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St. John's Wort and Depression

By Joseph Pepping, PharmD

USED EXTENSIVELY FOR DEPRESSION, ANXIETY, AND SLEEP DISORders, St. John's wort (SJW) is the second leading herbal remedy sold in the United States; 1998 retail sales totaled more than $140 million.[1] Several ancient physicians, including Hippocrates, mentioned SJW (*Hypericum perforatum*) in their writings. It was believed that the plant had the ability to "protect one from evil spirits." Traditional indications have included treatment of hysteria and depression, contusions, burns, neuralgia, gastroenteritis, ulcers, and menorrhagia.[2,3] Most recent clinical research has focused on use in mild-to-moderate depression.[2-5]

Pharmacology

SJW contains numerous biologically active constituents: hyperforin, hypericin, pseudohypericin, a broad range of flavonoids, carotenoids, and xanthone.[2-5] Previous depression studies have focused on napthodianthrones, hypericin, and pseudohypericin as the markers of pharmacological activity.[2,4,5] However, recent evidence suggests that hyperforin is the most pharmacologically active entity.[6,7]

Mechanism of Action

Hyperforin appears to be a non-competitive reuptake inhibitor of several neurotransmitters, including serotonin (5HT), dopamine (DA), norepinephrine (NE), GABA, and L-glutamate.[8] It appears to be the only known antidepressant that inhibits reuptake of serotonin, norepinephrine, and dopamine to the same extent.[3] By elevating intracellular Na^+ in the presynaptic terminal to affect the intra/extracellular Na^+ gradient, hyperforin effectively attenuates uptake of Na^+ from the synaptic cleft, which is essential for neurotransmitter reuptake.[8] This mechanism of action differs significantly from those of SSRIs, which bind competitively to serotonin reuptake sites.[8] Hyperforin affects the Na^+ transport mechanism in a dose-dependent and rate-limited fashion.[8] SJW's weak inhibitory effect on monoamine oxidase appears to be of little consequence at pharmacological doses.[2,5]

Clinical Trials

Two recent meta-analyses focused on well-designed randomized, double-blind, controlled trials (RDBCTs) and comparative studies.[9,10] Using strictly defined criteria, both concluded that SJW was as effective as conventional antidepressants and more effective than placebo in treating mild-to-moderate depression.

A six-week RDBCT studied the effects of 800 mg/d standardized SJW extract (LoHyp-57) vs. 20 mg/d fluoxetine (Prozac®) in 149 elderly outpatients with mild-to-moderate depression as determined by ICD-10 criteria.[11] Only patients suffering their first psychiatric disorder without symptoms of dementia were included. The efficacy of both regimens, as determined primarily by decreases in the Hamilton Rating Scale for Depression (HAMD) and secondarily by the Clinical Global Impression Scale (CGI) and Self-Rating Depression Scale (SDS), was found to be equivalent. Six of the 12 SJW patients who developed adverse drug reactions (ADRs) withdrew from the study, compared to eight of 17 fluoxetine patients. The relatively high incidence of ADRs may have been influenced by extensive ADR disclosure prior to informed consent. No information regarding duration of illness, previous psychotropic medication use, or concurrent disease states was included. *Level II, no major limitations* (*See Figure 1 for an explanation of the evaluation standards and scales used in rating clinical studies.*)

In a six-week, RDBCT of 209 severely depressed patients (as defined by HAMD and ICD-10 criteria), 1,800 mg/d standardized SJW extract (LI-160) appeared as effective as 150 mg/d imipramine.[12] The multisite study included 38 hospitalized and 171 outpatients with a minimum of two prior severe depressive episodes of at least two weeks' duration. Patients with psychotic symptoms, suicidal tendencies, pronounced agitation, drug or alcohol dependency, hallucinations, or delusions were excluded. A three- to five-day placebo washout period preceded the study. Patients whose HAMD scale improved more than 20% during washout were excluded (placebo responders). No other psychotropics were allowed with the exceptions of chloral hydrate for sleep disorders and lithium for patients who had been on the drug for a minimum of three months prior to the study. Neurological and psychiatric assessments and laboratory tests (CBC, LFTs, and Scr) were performed at baseline and days 7, 14, 28, and 42. HAMD ratings decreased in both groups with no statistical difference. Using the CGI scale, response rates of "good" and "very good" were recorded for 61.2% of the SJW group compared to 70.1% of the imipramine group. One SJW patient and eight imipramine patients withdrew because of side effects. Issues of concern include lack of a placebo arm (left out for ethical reasons) and a 900 mg/d arm for comparison. In addition, no mention is made of the length of illness or the types and dosages of psychotropics that patients had previously used. Discrepancies in interpretation of data and reporting of results also were found. *Level II, major limitations*

The first three-arm RDBCT compared 1,050 mg/d hypericum extract (STEI 300R) with 100 mg/d imipramine and placebo over eight weeks.[13] The trial enrolled 263 patients with moderate depression according to ICD-10 classification and HAMD scores; strict inclusion/exclusion criteria were appropriate. Patients stopped antidepressant medications one week prior and were assessed at baseline and at weeks 1, 2, 4, 6, and 8. Change in the HAMD between baseline and week 8 was the primary outcome criterion. Secondary outcome criteria included Hamilton Rating Scale for Anxiety (HAMA), CGI, the Zung Self-Rating Depression Scale, and a quality of life scale (SF-36). The safety evaluation included adverse reaction monitoring, ECG, vital signs, and physical exams. Results of both primary and secondary outcomes showed SJW and imipramine to be comparable to each other and superior to placebo. Only SJW showed a statistically significant advantage over placebo according to confidence intervals, while imipramine had "a strong tendency toward superior efficacy over placebo,"[13] probably because of a very high (> 60%) response rate in the placebo group. HAMA and CGI results were comparable. Minor adverse events were reported by 22% of SJW patients (primarily

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nausea), 46% of imipramine patients (primarily anticholinergic and GI symptoms) and 19% of the placebo group (comparable to the SJW group with less nausea). Although the imipramine dose is within therapeutic range, it is at the low end. The investigators stated that an "intent-to-treat" analysis was used, but this was not the case: Only 251/263 patients were included in the efficacy evaluation. No discussion of dropouts was provided. *Level II, major limitations*

Adverse Effects

A multicenter open SJW study noted adverse events in 2.4% of 3,250 subjects, necessitating discontinuation in 1.5%.[14] The most common were GI irritation, restlessness, fatigue, and allergic reactions (0.3-0.6%). A review of controlled trials indicated that 19.8% and 35.9% of patients taking SJW and tricyclic antidepressants, respectively, reported side effects.[2] Dry mouth, dizziness, constipation, hypotension, hypertension, and confusion have also been reported.[2,5,14] Photosensitivity reactions in fair-skinned people have been reported, especially with IV hypericin or oral doses > 900 mg/d.[2]

Contraindications

Contraindications include ultraviolet light treatments[5,15,16] and antidepressant use.

Pregnancy and Lactation

SJW should be avoided in pregnancy; animal studies show uterotonic and possible abortifacient properties.[15] Amounts of active constituents secreted in breast milk are as yet unknown.

Drug Interactions

Because SJW extract increases neurotransmitter levels of 5HT, NE, DA, and GABA, there is potential for additive toxicity with conventional antidepressants,[2,3,5-7] as evidenced by at least five case reports of serotonin syndrome-type reactions in elderly patients.[17]

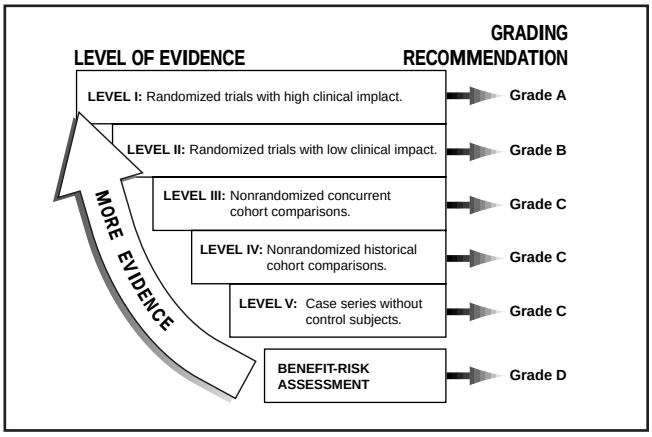
In an attempt to decrease the side effects of standard antidepressants in patients who cannot tolerate therapeutic doses, some physicians are adding SJW to low doses of standard antidepressants. Close monitoring is essential.[17] When switching from standard agents to SJW, or vice versa, a seven-day washout period is recommended.

Although some authorities warn against concurrent use with L-dopa and 5-HT, these warnings are based on theory; no clinical or animal evidence documents adverse effects or interactions.

SJW has been shown to lower serum levels of theophylline, cyclosporin, and indinavir to a clinically significant extent.[18] Breakthrough bleeding also has occurred in women on oral contraceptives, possibly because of

Figure 1

Level of evidence and grading recommendation



lower levels of ethinylestradiol.[19] Lower digoxin levels could be associated with induction of an intestinal transporter glycoprotein,[20] rather than with induction of CYP3A4 hepatic enzymes believed responsible for lower levels of other drugs. Although lower warfarin levels have occurred in a patient taking SJW, other reports demonstrate a consistent INR lowering in patients who begin concurrent SJW.[21]

Formulation and Dosage

The most commonly studied dosage of SJW for mild-to-moderate depression in adults is 300 mg of a standardized extract tid. Currently, most products are standardized to hypericin content (usually 0.3%, with hyperforin 2-4%). However, as mentioned above, current research indicates that standardization to the more pharmacologically active hyperforin (4-5%) is more appropriate.[6-8] The empiric dosage of SJW for mild-to-moderate depression in adults is 300 mg of a standardized extract tid. When an extract standardized to hyperforin is used, the dose, based on clinical studies, is 30-45 mg/d in divided doses.

The author could not find any clinical studies of SJW to treat depression in children.

Conclusion

The standardized extracts of SJW tested in clinical trials appear to be a clinically proven alternative to current prescription antidepressants for treatment of mild-to-moderate depression. (*See Table 1 for U.S product equivalents.*) In one study, twice the usual dose was effective for severe depression. Recent clinical trials have demonstrated that these extracts are as effective as other antidepressants and consistently superior to placebo.[9-12] Additionally, the side effect profile of SJW appears to be superior to currently approved U.S. antidepressant medications.[11]

Table 2

European and U.S. product equivalents

European Product	U.S. Equivalent	U.S. Manufacturer/Importer	Standardized
Jarsin® 300	Kira®	Lichtwer Pharma	Hypericin
LI-160®	Kira®	Lichtwer Pharma	Hypericin
LI-160 WS®	Quanterra Emotional Support®	Warner-Lambert	Hypericin
Neuroplant®	Movena®	Schwabe	Hyperforin
Neuroplant®	Perika®	Schwabe	Hyperforin

Source: Hardy M, McDermott J. Integrating herbs and botanicals into patient care. Presented at: The 147th annual meeting of the American Pharmaceutical Association; March 11, 2000;Washington, DC.

Recommendation

Available evidence supports a Grade B recommendation for short-term use of SJW for mild-to-moderate depression. Patients should be aware that there are many potential drug interactions; use should be supervised by a knowledgeable health care provider. A three-year NIH study currently underway will provide additional information regarding long-term effectiveness of SJW in the treatment of depression. *Grade B* ❖

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Glucosamine Sulfate for Treatment of Osteoarthritis

By Susan Brownsberger and Cydney E. McQueen PharmD

THE 16 MILLION AMERICANS AFFLICTED WITH PAINFUL and often disabling osteoarthritis (OA) generate more than 7 million physician visits yearly.[1,2] Since there is no cure and available pain medications have many side effects, OA is a prime disease candidate for alternative practices. Additionally, one study has suggested that long-term non-steroidal anti-inflammatory drug (NSAID) use may actually promote joint cartilage degeneration by inhibiting mucopolysaccharide synthesis needed in the production of new cartilage components.[3] Glucosamine gained popularity among arthritis sufferers following the publication of *The Arthritis Cure* by Jason Theodosakis, MD.[4] Although glucosamine may not provide the cure implied by Theodosakis' title, the evidence supports its use in reducing OA symptoms.

Pharmacology/Mechanism of Action

Glucosaminoglycans, linear polymers of repeating disaccharides made from the amino sugar glucosamine and derived from glucose, are key components in human joint cartilage matrix. Ionization of sulfate molecules aids tensile strength and elasticity in the matrix. Supplemental glucosamine is proposed to provide the "building blocks" necessary to rebuild damaged cartilage. Animal and human evidence does lend support to the claim that progression of deleterious osteoarthritic cartilage changes is, at least, delayed, and, at best, reversed.[3,5]

Several glucosamine salt forms are available. This examination will be limited to glucosamine sulfate (GS), which has been widely tested in clinical trials and pharmacokinetic and safety studies. Concern over bioavailability of GS has been expressed, but pharmacokinetic studies (human and canine) using radiolabeled oral GS have shown fairly rapid absorption with 90-98% bioavailability.[6,7]

Clinical Trials

In 1994, Noack assessed 500 mg GS tid vs. placebo for four weeks for controlling OA symptoms.[8] (*See Table 1 for a summary of clinical trials.*) Nine centers enrolled 252 patients with unilateral or bilateral OA of the knee based on radiological staging of 1-3 and a Lequesne index (a validated assessment scale commonly used in OA trials) score of at least 4 points. Patients must have had symptoms present for at least six months, be ambulatory with limited motion, and have an erythrocyte sedimentation rate < 30 mm/h with no external signs of active inflammation. Exclusion criteria included intra-articular corticosteroids within two months, NSAID use within two weeks, recent trauma or lesions, weight < 75 kg or > 150 kg, and other rheumatic, hematologic, hepatic, or renal disorders. Concurrent disease treatments were allowed and recorded. Primary efficacy outcome measures were mean change in Lequesne index and overall success rate. A successful responder was defined by both a decrease in Lequesne index of 3 or more points and investigator judgment of good or moderate efficacy at endpoint.

In both the intent-to-treat and evaluable population analyses, response rates were statistically significant in favor of GS at four weeks ($P = 0.016$ and $P = 0.014$, respectively). Safety was assessed based on an adverse event questionnaire, dropout rates, vital signs, and laboratory findings; there were no significant differences between groups. Of the dropouts, 5/8 in the GS group and 8/13 in the placebo group were due to adverse events. The investigators concluded that GS resulted in significantly better improvement than placebo with comparable tolerability. *Level I, minor limitations* (*See Figure 1 on page 11.*)

Müller-Faßbender's 1994 study compared 500 mg GS tid to 400 mg ibuprofen (IBU) tid for four weeks in patients with OA of the knee.[9] The 199 subjects were hospitalized in a physical rehabilitation program and had unilateral or bilateral OA of the knee with a Lequesne index (modified to assess each knee individually) score of at least 7 points. OA symptoms must have been present for at least three months prior to enrollment. Patients had mild inflammation based on joint swelling, effusion, and erythema. Exclusion criteria were identical to the Noack study. Overall success rate was based on a decrease in the modified Lequesne index of 2 points if the enrollment value was > 12 or 1 point if the enrollment value was ≤ 12, as well as an end of treatment investigator judgment of good efficacy.

Both groups improved by an average of 6 points and there was no significant difference in efficacy between the GS and IBU groups at week 4 ($P = 0.67$). GS demonstrated a slower onset of effect than IBU, with greater effect seen after week 2. Safety was assessed based on an adverse event questionnaire, dropout rates, and hematologic testing; the only statistically significant difference was in adverse events rates. Six adverse events were reported in the GS group, resulting in one withdrawal. In the IBU group, 35 adverse events were reported, resulting in seven dropouts. Reports included

Table 1

Trials of oral glucosamine sulfate for symptoms of osteoarthritis

Study	Subjects	Level of Evidence	Control	Results	Limitations
Reginster[12]	106	Unknown	P	+	Unknown
Qiu[10]	178	II	I	=	Major
Noack[8]	252	I	P	+	Minor
Müller-Faßbender[9]	200	I	I	=	Minor
Lopes Vaz[11]	40	II	I	=	Major
Drovanti[5]	38	II	I	=	Major
Pujalte[16]	20	II	P	+	Major

* P = placebo; I = ibuprofen

GI upset, pruritis, flushing, and fatigue. The authors concluded that GS was as effective as IBU in short-term symptom control of OA of the knee with slower onset of pain and symptom relief, but with better tolerability. Although the 1,200 mg/d IBU dose is not the maximum used by many OA patients, it is within therapeutic range. *Level I, minor limitations*

In 1998, Qiu also assessed efficacy and safety of 500 mg GS tid vs. 400 mg IBU tid in 178 patients for four weeks, with two week's post-treatment observation.[10] The inclusion/exclusion criteria were not stated in the article, nor was there an a priori power calculation. Efficacy was assessed by 0-3 ratings (non-validated instrument) in knee pain and swelling at rest, during movement, and with pressure. Additional efficacy measures included improvement ratings and therapeutic utility judgments by the investigator. No statistically significant differences were observed during treatment. GS patients had significantly better (P = 0.01) improvement ratings two weeks after treatment. Post-treatment pain and swelling ratings were also better in the GS group, but not significantly so. Safety was determined through an adverse event questionnaire, dropout rates, lab values, and an overall safety judgment. Five GS patients reported adverse events with no dropouts. In the IBU group, 9/14 reported adverse events resulted in dropouts. These results reflect both statistically and clinically significant differences in favor of GS. *Level II, major limitations*

Shortcomings common to the trials above include relatively short duration and a connection to Rotta Research Laboratorium, which manufactures a GS product. These shortcomings were not present in a study by Lopes Vaz.[11] Study design and limitations were very similar to previously mentioned trials, doses of GS and IBU were identical, and results were also very similar. *Level II, major limitations*

The limitation of short duration was overcome in a recent study by JY Reginster, et al.[12] The three-year study tested 1,500 mg/d GS vs. placebo in 212 patients. At the end of treatment, placebo patients had a 6-10% worsening of symptoms, while GS patients improved 15-24% (JY Reginster, written communication, February, 2000). Endpoint radiographic evidence demonstrated joint space narrowing of 0.08-0.1 mm in the placebo group, matching the normal average loss in OA. No narrowing occurred in the GS patients. On the contrary, there was an increase of 0.07-0.12 mm, although this was not statistically significant. *Level and limitations unknown*

Radiographic evidence of the effects of GS on cartilage is also confirmed by results of another oral GS vs. placebo study.[5] Although clinical endpoints were in favor of GS, the study's primary significance comes from electron microscopy examination of cartilage from two GS and two IBU patients after 30 days of treatment. Cartilage in the GS patients appeared smooth with ordered collagen fibrils, while cartilage in the placebo patients had the typical rough arthritic appearance with disordered fibrils. The small number of subjects makes these results hard to generalize, but they also confirm animal studies demonstrating similar positive changes with GS supplementation. *Level II, major limitations*

Side Effects

The most commonly reported side effects are mild GI upset, diarrhea, pruritis, and headache.[4,5,8-10] GI effects are the most common; the highest overall incidence rate observed in trials was 6%.[9,10]

Contraindications

Concern has existed that competitive inhibition of glucose conversion to glucosamine could raise blood sugar levels in diabetics. The only study to monitor glucose found no problems (JY Reginster, written communication, February, 2000); however, extra initial monitoring in diabetic patients is prudent.

A diagnosis of OA should be determined before recommending therapy; GS has not been studied for other

types of arthritis.

Interactions

No known interactions have been identified.

Pregnancy/Lactation

GS has not been tested in pregnancy or lactation and should be avoided in this population without physician recommendation and supervision.

Formulation and Dosage

The most commonly studied dose is 500 mg tid. A 1,500 mg daily dose may be taken, but there are anecdotal reports of increased diarrhea and flatulence with this regimen.

Glucosamine is available in several salt forms—sulfate, N-acetyl-glucosamine (NAG), and HCl. NAG may be a future option as serum glucosamine levels increase after ingestion of both NAG and a polymeric form,[13] but no clinical trial data are yet available. A recent trial of glucosamine HCl vs. placebo did not show differences between groups, lending credence to the claim that the sulfate moiety is important for efficacy.[14]

Glucosamine is commonly marketed in combination with chondroitin sulfate, a large molecule with restricted bioavailability.[15] It is not yet known if combination products are more effective than GS alone. A large, four-year NIH study currently is testing GS and GS plus chondroitin against placebo.

Conclusion

Clinical studies have shown GS to be effective in reducing the symptoms of OA and to have similar efficacy as IBU 400 mg tid with significantly fewer side effects.

Recommendation

The available evidence supports a Grade A recommendation for short-term GS use for mild-to-moderate OA symptoms. When full results of the Belgian study[12] become available for evaluation, it may be possible to recommend long-term use.

Additional long-term studies are needed to further characterize any disease-modification potential and to determine if a lower maintenance dose is effective. Comparisons to other NSAIDs, acetaminophen, and COX-2 inhibitors are also needed, and use in severe OA has yet to be examined. *Grade A* ❖

Ms. Brownsberger is a doctoral candidate at the University of Missouri-Kansas City School of Pharmacy.

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Comments by Cydney E. McQueen, PharmD:

Both **folic acid** and **vitamin B_{12}** are essential to proper nerve functioning. Clinical trials have shown improvement in memory and cognitive function in very aged subjects with nutritional deficiencies, but no evidence was found to support improved memory in younger, healthy adults.

DMAE serves as a precursor to the neurotransmitter, acetylcholine. The p-acetamidobenzoate salt form (deanol) enzymatically metabolizes to phosphatidyl choline. Clinical studies in patients with Alzheimer's, dementia, various dyskinesias, and hyperkinetic children have had differing results. Those with some positive results used doses of 0.9-2 g/d. Few studies have specifically looked at memory effects; one demonstrated minor improvement in senile patients. DMAE side effects include headache, vivid dreams, dyskinesia, drowsiness, increased BP, and cholinergic symptoms.

Panax ginseng, has complex pharmacological action—some components have CNS stimulating activity, others are CNS depressants. Some human studies have shown improvement in memory and cognitive performance in both healthy and debilitated patients. Ginseng affects adrenal, pituitary, and thymus glands. It is usually well tolerated, but a few reports exist of serious adverse events. Ginseng can prolong thrombin time and aPTT, thereby interacting with warfarin therapy.

Huperzine A, an alkaloid from an extract of *Huperzia serrata*, is a potent and selective acetylcholinesterase inhibitor. The dosage used in a clinical trial in patients with senile, presenile, and multi-infarct dementia with positive results was 50 mcg bid. Side effects reported have been mild (dizziness) to none.

L-tyrosine is a precursor to epinephrine, norepinephrine, and dopamine. A recent study on military cadets demonstrated benefit on cognitive function, task performance and memory, using 10 g/d. Other studies with minor positive results have used 150 mg/kg/d doses. A dose of 150 mg/d is unlikely to provide any benefit.

Piperine is extracted from ordinary pepper. It increases bioavailability of many drugs due to increased membrane permeability and non-selective inhibition of CYP 450 isoenzymes. Examples from published data include increased blood levels of propranolol and theophylline when given with piperine 20 mg daily.

The vitamin and tyrosine doses may or may not provide any benefit, but are certainly within safe ranges. Increased acetylcholine may aid patients with disease states involving decreased levels, but has not been shown to aid memory in otherwise healthy adults. Patients on prescription drugs may experience increased side effects due to higher blood levels. Recommend avoiding use by patients with hypertension or on warfarin or anticholinergic therapy. ❖

In Future Issues:

St. John's Wort and Drug Interactions
Are Natural Vitamins Better?
DSHEA: Implications for the Pharmacist