

# ***Rhodiola rosea*, folic acid, zinc and biotin (EndEP®) is able to improve ejaculatory control in patients affected by lifelong premature ejaculation: Results from a phase I-II study**

TOMMASO CAI<sup>1</sup>, PAOLO VERZE<sup>2</sup>, PAOLO MASSENIO<sup>3</sup>, DANIELE TISCIONE<sup>1</sup>, GIANNI MALOSSINI<sup>1</sup>, LUIGI CORMIO<sup>3</sup>, GIUSEPPE CARRIERI<sup>3</sup> and VINCENZO MIRONE<sup>2</sup>

<sup>1</sup>Department of Urology, Santa Chiara Regional Hospital, I-38123 Trento;

<sup>2</sup>Department of Urology, University Federico II of Naples, I-80121 Naples;

<sup>3</sup>Department of Urology and Renal Transplantation, University of Foggia, I-71121 Foggia, Italy

Received September 13, 2015; Accepted April 21, 2016

DOI: 10.3892/etm.2016.3595

**Abstract.** The therapeutic armamentarium currently available for the treatment of premature ejaculation (PE) is not highly satisfactory. However, phytotherapeutics appear to be an interesting option for PE management. The present study aimed to evaluate the tolerability and efficacy of a phytotherapeutic combination of *Rhodiola rosea*, folic acid, biotin and zinc (EndEP®) in the treatment of patients affected by lifelong PE. All patients affected by lifelong PE who were attending three Urological Institutions from July to December 2014 were enrolled in this prospective, multicentre, phase I-II study. All patients were assigned to receive oral tablets of EndEP® (one tablet per day) for 90 days. Clinical and instrumental analyses were carried out at enrolment and at the end of the study. International Prostatic Symptom Score (IPSS), International Index of Erectile Function (IIEF)-15, Premature Ejaculation Diagnostic Tool (PEDT) and Short Form (SF)-36 questionnaires were used. The intravaginal ejaculation latency time (IELT) for each event was also evaluated using the stop-watch technique. The main outcome measure was the difference from baseline in PEDT questionnaire and mean IELT at the end of the follow-up period. In total, 91 patients (mean age, 32.3±5.6 years) were analysed. The baseline questionnaires mean scores were 1.1±1.6, 26.1±2.9, 15.3±3.4 and 98.2±0.5, for

IPSS, IIEF-15, PEDT and SF-36, respectively. The mean IELT at baseline was 73.6±46.9s. At the follow-up examination (90 days after the start of treatment), no statistically significant differences were identified in terms of IPSS (1.4±1.5) or IIEF-15 (26.3±3.1) compared with the pre-treatment values (P=0.19 and P=0.64, respectively). A statistically significant difference was detected between the mean IELT at enrolment and after treatment (73.6±46.9 vs. 102.3±60.0; P<0.001) and SF-36 questionnaire (98.2±0.5 vs. 99.4±0.1; P<0.001). Fifty-five patients reported improvement in the control of ejaculation (60.4%). Very few adverse events were reported (4.4%). In conclusion, it was found that EndEP® significantly improved ejaculatory control and the quality of sexual life in patients affected by lifelong PE, with a very low rate of adverse events.

## **Introduction**

Premature ejaculation (PE) is a common type of sexual dysfunction that affects approximately 20-30% of all men ranging from 18 to 55 years of age (1,2). PE is detrimental to self-confidence and the relationship with a partner (3,4). Lifelong PE is that which occurs from the first sexual experience and remains a problem throughout life. Ejaculation occurs too rapidly, either prior to vaginal penetration or <2 min afterwards (3,4). Currently, pharmacotherapy is the primary treatment for lifelong PE; however, PE is an off-label indication for all medical treatments (with the exception of dapoxetine in some countries) (3). Chronic selective serotonin reuptake inhibitors (SSRIs) and on-demand topical anaesthetic agents are the only drugs to have consistently shown efficacy in PE (3). Although there is some evidence of good efficacy in PE, all drugs have shown several adverse effects, such as fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration that, in the majority of cases, cause a high rate of patient drop-out (3,5). In this sense, the therapeutic armamentarium for PE treatment is not highly satisfactory.

Phytotherapeutics are an interesting treatment option because of their generally low incidence of side effects and high

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*Correspondence to:* Professor Tommaso Cai, Department of Urology, Santa Chiara Regional Hospital, 9 Largo Medaglie d'Oro, I-38123 Trento, Italy  
E-mail: ktommy@libero.it

**Abbreviations:** PE, premature ejaculation; 5-HT, 5-hydroxytryptamine; IPSS, international prostatic symptom score; IIEF, international index of erectile function; PEDT, premature ejaculation diagnostic tool; IELT, intravaginal ejaculation latency time; QoL, quality of life; PROs, patient-reported outcomes

**Key words:** premature ejaculation, *Rhodiola rosea*, folic acid, biotin, zinc, quality of life

acceptance by patients. The present authors have focused attention on certain compounds that may be useful for the treatment of PE. *Rhodiola rosea* is a noteworthy phytotherapeutic compound; it has been used for centuries in traditional medicine to stimulate the nervous system, enhance physical and mental performance and treat fatigue (6). The administration of *Rhodiola rosea* extract has been shown to elicit antidepressant activity (7). This effect is likely due to its activity on the serotonergic pathway (7). Moreover, it has been reported that folic acid plays important roles in the synthesis of serotonin, also known as 5-hydroxytryptamine (5-HT) (8). Therefore, it may be hypothesised that folic acid supplementation could cure premature ejaculation via the same mechanism, that is, by interacting with monoamine neurotransmitters in the brain, as an alternative to SSRIs (8). Moreover, biotin and folic acid contribute to normal psychological function and this effect should be useful in the management of patients with PE (8,9). Finally, the healthy human prostate accumulates a higher level of zinc than any other soft tissue in the body, and several prostate diseases arise from changes in zinc metabolism (10). The present study aimed to evaluate the tolerability and efficacy of a combination of *Rhodiola rosea*, folic acid, biotin and zinc (EndEP<sup>®</sup>) in the treatment of patients affected by lifelong PE. To the best of our knowledge, this is the first study to assess the efficacy of a phytotherapeutic compound on PE in a phase I-II trial.

## Materials and methods

**Study design.** All patients with a clinical and instrumental diagnosis of lifelong PE according to the European Association of Urology (EAU) guidelines and the International Society for Sexual Medicine (ISSM) recommendations (3,4), attending three Italian tertiary Urological Institutions (Department of Urology of Santa Chiara Regional Hospital, Trento; University of Naples Federico II, Naples; University of Foggia, Foggia) from July to December 2014 were enrolled in this prospective, multicentre, phase I-II study. All patients underwent clinical and instrumental examinations and International Prostatic Symptom Score (IPSS), International Index of Erectile Function (IIEF-15), Premature Ejaculation Diagnostic Tool (PEDT) and Short Form (SF)-36 questionnaires were administered. Moreover, a stop-watch estimation of intravaginal ejaculation latency time (IELT) and all patient-reported outcomes (PROs) were collected. In addition, urine examination and urine culture were performed. Following enrolment, all patients received oral tablets of EndEP<sup>®</sup> (one tablet/day) for 90 days.

**Inclusion and exclusion criteria.** PE was defined in accordance to the ISSM as follows: 'A male sexual dysfunction characterised by ejaculation which always or nearly always occurs before or within about 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as stress, bother, frustration and/or the avoidance of sexual intimacy' (4). Patients were eligible for inclusion if they met all the following criteria: Aged between 18 and 45 years; in a stable relationship with a partner for  $\geq 6$  months and engaging in sexual intercourse once a week or more often; and affected by life-long

PE (with a baseline IELT  $\leq 60$ s) (4). All enrolled patients were naive to any therapy for PE. All patients affected by major concomitant diseases such as diabetes, liver and/or renal failure; with known anatomical abnormalities or malignancy of the urinary tract or bladder, upper tract stones, diverticula, foreign bodies, prostatitis, active urinary tract infection, chronic retention or polycystic kidney disease were excluded. All patients with concomitant pharmacological therapy for erectile dysfunction, with clinical suspicion of secondary PE and all patients in chronic therapy for depression (SSRIs) were also excluded. In cases of clinical suspicion of secondary PE due to urinary tract infections or sexually transmitted disease, such as *Chlamydia trachomatis*, *Ureaplasma urealyticum* or *Neisseria gonorrhoeae*, a Meares-Stamey test and urethral swab were performed, in line with Cai *et al.* (11). All patients with positive microbiological culture were excluded. Moreover, all patients with an allergy to one or more of the components of EndEP<sup>®</sup> were also excluded.

**Study and treatment schedule.** On arrival at each Centre, all eligible individuals signed a standard informed consent form for off-label therapy and new drugs under investigation, underwent a baseline questionnaire and urological examination with anamnestic interview, in accordance with the procedure described in EAU guidelines (3). All patients who met the inclusion criteria underwent oral therapy with EndEP<sup>®</sup> (one tablet/day) for 90 days. All patients were contacted by telephone on day 30 of the therapy to ensure the dosing and timing of treatment was correct. Each subject was scheduled for follow-up examination at 90 days from starting therapy, with a urological visit, and IPSS, IIEF-15, PEDT and SF-36 questionnaires. Moreover, all PROs were collected. No placebo arm was included. The possible biases caused by the lack of placebo arm were considered in the analysis of the results. Figure 1 shows a flow-chart of the study protocol. Clinical failure was defined as the persistence of symptoms following the treatment, or the suspension of therapy for significant reported adverse effects. In addition, spontaneously reported adverse events, or those noted by the investigator, were recorded during the whole study period. All subjects gave written informed consent before entering the study. The study was conducted in line with Good Clinical Practice guidelines, with the ethical principles laid down in the latest version of the Declaration of Helsinki. Ethical approval was not required due to the fact that the compound is registered in the Italian Pharmacopeia for clinical use as a nutraceutical.

**Questionnaires and urological examinations.** The validated Italian versions of the IPSS (12), IIEF-15 (13) and PEDT (14) were administered to each patient. In line with Jannini *et al.*, a careful urological visit with disease history collection was performed at arrival at each Centre (15). Moreover, patient quality of life (QoL) was measured using an Italian version of the SF-36 Health Survey, a test particularly suitable for chronic conditions (16). The questionnaire was offered to each patient on arrival at the Centre. All questionnaires were also used when determining the efficacy of clinical therapy. The patients and their partners were interviewed individually and each was requested to give an independent estimation of IELT. Pre-treatment IELT was measured during a 4-week baseline period; the patients were

provided with a stop watch and instructions on how to measure IELT, and were requested to experience coitus at least four times, as reported by Pastore *et al* (17). Couples were instructed not to use condoms or any topical anaesthetic cream, and not to pause during intercourse or have interrupted intromission. Furthermore, the patients were instructed that if intercourse took place more than once in a single session, only the first intercourse was to be measured (17).

**Composition and characterisation of the extracts used.** All patients were orally administered EndEP<sup>®</sup> once daily, as a tablet in the morning immediately after breakfast. Each EndEP<sup>®</sup> tablet (450 mg) contained 200 mg *Rhodiola rosea*, 10 mg zinc, 200 µg folic acid and 50 µg biotin. All compound analyses were carried out according to the methods described by Fiamegos *et al* (18).

**Statistical analysis.** Normal distribution of the variables was assessed using the Kolmogorov-Smirnov test, histograms, and P-P plots. If necessary, the data were log (ln) transformed to achieve a normal distribution. Data were analysed based on the intention-to-treat approach. General characteristics of the study participants were expressed using descriptive statistics (means, standard deviation and ranges). For each dependent variable, changes from baseline were calculated by subtracting the baseline value from the end-of-trial value. Analysis of variance was used for comparing means, and the Bonferroni adjustment test was used at the second stage of the analysis of variance. The sample size was calculated prospectively under the following conditions: Difference between the groups=10% (reduction in PEDT questionnaire score),  $\alpha$  error level=0.05 two-sided, statistical power = 80% and anticipated effect size (Cohen's  $d=0.5$ ). The calculation yielded 72 individuals. Assuming a dropout rate of approximately 20%, 86 patients should be enrolled into the study. The main outcome measure was the difference from baseline in PEDT questionnaire, mean IELT and PROs at the end of the follow-up period.  $P<0.05$  was considered to indicate a statistically significant difference. SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA) was used to conduct the statistical analyses.

## Results

**Study population.** From a total population of 95 enrolled patients, 3 patients were excluded for lack of information and 1 patient was lost during follow-up; thus, 91 patients (mean age, 33.6±9.4 years) were finally analysed. Anamnestic and clinical data at enrolment are presented in Table I.

**Compliance with treatment schedule and adverse effects.** Compliance was observed in 91 patients (95.8%). Accordingly, compliance to the study protocol was high. The EndEP<sup>®</sup> formulation was well tolerated in all patients analysed and there were no significant drug-related side effects. Four of the 91 patients (4.4%) had mild adverse effects that did not require the treatment to be suspended. The most common adverse effects were mild nausea and mild headache.

**Clinical and questionnaire results at follow up.** At the follow-up examination (90 days after treatment initiation), statistically

Table I. Patient sociodemographic, anamnestic and clinical characteristics at the time of enrolment.

Characteristic	Values
Total no. of patients	91
Age, median ± SD	33.6±9.4
Educational level, n (%)	
Primary school	-
Secondary school	53 (58.2)
Post-secondary education	38 (41.8)
Sexually active in the past month, n (%)	91 (100)
BMI in kg/m <sup>2</sup> , mean ± SD	25.9±5.2
Smoking, n (%)	30 (32.9)
Alcohol use, n (%)	11 (12.0)
No. of partners, n (%)	
1	88 (96.7)
≥1	3 (3.3)
Symptom scores at baseline, mean ± SD	
IPSS	1.1±1.6
IIEF-15	26.1±2.9
PEDT	15.3±3.4
SF-36	98.2±0.5
IELT at baseline, sec	73.6±46.9

SD, standard deviation; BMI, body mass index; IPSS, international prostatic symptom score; IIEF, international index of erectile function; PEDT, premature ejaculation diagnostic tool; SF, short form; IELT, intravaginal ejaculation latency time.

significant differences were identified between mean IELT time at enrolment and following treatment (73.6±46.9 vs. 102.3±60.0s;  $P<0.001$ ), PEDT score (15.3±3.4 vs. 12.2±3.2;  $P<0.001$ ) and SF-36 questionnaire score (98.2±0.5 vs. 99.4±0.1;  $P<0.001$ ). Moreover, 55 out of 91 patients reported improvement in control of ejaculation (PRO evaluation; 60.4%). At the follow-up examination (3 months after treatment), no statistically significant differences were found in terms of IPSS or IIEF-15 scores ( $P=0.19$  and  $P=0.64$ , respectively). Table II shows all questionnaire results at enrolment and at the follow-up visit.

## Discussion

Despite PE being among the most common types of sexual dysfunction in male patients and regardless of the increasing interest in PE in the field of sexual medicine, highly satisfactory treatments in terms of efficacy and safety are lacking (19). Moreover, although dapoxetine as an on-demand SSRI, several daily SSRIs and local anaesthetics have been introduced for the treatment of PE, numerous patients continue to suffer from PE due to a lack of definite treatment (19). This is probably due to i) high dropout rates from the treatment and ii) the high prevalence of adverse events (5). A previous study reported that 12.6% of patients (6/48) dropped out from a 6-week daily SSRI trial due to side effects (20). The reported side effects were fatigue, drowsiness, nausea and vomiting, dry mouth,

Table II. Questionnaire results at enrolment and at the follow-up visit.

Symptom	Values (mean ± SD)		P-value
	Enrolment	Follow-up visit	
Symptom scores			
IPSS	1.1±1.6	1.4±1.5	0.19
IIEF-15	26.1±2.9	26.3±3.1	0.64
PEDT	15.3±3.4	12.2±3.2	<0.001
SF-36	98.2±0.5	99.4±0.1	<0.001
IELT, sec	73.6±46.9	102.3±60.0	<0.001

SD, standard deviation; IPSS, international prostatic symptom score; IIEF, international index of erectile function; PEDT, premature ejaculation diagnostic tool; SF, short form; IELT, intravaginal ejaculation latency time.

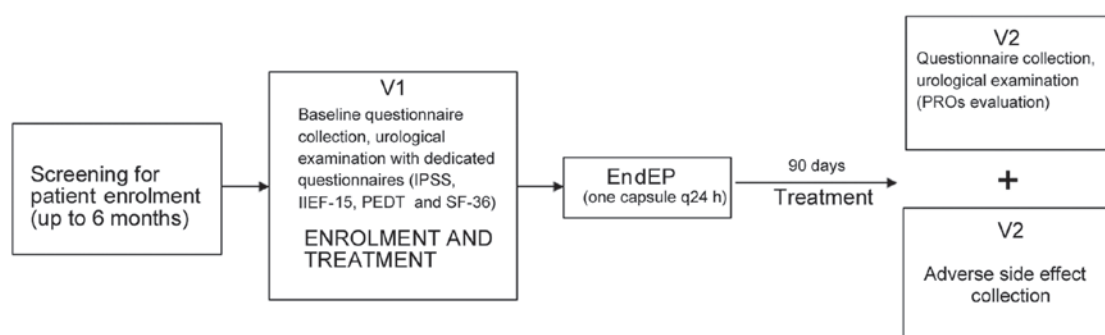


Figure 1. Study flow-chart in accordance with consolidated standards of reporting trials criteria. IPSS, international prostatic symptom score; IIEF, international index of erectile function; PEDT, premature ejaculation diagnostic tool; SF, short form; PROs, patient reported outcomes; q24 h, once every 24 h, V1, Visit 1, at the time of enrolment; V2, Visit 2, at the follow-up, 90 days after the start of treatment.

decreased libido and erectile dysfunction (5,20). Another important aspect to highlight is that even if the preferred management of PE is on-demand dapoxetine or daily SSRIs, many urologists had used other treatment options in 35% of the initial treatment cases and 50% of the second-line treatment cases (21). This demonstrates that there is a deficiency in the management of PE patients. The results of the present study show that the use of a combination of *Rhodiola rosea*, folic acid, biotin and zinc (EndEP®) is able to improve a patient's ejaculatory control, with a higher IELT and higher level QoL. Moreover, a high level of treatment compliance has been reported, probably due to the low frequency of adverse events and the efficacy of the treatment in terms of ejaculatory control improvement.

Ejaculation is controlled by a complex reflex arc that involves the central and peripheral nervous systems, with an important role of a single neurotransmitter, 5-HT (22). Chen *et al* previously demonstrated that *Rhodiola rosea* extract is able to improve the level of 5-HT in the hippocampus in an animal model (7), highlighting the role of this extract in the modulation of the level of serotonin. Moreover, Hung *et al* in a systematic review concluded that *Rhodiola rosea* might have beneficial effects on physical performance, mental performance and certain mental health conditions (23). Even if no specific study had been performed on patients affected by PE, it could be hypothesised that *Rhodiola rosea* would effect an

improvement of ejaculatory control and thereby improve QoL and sexual satisfaction. An important aspect to highlight is the low prevalence of adverse events; of the 446 subjects examined in the 11 clinical trials included in another review, five adverse events were mentioned in only three studies (24). Moreover, folic acid has been shown to influence the metabolism of 5-HT (25). An animal study confirmed that folic acid relieves depression, possibly through the 5-HT receptor (25). Recently, Yan *et al* investigated the role of serum folic acid levels in patients with erectile dysfunction and/or PE (26). The authors concluded that there were positive correlations between serum folic acid concentrations and questionnaire results on sexual function (26). These findings demonstrated a strong association between serum folic acid levels and sexual dysfunction, possibly due to an effect of folic acid on the metabolism of nitric oxide and 5-HT (26). Moreover, the impact of several ions on male sexual function has been investigated (27). In particular, zinc ion has been demonstrated to have an important role in prostate health and in ejaculatory reflex health (28). Finally, biotin contributes to normal psychological and sexual function and this effect should be useful in the management of patients with PE (29).

The present study shows some strengths of the treatment. Firstly, the use of phytotherapy for the treatment of PE was well accepted by the patients (95.7% compliance to the protocol). Moreover, the very low prevalence of adverse

events contributed to the high compliance with the protocol. Furthermore, the exclusion of all patients with concomitant therapy for PE is a very important aspect to highlight, as it enabled the present study to demonstrate the effects of EndEP® alone. However, even if the results are encouraging, this study has several limitations. Firstly, it lacks a placebo arm; however, this study was planned without a placebo arm as we consider it unethical to not treat patients with PE when it impacts their QoL. Moreover, the short follow-up period did not allow the possible long-term adverse side effects to be evaluated.

In conclusion, the present study found that EndEP® significantly improved the ejaculatory control and quality of sexual life of patients affected by lifelong PE, with a very low rate of short- and mid-term adverse events. This is the first study to address the tolerability and efficacy of a phytotherapeutic compound in the management of lifelong PE in a phase I-II trial.

### Acknowledgements

The authors are grateful to Professor John Denton from the University of Florence for manuscript language revision.

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