression. Brenner et al. concluded that hypericum is as well tolerated as sertraline. Schrader concluded that hypericum was significantly more tolerable than fluoxetine. The response rate for hypericum was greatest in both studies; however, it was significantly greater in comparison to fluoxetine only (20%) and only 7% greater than sertraline. This could be due to the fact that neither study used a placebo group and Schrader (2000) had a significantly larger sample size than Brenner et al. (2000). There may have been significant differences in response rates with larger sample sizes.
Brenner et al. (2000) conducted the study for only seven weeks and Schrader (2000) conducted his study for only six weeks. Due to depression spontaneously beginning remission at six weeks the short term duration hinders their findings and there is no controlled data for continuation treatment. These studies varied in the hypericum preparations and dosages used which could arguably also make a difference in the response rates or the tolerability. There is no mention of whether participants in psychotherapy were included or excluded in this study.

Schrader (2000) used the ICD-10 criteria with no specific information given regarding their clarification of this criteria and Brenner used the DSM-IV criteria. Brenner et al. (2000) study was conducted in the United States and was supported by Lichtwer Pharma AG, Berlin, Germany with no author disclosures made. Schrader (2000) study was conducted in Europe and was funded by the German medical insurance system with no author disclosures made.

Davidson et al. (2002) study failed to support the efficacy of hypericum in moderately severe major depression. The authors mentioned this study demonstrated the importance of including inactive (placebo) and active comparators in trial testing. Without a placebo, hypericum could have been considered as effective as sertraline. By including the placebo group with an FDA-approved drug they were able to measure how sensitive the study was to detecting antidepressant effects. This study went for eight weeks then had controlled data for an additional eighteen week continuation treatment. This study excluded participants who were in therapy two months prior to study or in ongoing therapy to treat depression. Davidson et al. (2002) maintains that hypericum may be used by patients for milder depression due to its availability, but further study needs to be conducted to show clearer evidence of efficacy. The authors also maintain that further studies need to be performed before hypericum can be determined safe and effective in moderately severe major depression. As mentioned earlier several agencies, NCCAM, NIMH
and ODS, funded this large scale study. The author, Jonathan R. T. Davidson M.D. discloses that he holds stock in a multiple number of pharmaceutical companies including Pfizer and Lichtwer and has received speaker fees and grant support from these same companies and funding agencies.

**Discussion**

These studies have shown that it is still unknown what role SJW should play in the management of depression. The results indicate that SJW was no more effective for treating moderate, severe major depression than placebo. The evidence shows that SJW may be useful in treating mild major depression and most of the studies have shown that SJW was as tolerable as conventional antidepressants.

These studies suggested that hypericum was well tolerated with an incidence of common adverse reactions less than that from amitriptyline, imipramine, fluoxetine or sertraline and similar to that of placebo. The most common adverse events that were noted in these studies included headache, gastrointestinal symptoms, allergic reactions, restlessness, nervousness, dizziness, confusion, tiredness, fatigue and sedation. Adverse events have been suggested to be dose dependent and usually subsided with long term use of SJW. Long-term safety remains questionable since the hypericum data reviewed here have not been compiled for more than four-eight week duration, with the exception of Davidson et al. (2002) study that continued for an additional eighteen weeks. SJW has not been associated with serious adverse events in humans and appears well tolerated.

Vorbach, Arnoldt & Hubner (1997) concluded that SJW had a clear tolerability advantage, and was as effective as imipramine in treating severe major depression. Davidson et al. (2002) and Shelton et al. (2001), on the other hand, concluded that their studies failed to support the
efficacy of SJW in moderate or severe major depression. Davidson et al. maintained that SJW may be most effective in milder depression but further study of this possibility needs to be conducted to show clearer evidence of efficacy. Shelton et al. however, called into question the findings of prior research reports that had consistently shown SJW as having superiority over placebos and conventional antidepressants. They concluded that there was no evidence that supported the use of SJW in patients with mild, moderate or severe depression and rejected the multiple previous research and clinical findings showing the efficacy of SJW for mild to moderate depression.

There were several different hypericum preparations used in these clinical trials. They had been standardized to different concentrations of hypericin and hyperforin, and were also administered at different dosages. Laakmann et al. (1998) reported that hyperforin might be the active ingredient not hypericin. It is unknown how the use of different products and dosages may alter the outcomes in terms of adverse drug reactions or efficacy.

**Recommendations for Future Research**

Further research studies are needed before the antidepressant efficacy and tolerability of SJW can be fully determined. Continued comparative trials of SJW, conventional antidepressants (other SSRIs, venlafaxine and bupropion), and placebo would provide additional research evidence about their relative efficacy and tolerability. Comparative trials need to investigate the long-term effects and the relative efficacy of using different preparations and doses (Linde et al., 1996). Future studies should consist of longer trials using consistent measurement tools and formal standard mechanisms for the assessment of adverse events. This would help improve the evaluation of efficacy and tolerability of SJW compared with other antidepressants. There also need to be more studies in the Unites States that clearly indicate whether other treatments are
used in conjunction with the medication. More knowledge is needed on the effects of SJW in overdose, its drug interactions, its side effects, specifics about its mechanism of action and the relative components that contribute to the antidepressant effects. It would also be helpful to have studies comparing hypericin and hyperforin with standardized content attempting to determine which one elicits the antidepressant effect. SJW has been found to be helpful in other psychiatric disorders (obsessive-compulsive disorder, social phobia, and seasonal affective disorder) other than mild to moderate depression. These findings would add further research evidence to determine the safety and effectiveness of SJW.

According to the National Institute of Health (2003) the SJW clinical trials that are in process include, NCCAM, NIMH, and ODS are funding and currently recruiting patients for a study to assess the effectiveness and safety of SJW and citalopram, each compared to a placebo, for the treatment of minor depression. NCCAM is also currently funding and recruiting patients for studies to determine the effectiveness of SJW as compared to placebo in the treatment of obsessive-compulsive disorder and social phobia. NCCAM is no longer recruiting patients and is in the process of evaluating the effects of SJW on the effectiveness of birth control pills.

There is an abundance of research about the consumers' and practitioners' views of alternative and complementary therapies, but very little on their views specifically using SJW. The majority of these studies, as well as the SJW studies, are based in European countries. More research based in the United States is needed. This would lead to better comparisons of the American population and give Americans more meaningful results. More research needs to be done on why consumers are choosing SJW and what kind of education or support is needed from their practitioner. Studies also need to be done on the practitioner focusing on some of the following issues: practitioners views of SJW use, how to work with the patient who wants to try
an herbal product before a conventional medication and how does the practitioner take part in recommending and educating the patient about these alternative choices. Answers to these issues would offer the consumer and practitioner guidelines for safer and more effective treatment.

**Clinical Implications**

In reviewing these studies, SJW has been shown to be ineffective in the treatment of moderate to severe major depression, and it may be effective in the treatment of mild major depression but more rigorous trials are needed. Studies show SJW was as tolerable as standard antidepressants; however, due to the high mortality and morbidity of untreated or undertreated depression it is important that consumers consult with expert clinicians so the severity of their depression is accurately diagnosed and the best treatment is received.

Since SJW has taken a place in the health care arena there are a few issues that need to be addressed. First, APRNs need to acknowledge the existence of alternative treatment. Second, despite data regarding the efficacy of SJW, there is a lack of regulatory oversight that complicates recommending its use. Last, there needs to be more quality control of SJW preparations. According to the United States Food and Drug Administration (2003) news release, the FDA is proposing a new regulation to require “current good manufacturing practices”. The proposed rule would establish standards to ensure that dietary supplements and ingredients are labeled and manufactured to accurately reflect all ingredients in the product (active constituents and others).

It is difficult for practitioners to recommend SJW when there is a lack of regulatory oversight or quality control procedures in place to standardize the preparations; however, APRNs and consumers can gain more knowledge about SJW so it can be used appropriately and does not
jeopardize the consumer's safety. This knowledge of SJW's clinical implications is of utmost importance; therefore, SJW's potential side effects and drug interactions are discussed further.

A potentially serious adverse effect is photosensitivity, but this has appeared to occur with extreme rarity. Severe phototoxicity has been reported in cattle and sheep grazing on the plant, but not in humans taking therapeutic antidepressant doses (Wheatley, 1997). Because of the photosensitivity risk, it is suggested that patients not sunbathe (naturally or artificially) while taking SJW, and not concurrently use photosensitizing drugs such as trimethoprim/sulfamethoxazole (Septra, Bactrim), chlorpromazine, doxycycline or tetracycline, (Rey & Walter, 1998).

There have been two anecdotal reports of mania or hypomania that had been reported in association with SJW (Nierenberg, Burt, Matthews & Weiss, 1999). There have also been reports that migraines may increase in duration or intensity and there have been isolated reports of seizures occurring with SJW. These are clearly some areas where more research is needed.

According to Stevinson & Ernst (1999), SJW appears to be as safe as, or possibly safer than, many conventional antidepressants. Data on the safety of SJW in overdose and drug interactions with other drugs remain scarce. Most trials exclude subjects already taking psychotropic drugs; therefore, few studies in this area have been done. Medications for hypertension, asthma, menopausal symptoms or circulatory drugs have been allowed during hypericum trials with no evidence of interactions (Stevinson & Ernst, 1999). Wang et al. (2001) found that short term administration (4 days) of SJW had no effect on cytochrome P450 (CYP) isoenzyme activities and that a greater than fourteen day administration of SJW resulted in a significant and selective induction of CYP3A4 activity in the intestinal wall. SJW did not alter the CYP2C9, CYP1A2, or CYP2D6 activities.
More than half of all prescription drugs are metabolized by CYP3A enzymes and decreased efficacy of these medications should be anticipated when they are co-administered with SJW (Markowitz, Donovan, DeVane, Taylor, et al., 2003). This could lead to potential herb-drug interactions with numerous psychotropic agents such as, MAOIs, TCAs, SSRIs, dopamine agonists, and atypical antipsychotics, such as olanzapine and risperdal (Roby, Anderson, Kantor, Dryer, & Burstein, 2000). Other potential interactions include, concurrent use of antabuse and flagyl, caffeine, theophylline, protease inhibitors, cyclosporine, anesthetics, amphetamine-like drugs, over-the-counter drugs especially cough and cold remedies, drugs with dextromethorphan, ephedrine, pseudoephedrine, phenylpropanolamine, and other herbal agents such as cocaine, 1-tryptophan, yohimbe, ma haung, ginseng, and feverfew (Billa, Gallori & Vincieri, 2002). SJW has also been found to increase viral loads with patients who are HIV positive, may increase organ failure with transplant patients and can possibly cause birth control failure (Wang et. al., 2001). SJW has been found to not potentiate alcohol. The use of SJW is contraindicated in pregnancy, lactation, and pheochromocytoma (Boullata & Nace, 2000).

The potential of SJW to interact with standard prescribed antidepressants is of great concern. The interactions could produce a serotonin syndrome (severe myoclonus with hyperpyrexia, gastrointestinal symptoms, sweating, seizures and coma) or a hypertensive crisis. Serotonin syndrome is a toxic interaction that occurs when an SSRI is combined with another drug that potentiates serotonin transmission, such as SJW, lithium, MAOI, and other psychotropic medication. Although there are no studies or reports concerning the development of this syndrome with SJW, it is important to warn patients of the risks involved due to its possibly fatal outcome.
Due to the lack of information regarding SJWs mechanism of action, the potential for MAO inhibitor-like drug interactions cannot be excluded. Fluoxetine’s long half-life would mean that the interactions can occur for some time after its discontinuation. No studies about washout periods following discontinuation of SJW have been conducted (Gaster & Holroyd, 2000). A conservative approach is to wait two weeks after ceasing SJW or after stopping an antidepressant before commencing with another agent. Gaster & Holroyd found no empirical studies or reports of dietary interactions with SJW. Given the potential for MAO inhibition with SJW, restriction of foods containing tyramine is wise.

Conclusion

Consumers believe it must be safe if it is a natural product and marketed as such (Linde et al., 1996). This is a myth that needs to be dispelled. Gaining knowledge is the primary issue for consumers and APRNs in using SJW safely and effectively. Consumers need to be educated on the misperceptions about SJW and the hazards of self-treating with herbal products. APRNs have an immediate professional responsibility to educate themselves regarding herbal remedies (Glisson, Crawford & Street, 1999). The acceptance and knowledge obtained will strengthen and fortify the quality of care delivered to the patient.

Glisson et al. (1999), McEnany (1999), and Meines (1998) acknowledged that APRNs have an opportunity to develop a unique role in the field of herbal and alternative medicine. Patients may see APRNs as more open-minded and receptive to alternative therapies than physicians. It is of utmost importance that APRNs become more educated about alternative treatments through undergraduate and graduate nursing school programs and through continuing education opportunities. Eliciting alternative treatment information from their patient would allow the APRN to assess the possibility of potential drug interactions, and convey to the patient the
practitioner's recognition of alternative treatments. The potentially unsafe behaviors of SJW use can be identified and the APRN has the opportunity to educate their patient.

Through collaboration, communication, and education APRNs can provide their patients with the knowledge and skills they need to have freedom of choice and make informed decisions about their health care (Meines, 1998). By eliciting alternative treatment information and providing education to the patient the APRN will be able to deliver safe, quality care in an integrated healthcare system.
APPENDIX
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Diagnosis</th>
<th>Compound &amp; Dosage</th>
<th>Compared to &amp; Dosage</th>
<th>Sample Size &amp; Length of Study</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Schrader, Meir &amp; Brattstrom (1998)</td>
<td>Mild-Moderate Major Depression</td>
<td>Hypericum ZE 117 (1mg hypericin) at 500mg/day</td>
<td>Placebo</td>
<td>162 /6 weeks</td>
<td>HAM-D response rate $p&lt;0.001$ with hypericum superior</td>
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<tr>
<td>Laakmann, Schule, Baghai &amp; Kieser (1998)</td>
<td>Mild-Moderate Major Depression</td>
<td>Hypericum WS 5572 (5% hyperforin) and WS 5573 (0.5% hyperforin) both at 900mg/day</td>
<td>Placebo</td>
<td>147/ 6 weeks</td>
<td>HAM-D response rate 49% for WS 5572, 39% for WS 5573 &amp; 33% for placebo</td>
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<tr>
<td>Wheatley (1997)</td>
<td>Mild-Moderate Major Depression</td>
<td>Hypericum LI 160 (0.3% hypericin) at 900mg/day</td>
<td>Amitriptyline at 75mg/day</td>
<td>165/ 6 weeks</td>
<td>HAM-D response rate 62% for hypericum &amp; 78% amitriptyline</td>
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<tr>
<td>Brenner, Azbel, Madhusodanan &amp; Pawlowska (2000)</td>
<td>Mild-Moderate Major Depression</td>
<td>Hypericum LI 160 (0.3% hypericin) at 900mg/day</td>
<td>Sertraline at 50 then 75mg/day</td>
<td>30/ 7 weeks</td>
<td>HAM-D response rate 47% hypericum &amp; 40% sertraline</td>
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<td>Author/Year</td>
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<td>Schrader, on behalf of the study group (2000)</td>
<td>Mild-Moderate Major Depression</td>
<td>Hypericum ZE 117 (1mg hypericin) at 500mg/day</td>
<td>Fluoxetine at 20mg/day</td>
<td>240/ 6 weeks</td>
<td>HAM-D response rate 60% for hypericum &amp; 40% for fluoxetine</td>
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<tr>
<td>Schrader et al. (2001)</td>
<td>Severe Major Depression</td>
<td>Hypericum LI 160 (0.3% hypericin) at 900 then 1,200mg/day</td>
<td>Placebo</td>
<td>200/ 8 weeks</td>
<td>Those completing 8 weeks, HAM-D, response rate 32.9% for hypericum &amp; remission 20.3%. Response rate 20.7% for placebo &amp; remission 10.3%.</td>
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<tr>
<td>Vorbach, Arnoldt &amp; Hubner (1997)</td>
<td>Severe Major Depression</td>
<td>Hypericum LI 160 (0.3% hypericin) at 1800mg/day</td>
<td>Imipramine at 150mg/day</td>
<td>209/ 6 weeks</td>
<td>HAM-D response rate 35% hypericum, 41% imipramine</td>
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<td>Author/Year</td>
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<tr>
<td>Davidson et al. (2002)</td>
<td>Severe Major Depression</td>
<td>Hypericum LI 160 (0.3% hypericin) at 900-1,500mg/day</td>
<td>Placebo and Sertraline 50-100mg/day (was an active comparator to evaluate study’s sensitivity)</td>
<td>304/ 8 weeks</td>
<td>HAM-D response rate 23.9% hypericum, 31.9% placebo &amp; 24.8% sertraline. Sertraline superior to hypericum on CGI at p=0.01, no difference with hypericum and placebo.</td>
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References


