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Safety and Efficacy of the Herbal Drug *Hypericum Perforatum* for the Treatment of Premature Ejaculation

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ABSTRACT

INTRODUCTION: Premature ejaculation (PE) is one of the most prevalent forms of male sexual dysfunction. The benefits of *Hypericum perforatum* for treatment of PE are unknown, although it is hypothesized that its effect on depression and neurotransmitter activity may be beneficial. The authors assessed the efficacy and safety of *H. perforatum* for the treatment of PE.

METHODS: A prospective, double-blind, randomized, placebo-controlled design was used. Participants were 50 married men with PE. They were 18-50 years old and were evaluated between January 2007 and December 2008. Patients were randomly assigned to one of 2 equal groups. Group 1 received 3 daily tablets of *hypericum* extract (150 mg per tablet). Each tablet contained 160µg of hypericin. Group 2 received a placebo. All participants recorded intravaginal ejaculation latency time (IELT) and completed the International Index of Erectile Function (IIEF-5) questionnaire before and after treatment. Side effects were self-reported using a questionnaire. Results were compared using chi-square and paired *t* tests.

RESULTS: Forty-two patients completed the study. *Hypericum* extract was discontinued due to anejaculation (n = 2) and erectile dysfunction (n = 1); 5 patients taking the placebo were lost to follow-up. There was a significant group difference in mean IELT ($P < .001$); IELT increased from 1.17 minutes to 5.8 minutes in the group taking *hypericum* extract. Patients taking *hypericum* extract also had significantly higher IIEF-5 ratings for the measures of intercourse satisfaction and overall satisfaction ($P < .001$). There were no significant group differences in mean IIEF-5 ratings of orgasmic function, erectile function, or sexual desire. Mild adverse events of headache, constipation, and photosensitivity were seen in 6 patients (27%) taking *hypericum* extract.

CONCLUSION: *H. perforatum* (St. John's wort) may be an effective and safe treatment for PE, possibly because of its effect on neurotransmitters such as serotonin.

Abbreviations and Acronyms

5HT = 5-hydroxytryptamine
IELT = intravaginal ejaculation latency time
IIEF-5 = International Index of Erectile Function
PE = premature ejaculation
SJW = St. John's wort
SSRI = selective serotonin reuptake inhibitors

KEYWORDS: *Hypericum perforatum*; Premature ejaculation; IELT; IIEF-5; Drug therapy.

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original study

Safety and Efficacy of the Herbal Drug *Hypericum Perforatum* for the Treatment of Premature Ejaculation

INTRODUCTION

Premature ejaculation (PE) is one of the most frequent male sexual complaints. It is estimated that 20% to 30% of men experience PE at some point in their lifetime; however, the prevalence depends on the definition employed [1,2]. A universally accepted definition of PE has yet to be established, but the *Diagnostic and Statistical Manual of Mental Disorders* [3] defines it as, "persistant or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it." PE frequently leads to marked distress or interpersonal difficulty.

Intravaginal ejaculation latency time (IELT) is the numerical indicator most frequently used to assess PE treatments during clinical trials [4-6]. An IELT of < 2 minutes has been considered consistent with the diagnosis of PE [7].

Pharmacological treatment of PE includes selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, phosphodiesterase (PDE) inhibitors, and topical anesthetics [8-10]. *Hypericum perforatum* (*H. perforatum*), also known as St. John's wort (SJW), is a widely used over-the-counter drug for treatment of depression. Its increase in popularity seems to indicate a growing need for an alternative drug that may be able to avoid the undesirable adverse effects associated with some of the most commonly prescribed synthetic antidepressants. SJW is widely prescribed in the United States and Europe, and its use in other countries is increasing [11]. It is by far the most commonly prescribed antidepressant in Germany, where physicians prescribe it 4 times more often than fluoxetine.

A meta-analysis published in 2001 [12] analyzed 22 randomized controlled trials and concluded that SJW is significantly more effective than placebo and as effective as standard antidepressants in the treatment of depression. Two double-blind randomized controlled studies compared SJW with 2 SSRIs (fluoxetine and sertraline). Both studies found similar clinical improvements in depressive symptoms as evidenced by significantly reduced scores on the Hamilton Rating Scale for depression [13,14]. Several randomized-sample studies [13,15] have shown that *H. perforatum* was more effective than a placebo and at least as effective as imipramine and fluoxetine in the treatment of mild to moderate depression. The studies further showed that *H. perforatum* had more benefits than the other drugs, including decreased side effects and an increased ability of patients to tolerate the medication. However, some limitations to the studies using *H. perforatum* have been noted, and studies measuring the effect of *Hypericum* in major depression have reported conflicting results [16].

Hypricin and hyperforin, 2 isolates of *H. perforatum*, are among the most researched active components of SJW. They have been found to inhibit synaptosomal uptake of several neurotransmitters, including serotonin, norepinephrine, and gamma-aminobutyric acid (GABA) [15,17,18].

Treatment of PE in the field of urology is challenging, but antidepressive medications have been part of the standard management protocol. The benefits of *H. perforatum* for treatment of PE are unknown, although it is hypothesized that its effect on depression and neurotransmitter activity may be beneficial. Therefore, the purpose of the present investigation was to assess the efficacy and safety of *H. perforatum* for the treatment of PE.

METHODS

Participants

A total of 50 married men with PE presented to the authors' urology clinic between January 2007 and December 2008. The patients ranged in age from 18-50 years.

PE was defined as IELT of < 2 minutes, occurring more than 50% of the time while attempting sexual intercourse, and causing significant distress for the patient and his partner. The diagnosis was made by a physician. Patients were included if they had a stable sexual relationship with a female sexual partner for at least 1 year and had sexual intercourse more than once a week.

Exclusion criteria included: (1) patients with psychiatric disorders or concurrent erectile dysfunction; (2) patients taking medication known to impair sexual function; (3) patients with a history of previous pelvic or spinal surgery, chronic prostatitis, or urethritis; (4) patients with other sexual disorders such as decreased libido; (5) patients receiving other treatments for PE.

Procedures

The study was approved by the ethics committee of the authors' institution. A prospective, randomized, double-blind, placebo-controlled design was used.

Patients were randomly assigned to one of 2 equal groups by blocked random allocation sequence. The mean age of the patients in group 1 and group 2 was 30.68 years and 31.7 years, respectively.

Patients in group 1 were treated with 3 daily tablets of *Hypericum* extract (Goldarou Comp. Isfahan), given at a dose of 150 mg per tablet. Each tablet contained 160µg of hypericin. Patients in group 2 received identical placebo pills that did not appear to be factitious. Participants in both groups received

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identical instructions. The medications were dispensed by a pharmacologist who did not know the purpose of the research. The investigators did not know which individual patients were receiving the placebo or the *Hypericum* extract.

Before beginning treatment, all patients were asked to measure IELT by using a stopwatch. They recorded the average IELT in seconds from 3 consecutive separate occasions of intercourse. All participants also completed the International Index of Erectile Function (IIEF-5) questionnaire [19]. Thirty days after completing the study, patients were asked to measure their IELT and complete the IIEF-5 questionnaire a second time. Side effects were self-reported using a questionnaire.

Data before and after treatment were compared using the paired *t* test for continuous data and chi-square test for categorical data. Because of the large number of paired comparisons, a conservative probability level of $P < .001$ was considered statistically significant. A power analysis was not conducted. Therefore, the possibility of type II error exists with this sample size.

RESULTS

Of the 50 original participants, 42 (84%) completed the study (22 in group 1; 20 in group 2). In group 1, therapy was discontinued due to anejaculation in 2 patients and erectile dysfunction in 1 patient. In group 2, 5 patients did not return to complete the study.

Table 1. Pretreatment Means and Standard Deviations (SD) of Outcome Measures for Patients Receiving *Hypericum* Extract (n = 22) and a Placebo (n = 20); Probability of Significant Group Differences.

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Measure	Group	Mean	SD	*P*
Intravaginal ejaculation latency time (s)	Drug	70.23	21.07	.68
	Placebo	67.50	21.18	
Intercourse satisfaction (score)	Drug	3.59	1.01	.34
	Placebo	3.25	1.25	
Overall satisfaction (score)	Drug	9.59	1.26	.91
	Placebo	9.55	1.00	
Orgasmic function (score)	Drug	9.41	0.50	.06
	Placebo	9.15	0.37	
Erectile function (score)	Drug	27.14	1.61	.71
	Placebo	26.95	1.57	
Sexual desire (score)	Drug	9.82	0.39	.88
	Placebo	9.80	0.41	

The mean age for patients in group 1 and group 2 was 30.7 years and 31.7 years, respectively, with no significant group difference ($P = .57$). The mean duration of marriage for patients in group 1 and group 2 was 3.7 years and 4.1 years, respectively, with no significant group difference ($P = .82$).

Treatment Effects

Pretreatment Group Differences. Table 1 contains the pretreatment means and standard deviations for the measures of IELT and the 5 categories of the IIEF-5 (intercourse satisfaction, overall satisfaction, orgasmic function, erectile function, sexual desire) and the probability of significant group differences. The mean IELTs were 70.23 seconds and 67.50 seconds for patients in groups 1 and 2, respectively. These times are indicative of PE. There were no significant pretreatment group differences in any variable ($P > .001$).

Intragroup Effect of Drug Treatment. Table 2 contains the means and standard deviations of the outcome measures before and after receiving *Hypericum* extract and the probability of significant differences due to treatment. After 4 weeks of treatment, the mean IELT had significantly increased from 70.23 seconds (1.17 minutes) to 349.09 seconds (5.8 minutes) ($P < .001$). There was also a significant increase in mean ratings of intercourse satisfaction and overall satisfaction, and a significant decrease in the mean rating of erectile function ($P < .001$). There were no significant differences in orgasmic function or sexual desire.

Intragroup Effect of Placebo Treatment. Table 3 contains the means and standard deviations of the outcome measures before and after receiving the placebo and the probability of significant differences due to treatment. After 4 weeks of placebo treatment, the mean IELT had significantly increased from 67.5 seconds to 99 seconds ($P < .001$). There was also a significant decrease in the IIEF-5 variable of erectile function ($P < .001$). There were no placebo treatment effects for the remaining IIEF-5 variables.

Group Differences in Treatment. Table 4 contains the means and standard deviations of the outcome measures following treatment with *Hypericum* extract or the placebo, and the probability of significant group differences. There were significant group differences in mean IELT ($P < .001$); patients taking the *Hypericum* extract had a significantly longer IELT than the patients taking the placebo. Patients taking *Hypericum* extract also had significantly higher IIEF-5 ratings for the measures of intercourse satisfaction and overall satisfaction

Table 2. Means and Standard Deviations (SD) of Outcome Measures Before and After Treatment for Patients Receiving *Hypericum* Extract (n = 22); Probability of Significant Differences.
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Measure	Time	Mean	SD	*P*
Intravaginal ejaculation latency time (s)	Before	70.23	21.07	<.001
	After	349.09	119.16	
Intercourse satisfaction (score)	Before	3.59	1.01	<.001
	After	7.32	1.32	
Overall satisfaction (score)	Before	9.59	1.26	<.001
	After	12.68	1.13	
Orgasmic function (score)	Before	9.41	0.50	.042
	After	9.23	0.43	
Erectile function (score)	Before	27.14	1.61	<.001
	After	25.18	1.44	
Sexual desire (score)	Before	9.82	0.39	.083
	After	9.95	0.21	

Table 3. Means and Standard Deviations (SD) of Outcome Measures Before and After Treatment for Patients Receiving the Placebo (n = 20); Probability of Significant Group Differences.
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Measure	Time	Mean	SD	*P*
Intravaginal ejaculation latency time (s)	Before	67.5	21.18	<.001
	After	99	37.26	
Intercourse satisfaction (score)	Before	3.25	1.25	.008
	After	3.75	1.37	
Overall satisfaction (score)	Before	9.55	1.00	.014
	After	10.05	0.89	
Orgasmic function (score)	Before	9.15	0.37	.01
	After	9.45	0.51	
Erectile function (score)	Before	26.95	1.57	<.001
	After	25.8	1.61	
Sexual desire (score)	Before	9.8	0.41	.163
	After	9.7	0.57	

(*P* < .001). There were no significant group differences in mean orgasmic function, erectile function, or sexual desire.

Adverse Events

Adverse events were seen in 6 patients (27%) taking *Hypericum* extract: headache (n = 3), constipation (n = 2), and photosensitivity (n = 1). None of these 6 patients discontinued treatment. There was 1 report of nausea in the patients taking the placebo.

DISCUSSION

PE is ejaculation occurring without the control or desire of the

Table 4. Posttreatment Means and Standard Deviations (SD) of Outcome Measures for Patients Receiving *Hypericum* Extract (n = 22) and a Placebo (n = 20); Probability of Significant Group Differences.
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Measure	Group	Mean	SD	*P*
Intravaginal ejaculation latency time (s)	Drug	349.09	119.16	<.001
	Placebo	99	37.26	
Intercourse satisfaction (score)	Drug	7.32	1.32	<.001
	Placebo	3.75	1.37	
Overall satisfaction (score)	Drug	12.68	1.13	<.001
	Placebo	10.05	0.89	
Orgasmic function (score)	Drug	9.23	0.43	.136
	Placebo	9.45	0.51	
Erectile function (score)	Drug	25.18	1.44	.196
	Placebo	25.8	1.61	
Sexual desire (score)	Drug	9.95	0.21	.073
	Placebo	9.7	0.57	

patient, and the diagnosis should only be made when there is marked distress [20]. PE is one of the most prevalent sexual dysfunctions in males and is reported to be more prevalent than erectile dysfunction [21]. Although some biological and psychological conditions have been proposed as contributing to PE, the exact pathogenesis remains to be clarified [22].

Pharmacologic treatment for certain ejaculatory disorders exists, such as the off-label use of SSRIs for PE. Recent research has elucidated more about the role of serotonin and dopamine at the central level in the physiology of both arousal and orgasm [23]. There has been emphasis on identifying the biological basis of ejaculation and its dysfunction. At present, the most studied neurotransmitter in the neurophysiology of ejaculation seems to be 5-hydroxytryptamine (serotonin) [23]. In contrast to the presynaptic 5-HT1a autoreceptors, the 5-HT1b and 5-HT2c receptors have been shown to prolong ejaculatory latency [24].

The exact physiological mechanisms contributing to the positive results of *Hypericum* extract on PE in the present study are not known and require further study. However, the authors hypothesize that its effect on neurotransmitters may have been involved. Preclinical studies have found that SJW inhibits the synaptic reuptake system of serotonin and norepinephrine [25-27]. Most of this herb's pharmacological activities are attributable to hypericin and hyperforin [26]. SJW up-regulates serotonin receptors and also has a significant affinity for opiate sigma receptors, which may contribute to its antidepressant effect [27]. The antidepressant effect of SJW may also be mediated via reduction of corticotropin-releasing hormone (CRH) secretion, through suppression of interleukin-6 (IL-6) release [28].

There exists some controversy about whether or not SJW interferes with the action of other prescribed medications. Will-Shahab et al [19] reported that reduced-hyperforin SJW preparations are less likely to interact with drugs and may substantially lower the risk of serious herb-drug interactions. Studies have been designed to investigate the effects of a specific SJW extract (Ze 117) on the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel, which are the 2 pharmacologically effective components of the low-dose contraceptive Lovelle [19,29,30]. The authors reported that the intake of reduced-hyperforin SJW preparations is less likely to interact with drugs and may substantially lower the risk of serious herb-drug interactions. However, another study showed the risk of interactions of SJW with other drugs and the possible mechanisms of these interactions [31]. For example, SJW extracts may interact with the hormonal components of oral contraceptives, thus causing spotting or break-through bleeding. Additional studies are needed to show whether or not SJW is a benign treatment.

In an observational study undertaken in 2007, Schulz [32] reported an incidence of adverse events between 1-3% for SJW, which was 10 times less frequent than those commonly associated with synthetic antidepressants. The adverse effects of SJW were found to include headache, itching, dizziness, constipation, and fatigue [33]. In the present study, SJW was effective on PE and had minor side effects of headache, constipation, and photosensitivity. Reported complications were fewer than those reported elsewhere from SSRIs such as fluoxetine and sertraline.

CONCLUSION

Hypericum extract significantly increased IELT and significantly improved some subjective scores on the IIEF-5 questionnaire, possibly due to its effect on neurotransmitters such as serotonin. It had few associated side effects when compared with classically used antidepressants. These results suggest that *H. perforatum* might be an effective and safe treatment modality for PE. Additional studies with larger numbers of patients and longer follow-up are needed to confirm this conclusion.

Conflict of Interest: none declared

REFERENCES

[1] Montorsi F. Prevalence of premature ejaculation: a global and regional perspective. *J Sex Med.* 2005;2(Suppl 2):96-102.

[2] McMahon CG, Abdo C, Incrocci L, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2004;1(1):58-65.

[3] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV TR*. 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.

[4] Rowland D, Perelman M, Althof S, et al. Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. *J Sex Med*. 2004;1(2):225-232.

[5] Waldinger MD, Schweitzer DH. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part II-proposals for DSM-V and ICD-11. *J Sex Med*. 2006;3(4):693-705.

[6] Hirsch M, Donatucci C, Glina S, Montague D, Montorsi F, Wyllie M. Standards for clinical trials in male sexual dysfunction: erectile dysfunction and rapid ejaculation. *J Sex Med*. 2004;1(1):87-91.

[7] Althof SE. Assessment of rapid ejaculation: review of new and existing measures. *Curr Sex Health Rep*. 2004;1(2):61-64.

[8] Wang WF, Chang L, Minhas S, Ralph DJ. Selective serotonin reuptake inhibitors in the treatment of premature ejaculation. *Chin Med J (Engl)*. 2007;120(11):1000-1006.

[9] Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int*. 2004;93(7):1018-1021.

[10] McMahon CG, Stuckey BG, Andersen M, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med*. 2005;2(3):368-375.

[11] Bent S, Ko R. Commonly used herbal medicines in the United States: a review. *Am J Med*. 2004;116(7):478-485.

[12] Whiskey E, Werneke U, Taylor D. A systematic review and meta-analysis of Hypericum perforatum in depression: a comprehensive clinical review. *Int Clin Psychopharmacol*. 2001;16(5):239-252.

[13] Schrader E. Equivalence of St John's Wort extract(Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol.* 2000;15(2):61-68.

[14] Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. *Clin Ther.* 2000;22(4):411-419.

[15] Woelk H. Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. *BMJ*. 2000;321(7260):536-539.

[16] Shelton RC. St John's wort (Hypericum perforatum) in major depression. *J Clin Psychiatry*. 2009;70(Suppl 5):23-27.

[17] Di Carlo G, Borrelli F, Ernst E, Izzo AA. St John's wort: prozac from the plant kingdom. *Trends Pharmacol Sci.* 2001;22(6):292-297.

[18] Kasper S, Anghelescu IG, Szegedi A, Dienel A, Kieser M. Superior efficacy of St. John's wort extract WS 5570 compared to placebo in patients with major depression: a randomized, double-blind, placebo-controlled, multi-center trial [ISRCTN77277298]. *BMC Med*. 2006;4:14.

[19] Will-Shahab L, Bauer S, Kunter U, Roots I, Brattström A. St John's wort extract (Ze 117) does not alter the pharmacokinetics of a low-dose oral contraceptive. *Eur J Clin Pharmacol*. 2009;65(3):287-294.

[20] Lue TF, Giuliano F, Montorsi F, et al. Summary of the recommendation on sexual dysfunctions in men. *J Sex Med*. 2004;1(1):6-23.

[21] Aschka C, Himmel W, Ittner E, Kochen MM. Sexual problems of male patients in family practice. *J Fam Pract.* 2001;50(9):773-778.

[22] McMahon CG, Abdo C, Incrocci L, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2004;1(1):58-65.

[23] Wolters JP, Hellstrom WJ. Current concepts in ejaculatory dysfunction. *Rev Urol*. 2006;8(Suppl 4):S18-S25.

[24] Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res*. 1998;92(2):111-118.

[25] Wonnemann M, Singer A, Siebert B, Muller WE. Evaluation of synaptosomal uptake inhibition of most relevant constituents of St John's wort. *Pharmacopsychiatry.* 2001;34(Suppl 1):S148-S151.

[26] Gobbi M, Moia M, Pirona L, Morizzoni P, Mennini T. In vitro binding studies with two hypericum perforatum extracts--hyperforin, hypericin and biapigenin-- on 5-HT6, 5-HT7, GABA (A)/benzodiazepine, sigma, NPY-Y1/Y2 receptors and dopamine transporters. *Pharmacopsychiatry.* 2001;34(Suppl 1):S45-S48.

[27] Teufel-Mayer R, Gleitz J. Effects of long-term administration of hypericum extracts on the affinity and density of the central serotonergic 5-HT1 A and 5-HT2 A receptors. *Pharmacopsychiatry*. 1997;30(Suppl 2):113-116.

[28] Thiele B, Brink I, Ploch M. Modulation of cytokine expression by hypericum extract. *J Geriatr Psychiatry Neurol.* 1994;7(Suppl 1):S60-S62.

[29] Ernst E. Second thoughts about safety of St John's wort. *Lancet*. 1999;354(9195):2014-2016.

[30] Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. Interaction of St John's wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception*. 2005;71(6):402-408.

[31] Wang Z, Gorski JC, Hamman MA, Huang SM, Lesko LJ, Hall SD. The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. *Clin Pharmacol Ther.* 2001;70(4): 317-326.

[32] Schulz V. Incidence and clinical relevance of the interactions and side effects of Hypericum preparations. *Phytomedicine*. 2001;8(2):152-160.

[33] [No authors listed]. Final report on the safety assessment of Hypericum perforatum extract and Hypericum perforatum oil. *Int J Toxicol*. 2001;20(Suppl 2):31-39.