A Randomized Clinical Trial of St. John's Wort for Smoking Cessation

Amit Sood, MD, Jon O. Ebbert, MD, Kavita Prasad, MD, Ivana T. Croghan, PhD,
Brent Bauer, MD, and Darrell R. Schroeder, MS

Abstract

Introduction: St. John's wort (SJW) is a widely used herbal supplement. The predominant mechanism(s) accounting for the activity of SJW *in vivo* are, however, unclear. The purpose of this study was to investigate the efficacy of SJW for smoking cessation.

Methods: We conducted a randomized, blinded, placebo-controlled, three-arm, dose-ranging clinical trial. A total of 118 subjects were randomly allocated to receive SJW 300 mg, 600 mg, or a matching placebo tablet 3 times a day combined with a behavioral intervention for 12 weeks. Self-reported smoking abstinence was biochemically confirmed with expired air carbon monoxide.

Results: Mean age of the study participants was 37.6 ± 12.4 years; they smoked an average of 20.0 ± 6.6 cigarettes per day for 20 ± 12.1 years. The study dropout rate was high (43%). By intention-to-treat analysis, no significant differences were observed in abstinence rates at 12 and 24 weeks between SJW dose groups and placebo. SJW did not attenuate withdrawal symptoms among abstinent subjects. Abstinence rates did not differ by study group among subjects who took at least 75% of their study medication. No significant side-effects were noted with SJW.

Conclusions: In this randomized trial, SJW did not increase smoking abstinence rates. Our data, in combination with data from other studies, suggest that SJW has little role in the treatment of tobacco dependence.

Introduction

CIGARETTE SMOKING continues to be a significant public health problem that is exacerbated by a higher prevalence of use among lower socioeconomic classes.¹ Current smoking is associated with fewer years of education, mental illness, lower socioeconomic status, and lack of medical insurance.² Approximately 46 million Americans, or 18% of the population under the age of 65 years, were without health insurance in 2007.³ Unfortunately, currently available pharmacotherapeutic interventions recommended by the United States Public Health Service Clinical Practice Guideline are expensive. In order to make tobacco treatments more accessible to all individuals, systematic evaluations of less expensive and efficacious treatments are needed.

St. John's wort (SJW) is used clinically primarily as an antidepressant for mild to moderate depression. In a review of 34 clinical trials involving approximately 3000 patients, SJW in doses of 500–1000 mg/day was reported to be of comparable efficacy to synthetic antidepressants such as imipramine, amitriptyline, sertraline, and fluoxetine.⁴ *In vitro*,

SJW has been observed to (1) inhibit reuptake of norepinephrine, dopamine, and serotonin; (2) inhibit monoamine oxidase A and B; and (3) demonstrate significant affinity for adenosine, γ -aminobutyric acid (GABA) (A), GABA (B), and glutamate receptors.⁵ An increase in dopamine turnover with an increase in dopamine concentration has also been postulated. The predominant mechanism(s) accounting for the activity of SJW *in vivo*, however, are unclear. A combination of multiple mechanisms may be accounting for the therapeutic effect.⁶

SJW has been noted to attenuate signs of nicotine withdrawal in mice.⁷ In an open-label study of SJW for tobacco cessation involving 24 cigarette smokers, SJW at a dose of 900 mg per day for 3 months was associated with a 24% (9/37) smoking abstinence rate at end of treatment. Overall, the treatment was well tolerated with no significant adverse effects noted.^{8,9}

In order to further explore the efficacy of SJW for smoking cessation, we conducted a randomized, blinded, placebo-controlled, three-arm, parallel group, dose-ranging clinical trial. We sought to obtain preliminary data on the efficacy of

two different oral doses of SJW for increasing tobacco abstinence rates and decreasing symptoms of nicotine withdrawal among cigarette smokers attempting to achieve tobacco abstinence.

Methods

Subjects

The Mayo Foundation and Franciscan Skemp Institutional Review Boards reviewed and approved the study protocol prior to recruitment and enrollment.

Individuals interested in stopping smoking were recruited through press releases and local advertisements from the community surrounding Mayo Clinic in Rochester, MN and La Crosse, WI.

Subjects were eligible to participate if they were (1) at least 18 years of age; (2) smoked ≥ 10 cigarettes per day for the past year; (3) were willing to make a quit attempt; (4) were able to participate fully in all aspects of the study; and (5) had understood and signed the informed consent.

Subjects were excluded if they (1) met diagnostic criteria for current major depressive disorder as assessed by the Beck Depression Inventory, Second Edition $\leq 28^{10,11}$ or had a lifetime history of bipolar disorder or schizophrenia; (2) were currently (past 30 days) using antipsychotic or antidepressant medicines; (3) were currently (past 30 days) using treatments for tobacco dependence or an investigational drug; (4) ever used an herbal product for tobacco cessation; (5) had a recent history (past 3 months) of alcohol abuse or dependence as assessed by the CAGE questionnaire¹² and study investigators; (6) had a recent history of drug abuse as assessed by the Drug Abuse Screening Test 20 (DAST-20)¹³ and physician interview; (7) were pregnant, lactating, or of child-bearing potential or likely to become pregnant during the medication phase and not willing to use a reliable form of contraception; (8) had a history of any major cardiovascular events in the past 6 months including unstable angina, acute myocardial infarction, or coronary angioplasty; (9) had clinically significant acute or chronic progressive or unstable neurologic, hepatic, renal, cardiovascular, respiratory, or metabolic disease; (10) were currently taking medications known to interact with SJW including warfarin, anti-retrovirals, cyclosporine and tacrolimus, digoxin, nifedipine and verapamil, theophylline, all serotonergic drugs (serotonin reuptake inhibitors, tricyclic antidepressants, tramadol, venlafaxine, tryptophan, and buspirone), monoamine oxidase inhibitors, oral contraceptives, anticancer agents, migraine medications (sumatriptan and zolmitriptan), methadone, lithium, sibutramine, atorvastatin and simvastatin, midazolam, alprazolam, fexofenadine, omeprazole, and general anesthetics (fentanyl, propofol, and sevoflurane); (11) had another household member or relative participating in the study; (12) had a known allergy to SJW or a history of photosensitivity; (13) were professional drivers or operators of heavy machinery; or (14) had scheduled for a planned surgical procedure within 5 days of taking SJW.

Procedures

Potential subjects interested in participating in this study were instructed to call a toll-free number. During the phone call, subjects were prescreened for eligibility. If subjects

passed the phone prescreen, an appointment was made for a clinic visit. During the clinic visit, potential subjects were informed of the study, signed the informed consent, and completed a series of screening questionnaires in which baseline measures were collected.

Eligible subjects were randomized to one of three groups: (1) SJW 300 mg 3 times per day (900 mg/day); (2) SJW 600 mg 3 times per day (1800 mg/day); or (3) matching placebo. The starting dose was 900 mg/day for both of the groups receiving SJW, which was increased after 1 week to 1800 mg/day in the second group. The control group received matching placebo pills to mimic the titration schedule for those receiving the SJW. All study participants were provided behavioral intervention using the Smoke Free and Living It manual developed at Mayo Clinic.¹⁴ The randomization schedule was generated by the Division of Biostatistics using blocks of size 3 to ensure that an equal number of subjects were assigned to each treatment group.

Medication was given for 12 weeks with weekly (weeks 1–5) or biweekly clinic visits (weeks 6–12). Upon completing 12 weeks of medication, subjects were followed for an additional 12 weeks, during which they completed one phone visit (week 18) and one clinic visit (week 24).

To enhance study adherence and retention, subjects were remunerated to a total of \$120 for completion of all visits, prorated upon the number of visits completed.

St. John's wort

For medicinal purposes, SJW (i.e., *Hypericum perforatum*) typically consists of the dried flowering tops harvested during flowering time. The form of extract used in the current study was standardized extract (hydroalcoholic) standardized to hypericin (0.3%) prepared in capsules (300 mg or 600 mg). Methods of testing the product included both thin-layer chromatography and high-performance liquid chromatography. Our source of product was EUROMED S.A., Supplement and Nutrition Technologies Inc. distributed by Hi-Health Inc. The raw material for SJW used in the study was provided by EUROMED S.A., with the finished product provided by Supplement and Nutrition Technologies Inc. Supplement and Nutrition Technologies Inc. is a certified Good Manufacturing Practices manufacturer located in Chandler, AZ (Table 1). An Investigational New Drug application with the U.S. Food and Drug Administration was obtained prior to starting the study. Product was stored per the specifications of the supplier. Stability of the product was confirmed by end-of-study analysis of the hypericin content.

Assessments

At baseline, we collected demographic and tobacco use history information. We assessed nicotine dependence with the Fagerström Test for Nicotine Dependence¹⁵ and screened for depression with the Center for Epidemiologic Studies (CES-D) Depression Scale.¹⁶ Readiness to quit smoking was assessed using the Contemplation Ladder.¹⁷ Other scales used included the Beck Depression Inventory, Second Edition,^{18,19} CAGE,²⁰ and DAST-20. Subjects were instructed to keep a smoking diary, which included the Minnesota Nicotine Withdrawal Scale (MNWS).^{21,22} During each study visit, vital signs were measured, and side-effects and concomitant medications were recorded.

TABLE 1. QUALITY CONTROL TESTING DATA FOR ST. JOHN'S WORT

Test	Specification	Result
Impurity-level heavy metals (USP)	<10 ppm	Complies
Microbiology		
Total plate count	<5000 cfu/g	Complies
Yeast and molds	<100 cfu/g	Complies
Total coliforms	<10 cfu/g	Complies
<i>Escherichia coli</i>	Absent	Absent
<i>Salmonella</i> species	Absent	Absent
<i>Staphylococcus aureus</i>	Absent	Absent
<i>Pseudomonas aeruginosa</i>	Absent	Absent
Physical analytical test		
Disintegration	No more than 45 min	15 min
Weight variation	Average weight $\pm 0.967 \text{ g} \pm 2\%$	0.962g
Moisture		—
Loss on drying (USP)	<10.00%	4.87%
Active ingredients (mg/cap)		
St. John's Wort extract	300 mg	300 mg
Whey	190 mg	190 mg
Magnesium stearate	10 mg	10 mg
Gelatin capsule	100 mg	100 mg

USP, United States Pharmacopoeia; ppm, parts per million; cfu/g, colony-forming units per g.

Tobacco craving and nicotine withdrawal were assessed with a daily diary, which contained a tobacco use self-report and the Minnesota Nicotine Withdrawal Scale-Revised (MNWS-R).^{23,24,25} This measure consisted of the following nine items: desire or craving to smoke; anger, irritability, or frustration; anxiety or nervousness; difficulty concentrating; impatience; restlessness; increased appetite or hunger; insomnia, sleep problems, or awakening at night; and depressed mood or sadness. Based upon the previous 24 hours, items were rated on a 5-point scale ranging from 0 (not present) to 4 (severe). Daily nicotine withdrawal data were obtained from the information session visit to 2 weeks after the target quit date (TQD).

Compliance was assessed by conducting pill counts at each weekly visit and by self-reports of missed doses.

Smoking abstinence outcomes

The primary endpoint was the 7-day point-prevalence smoking abstinence rate at end of treatment (12 weeks), and secondary endpoints were the point-prevalence and prolonged abstinence rates at 6 months. For 7-day point-prevalence smoking abstinence, subjects were considered abstinent from smoking if they reported no tobacco use in the previous 7 days confirmed by expired carbon monoxide (CO) ≤ 8 ppm. Subjects were classified as meeting criteria for prolonged abstinence at a given visit if they reported no smoking after an initial 2-week grace period following their TQD and had an exhaled air CO measurement of ≤ 8 parts per million (ppm). Subjects reporting use of tobacco products other than cigarettes were considered treatment failures.

Statistical analyses

Smoking abstinence outcomes were analyzed using an intention-to-treat approach including an outcome for all

randomized subjects. For this analysis, subjects with missing smoking outcome information were classified as smokers. Fisher's exact test was used to compare smoking abstinence outcomes between each SJW dose group and placebo. A sample size of $N = 120$ (40 per group) was chosen for this phase II trial. Under the assumption that the 7-day point prevalence smoking abstinence rate at end of treatment for placebo was 15%,²⁶ we determined that this sample size would provide statistical power (one-tailed, $\alpha = 0.05$) of 82% to detect an end-of-treatment abstinence rate of 40% or greater for an active SJW group compared to placebo.

Daily diaries were used to assess nicotine withdrawal (composite withdrawal score) and craving (desire to smoke). Baseline scores were calculated using data from the 7 days prior to starting medication. Data from the first 2 weeks following TQD (i.e., days 8–21 following start of medication) were analyzed as change from baseline using a mixed linear model with a lag-1 autoregressive covariance structure used to take into account multiple observations per subject. The explanatory variables for these models were treatment group (placebo versus 900 mg/day versus 1800 mg/day) and time (in days, treated as a continuous variable). The frequencies of adverse events considered to be possibly, probably, or definitely related to study drug were summarized according to treatment group, with Fisher's exact test used to compare each SJW dose group versus placebo.

Results

A total of 118 cigarette smokers were enrolled (Table 2). Of these 118 subjects, 51 (43%) withdrew consent and dropped out of the study prior to the end of the medication phase. Of these, 45 (88%) were smoking at their last study visit prior to discontinuing study participation.

Smoking abstinence

No differences in smoking abstinence rates were observed between the groups at end of treatment (week 12) and week 24 (Table 3).

Smoking rates

Among subjects who returned for the week 12 visit and reported smoking, the mean cigarettes per day (cpd) did not differ significantly between groups [8.7 ± 7.2 cpd ($n = 15$) placebo; 9.5 ± 9.3 cpd ($n = 12$) for the 900 mg/day group; and 9.5 ± 6.4 cpd ($n = 16$) for the 1800 mg/day group].

Nicotine withdrawal and tobacco craving

Following TQD, nicotine withdrawal and craving were both observed to decrease significantly with time (withdrawal: estimate = -0.019 per day, standard error (SE) = 0.008, $p = 0.016$; craving: estimate = -0.031 per day, SE = 0.01, $p = 0.018$). However, no evidence of treatment differences for composite withdrawal score ($p = 0.36$) or craving ($p = 0.66$) were observed (Figs. 1 and 2)

Adverse events

In all cases, the frequency of adverse events did not differ significantly across groups (Table 4). Other events included single reports of anxiety, dizziness, increased sweating, and trouble concentrating in the placebo group, increased anger

TABLE 2. BASELINE CHARACTERISTICS OF SMOKERS ($N=118$) ENROLLED IN A STUDY OF ST. JOHN'S WORT FOR SMOKING CESSATION

Characteristic	Placebo ($N=39$)	900 mg/day ($N=40$)	1800 mg/day ($N=39$)
Age			
Mean $\pm$ SD	39.4 $\pm$ 13.0	38.3 $\pm$ 11.9	35.0 $\pm$ 12.2
Median (range)	39 (20–74)	39 (18–70)	32 (18–63)
Gender, N (%)			
Male	13 (33)	22 (55)	18 (46)
Female	26 (67)	18 (45)	21 (54)
Race, N (%)			
White, non-Hispanic	38 (97)	37 (92)	34 (87)
Other ^a	1 (3)	3 (8)	5 (13)
Marital status, N (%)			
Never married	13 (33)	13 (32)	14 (36)
Separated/divorced	9 (23)	12 (30)	11 (28)
Widowed	1 (3)	0 (0)	0 (0)
Married/living as married	16 (41)	15 (38)	14 (36)
Level of education, N (%)			
High school graduate or less	13 (33)	13 (32)	8 (21)
Some college or technical school	17 (44)	19 (48)	25 (64)
4-year college degree or more	9 (23)	8 (20)	6 (15)
Cigarettes per day			
Mean $\pm$ SD	19.4 $\pm$ 7.3	19.1 $\pm$ 7.2	21.0 $\pm$ 5.2
Median (range)	20 (10–40)	20 (10–40)	20 (10–30)
Number of years smoked			
Mean $\pm$ SD	21.7 $\pm$ 12.3	21.7 $\pm$ 12.3	16.6 $\pm$ 11.6
Median (range)	20 (4–50)	20 (2–57)	12 (2–46)
FTND			
Mean $\pm$ SD	4.7 $\pm$ 2.3	5.0 $\pm$ 2.0	5.2 $\pm$ 1.7
Median (range)	5 (1–10)	5.5 (0–9)	6 (2–8)
Contemplation Ladder			
Mean $\pm$ SD	8.5 $\pm$ 1.3	8.9 $\pm$ 1.0	8.6 $\pm$ 1.1
Median (range)	9 (6–10)	9 (6–10)	9 (6–10)
Previous stop attempts, N (%)			
None	5 (13)	8 (20)	7 (18)
1–2	20 (51)	17 (42)	18 (46)
3–5	11 (28)	12 (30)	10 (26)
6 or more	3 (8)	3 (8)	4 (10)
Other tobacco users in the household, N (%)			
No	22 (56)	24 (60)	23 (59)
Yes	17 (44)	16 (40)	16 (41)

^aThese include: American Indian/Alaska native ($n=5$), black/African American ($n=2$), Asian ($n=1$), and white Hispanic ($n=1$). SD, standard deviation; FTND, Fagerström Test for Nicotine Dependence.

TABLE 3. SMOKING ABSTINENCE OUTCOMES AMONG SMOKERS ($N=118$) ENROLLED IN A STUDY OF ST. JOHN'S WORT FOR SMOKING CESSATION

Time point	Placebo ($N=39$)	900 mg/day ($N=40$)		1800 mg/day ($N=39$)	
	# (%)	# (%)	p^a	# (%)	p^a
Week 12					
Point prevalence abstinence					
Self-reported	7 (18.0)	8 (20.0)	0.52	7 (18.0)	0.62
Biochemically confirmed	7 (18.0)	8 (20.0)	0.52	6 (15.4)	0.73
Continuous abstinence	2 (5.1)	4 (10.0)	0.35	2 (5.1)	0.69
Week 24					
Point prevalence abstinence					
Self-reported	6 (15.4)	7 (17.5)	0.52	7 (18.0)	0.50
Biochemically confirmed	4 (10.3)	7 (17.5)	0.27	7 (18.0)	0.26
Continuous abstinence	0 (0.0)	1 (2.5)	0.51	2 (5.1)	0.25

^aOne-tailed, Fisher's exact test comparing the given dose to placebo.

FIG. 1. Mean composite withdrawal score among smokers ($N = 118$) enrolled in a study of St. John's wort for smoking cessation. TQD, target quit date.

and sunburn in the 900 mg/day group, and abdominal bloating, dry mouth, and erectile dysfunction in the 1800 mg/day group.

Adherence

Medication adherence was assessed by conducting pill counts at each study visit. The number of subjects who took at least 75% of the prescribed doses was similar across groups: 53.8% (21/39) for placebo; 52.5% (21/40) for 900 mg/day; and 56.4% (22/39) for 1800 mg/day. Among those taking at least 75% of the prescribed doses of study drug, the biochemically confirmed 7-day point-prevalence abstinence rate at the end of the medication phase did not differ significantly across groups: 33% (7/21) for placebo; 38% (8/21) for 900 mg/day; and 27% (6/22) for 1800 mg/day.

Discussion

In this randomized blinded study, SJW did not significantly increase tobacco abstinence rates or decrease nicotine withdrawal compared to placebo. Study dropout was high, but no differences in abstinence rates were observed among subjects reporting use of $\geq 75\%$ of their assigned doses. SJW was well tolerated in a dose up to 1800 mg per day.

Previous studies have reported conflicting results with respect to the efficacy of SJW for increasing smoking abstinence. In a blinded, placebo-controlled study using SJW at 900 mg/day, 6/71 (8.5%) participants on SJW and 9/72 (12.5%) on placebo achieved prolonged smoking abstinence at 4 weeks [odds ratio (OR) = 0.65; 95% confidence interval (CI): 0.22–1.92]. At 6 months, 3 (4.2%) of subjects in the SJW group and 6 (8.3%) subjects on placebo were abstinent from smoking [OR = 0.49; 95% CI: 0.12–2.02]. No effect on tobacco withdrawal symptoms was observed.²⁷

In another study among 28 smokers who received SJW herb extract either 300 mg once a day or 300 mg twice daily taken for 1 week before and continued for 3 months after a TQD, the point prevalence and continuous smoking abstinence rate were both 18% at 3 months.²⁸ Fifteen (15) participants (54%) reported adverse events, mainly gastrointestinal. This study concluded that SJW plus individual behavioral support was unlikely to be an effective aid for smoking cessation.

However, some investigations have observed a beneficial effect of SJW for increasing smoking abstinence rates. In an open-label study with 37 cigarette smokers who received 900 mg/day of SJW for 3 months, the point prevalence of smoking cessation rate at 3 months was 24% (9/37).⁹ Despite

FIG. 2. Mean desire to smoke among smokers ($N = 118$) enrolled in a study of St. John's wort for smoking cessation. TQD, target quit date.

TABLE 4. ADVERSE EVENTS AMONG SMOKERS (N=118) ENROLLED IN A STUDY OF ST. JOHN'S WORT FOR SMOKING CESSATION CONSIDERED POSSIBLY, PROBABLY, OR DEFINITELY RELATED TO STUDY DRUG^a

Event	Placebo (N = 39) N (%)	900 mg/day (N = 40) N (%)	1800 mg/day (N = 39) N (%)
Insomnia	1 (2.6)	4 (10.0)	1 (2.6)
Fatigue	1 (2.6)	1 (2.5)	1 (2.6)
Headache	1 (2.6)	0 (0.0)	1 (2.6)
Sleep disturbance	0 (0.0)	2 (5.0)	0 (0.0)
Vivid dreams	0 (0.0)	1 (2.5)	1 (2.6)

^aOnly events that were reported by 2 or more study subjects are summarized above.

the small sample size, this abstinence rate was higher than the expected rate with placebo or no pharmacologic aids (approximately 15%).^{29,30} In the present study, we did observe a decrease in nicotine withdrawal and craving; however, there was no evidence of a difference across treatment groups.

Several possible hypotheses can be proposed as to why SJW did not demonstrate benefit for increasing smoking abstinence rates in our study. First, SJW may lack efficacy for tobacco abstinence. A review of the other pilot studies published with SJW suggests this to be the most plausible conclusion. Second, since we used an intention-to-treat analysis and had a high dropout rate, our study may have been underpowered to detect an effect. Our study was powered at 82% to detect an end-of-treatment abstinence rate of 40% or greater for an active SJW group compared to placebo (using a one-sided, $\alpha = 0.05$ level test) with a sample size per group of 40. With the significant attrition, conceivably a smaller effect may have been missed. Third, considerable variation exists in the available SJW preparations. Prior studies with SJW for smoking cessation contained differing amounts of the active ingredient.^{9,28} The present study used a dose of SJW with 0.3% hypericin. Different concentrations of the medication across different studies may influence the efficacy.

The major limitation of this study was a high dropout rate of 43%. The exact reasons for this are unclear. This observed dropout rate was higher than what has been observed in previous trials. A possible explanation may include a significant patient burden with taking numerous pills. SJW was only available in 300 mg and 600 mg formulations, and our study involved taking one tablet 3 times a day for 12 weeks, which could have adversely affected treatment adherence. SJW can also be obtained relatively inexpensively over the counter (\$15 per month's supply), which raises the possibility that subjects who found it helpful may have obtained it themselves to avoid the burden of study participation. Finally, the high dropout may relate to the fact that study participants did not find any effect from SJW and discontinued use of the product. The low adherence rate to SJW suggests that, even if SJW were efficacious, low uptake rate in the clinical setting would translate into an ineffective intervention.

In summary, we observed that SJW did not increase smoking abstinence rates and did not decrease tobacco withdrawal symptoms. The dropout rate in our study was high.

Given the lack of efficacy in several pilot studies, further testing of SJW for tobacco cessation may not be warranted.

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Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Jon O. Ebbert, MD
Mayo Clinic College of Medicine
200 1st Street Southwest
Rochester, MN 55905

E-mail: ebbert.jon@mayo.edu