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Review Article

Non-Hormonal Improvement of FSD by a Combination of Plant Extracts and Amino acids (Lady Prelox®)

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Abstract

A combination of plant extracts and amino acids, designated as PACR, consisting of 20mg French maritime pine bark extract (Pycnogenol®, Horphag Research Ltd.), 200mg of L-arginine and 200mg L-citrulline 50mg rose hip extract (ROSVITA®, Horphag Research Ltd.) per tablet (Lady Prelox®, Horphag Research Ltd.), has been tested in 3 clinical trials. Aim of the studies was to evaluate the effects of PACR on relief of symptoms of female sexual disorder (FSD) in pre-menopausal, peri-menopausal and post-menopausal women, with the aim of the Female Sexual Function Index (FSFI) self-reporting questionnaire.

The results of all studies indicated a significant improvement of sexual functions by PACR. No adverse effects were observed.

Oxidative stress was significantly reduced in two studies.

The proposed non-hormonal mechanism of action is based on NO-mediated vasculogenic and neurogenic effects.

PACR (Lady Prelox®) seems to provide a safe, natural supplement for relief from female sexual disorder for women of all ages.

ABBREVIATIONS

FSD: Female Sexual Dysfunction; FSAD: Female Sexual Arousal Disorder; HSDD: Hypoactive Sexual Desire Disorder; FOD: Female Orgasmic Disorder; FSFI: Female Sexual Function Index; PACR: Pine Bark Extract, L-Arginine, L-Citrulline, Rose Hip Extract

INTRODUCTION

Sexual dysfunction is defined by the WHO as follows: "The various ways in which an individual is unable to participate in a sexual relationship as she or he would wish" [1].

Female sexual dysfunction (FSD) especially was defined as "disorder of libido, arousal, orgasm and sexual pain that lead to personal distress and interpersonal difficulties" [1]. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [2] and the International Consultation of Sexual Medicine Committee on Definitions [3] introduced more specific classifications of the diverse female sexual dysfunctions as Female Sexual Arousal Disorder (FSAD), Female Orgasmic Disorder (FOD) and Hypoactive Sexual Desire Disorder (HSDD).

The problem of FSD has been neglected by the scientific community for a long period of time. It was the successful treatment of male sexual dysfunction with sildenafil, which generated the interest for sexual female problems.

World-wide epidemiological research revealed that FSD affects 41% of premenopausal women [4]. Remarkably, this percentage has been found with little variation in Europe, Asia, USA, South America and Australia as follows from the meta-analysis of 95 studies [4].

As FSD increases with age, starting with the onset of menopause, the overall prevalence of FSD for women will exceed the 41% rate, so it is a widespread, but underestimated health problem. According to the meta-analysis [4], FSD was associated with lubrication problems at a rate of 20.6% and 28.2% of the women reported HSSD symptoms. Therefore, main target for therapy is the improvement of women's desire and arousal.

The evaluation of FSD was done in the cited clinical studies by the self-reporting questionnaire based on the Female Sexual Function Index, FSFI ,which was re-validated in 2016 [5-7].

Etiology of FSD comprises of a complex network of psychological and biochemical reactions. Women seeking for assistance from their physicians for their sexual problems are examined first of all for psychological and physiological obstructions hindering a healthy sexual relationship. The following pharmacotherapy will be directed individually to the various aspects as HSDD, FSAD, FOD and dyspareunia.

The International Consultation on Sexual Medicine Report [8] lists the types of pharmacologic interventions for HSDD and FSAD.

Pharmacotherapy of FSAD

Hormone replacement therapy: Endocrine hormones exert

a strong influence on FSAD. Declining production of hormones in menopause or androgen hormone deficiency may lead to FSAD.

Fading production of estradiol, causing alterations in vaginal structure and acidity, results in sexual discomfort [7]. Consequently, Hormone Replacement Therapy (HRT) is indicated. However, many women are reluctant to HRT because of serious unwanted effects. The topical application of sex hormones avoids the systemic problems of HRT and improves FSAD effectively [9-11].

Low levels of testosterone have a negative impact on desire, arousal and orgasm [12]. Androgen deficiency is treated with testosterone patches and a transdermal cream, thereby increasing local testosterone levels, resulting in enhanced sexual arousal [13-17].

As a non-prescriptional supplement, Dehydroepieandrosterone (DHEA) is frequently recommended as its metabolisation delivers precursors to androgens and estrogens. It increases testosterone levels more than estrogen concentrations [16]. Use of DHEA is limited though by unwanted androgenic effects at high doses. However, DHEA applied intravaginally was effective in improving dyspareunia and libido without systemic androgenic effects [18-19].

Tibolone, a synthetic hormone, is metabolized to androgens as well as to estrogens. It improves FSAD and improves vaginal lubrication [20-25].

As there are frequently concerns about hormonal treatment, a variety of approaches aim at vasculogenic and neurogenic causes of FSD.

The neurogenic approach: Flibanserin inhibits serotonin secretion, which depresses sexual activity, and stimulates liberation of dopamine and noradrenaline [26-27]. Clinical trials with large numbers of women demonstrated statistically significant, but modest improvements in sexual desire [28]. Significant side effects as somnolence, dizziness, nausea and fatigue were observed in all clinical studies listed in the review of Lodise [29].

Further neurogenic pharmacological treatments with Bupropion, Trazodone, Melanocortin and Apomorphin have been reviewed by Kingsberg et al [8].

The vasculogenic approach: In analogy to treatment of male sexual disorder, the erectile dysfunction, numerous attempts were directed to increase the blood flow to female sexual organs.

Sildenafil relaxes smooth muscles by prolonging the stability of GMP, thereby increasing blood flow in clitoris and vagina. However, results of clinical studies were not absolutely convincing. Arousal and orgasm were improved in two studies, but no beneficial effects were reported in a third, larger study [30-32].

Following topical application, prostaglandin PGE1 [33] or a combination of vasodilators causes smooth muscle relaxation and improves arousal and orgasm [34].

The NO donor L-arginine, contained in ArginMax®, yielded positive results in treatment of FSD in clinical trials [35-36].

The vascular approach to stimulate arousal by enhancement of blood flow is not fully satisfying in treatment of FSD as the neurogenic component, desire, was not convincingly improved. A successful therapy of FSD has to consider the neurogenic and the vasculogenic approach simultaneously.

Combination of the neurogenic and vasculogenic approach: The branded extract from bark of the French maritime pine, Pycnogenol® (Horphag Research Ltd.), exerts vasculogenic effects by stimulating the NO producing endothelial nitric oxide synthase (e-NOS). Vasorelaxation and increased blood flow following oral intake of Pycnogenol® has been demonstrated in young volunteers [37].

Furthermore, neurogenic effects of the pine bark extract has been observed in clinical studies directed to climacteric disorders. In a randomized, double-blind, placebo-controlled study with 155 perimenopausal women (mean age 46), scores for sexual behavior from the Women Health Questionnaire [38] improved significantly ($p<0.001$) over a period of 6 months vs placebo after intake of 200mg/day Pycnogenol® [39]. Furthermore, libido improved significantly ($p<0.05$) according to the Menopause Symptoms Questionnaire after 100mg/day Pycnogenol® for 8 weeks in 38 women (mean age 46 years), whereas no changes were noted in the control group of 32 women with the same age [40].

Based on these improvements of sex life of menopausal women, a proprietary combination of 20mg Pycnogenol® with 200mg of the NO donors L-arginine and L-citrulline was developed to improve women's sex life and sexual function. 50mg rose hip extract was added to the combination to counteract oxidative stress. This combination, designated as PACR, tradename Lady Prelox® (Horphag Research Ltd), was successfully tested in 3 clinical studies. The evaluation of the efficacy of PACR was performed with the aid of the FSFI questionnaire, translated into Italian and Bulgarian language.

A study evaluating sexual function with the FSFI questionnaire with 100 premenopausal women, age between 37-45 years, was performed over a period of 8 weeks at the University of Siena, Italy [41]. All participants were instructed to follow a strict healthy lifestyle with diet, exercises and regular sleep. Half of the women received additionally 4 tablets Lady Prelox® daily. The total FSFI scores of the PACR group were significantly ($p<0.05$) higher compared to control. Scores under PACR increased from 15 at start to 28.5 and to 34 after 8 weeks. In the control group, the increase of FSFI was limited: From 15 at start to 23 at 4 and 8 weeks. Oxidative stress, expressed as plasma free radicals, decreased significantly with PACR intake. Reduction of oxidative stress in controls did not reach levels of significance.

In a randomized, double-blind, placebo-controlled study with 80 premenopausal women (age 40-50 years), the increase of female sexual function was evaluated at the University of Sofia by the FSFI, following oral intake of 4 tablets Lady Prelox® [42]. Sexual function scores increased by 60% after 1 month and ending with a total score of 73% after 2 months. According to Rosen et al., [5] the value of 26.5 delineates functional from dysfunctional sexual function, so that the treatment for 2 months with Lady Prelox® normalized the sexual function of the participants.

The elevation of scores for the diverse domains as desire, arousal, lubrication, orgasm, satisfaction and pain reduction varied in a narrow range between 71 and 76%.

Further evaluation of women's health with the Women's

Health Questionnaire [38] revealed an increase of scores for sexual behavior by 71% under PACR, in agreement with the results obtained by the FSFI questionnaire.

Total plasma antioxidant capacity increased significantly ($p<0.05$) versus placebo after 4 and 8 weeks of intake of PACR thus indicating a reduction of oxidative stress

In a single-blinded, placebo-controlled study at the University of Siena with 80 postmenopausal women, age 47-53 years, the PACR group received 4 tablets Lady Prelox® daily [43]. The scores from the nine item FSFI questionnaire increased in the PACR group from 44 to 70.9 after 4 weeks with a further small increase to 71.7 after 8 weeks. The scores for orgasm, satisfaction and diminished pain were almost doubled from 6 to 11 after 4 weeks.

No adverse effects exceeding climacteric symptoms were reported or observed in all 3 studies.

DISCUSSION AND CONCLUSION

The positive effect of PACR on FSD is based mainly on the activity enhancement of e-NOS [37,44]. The higher activity of e-NOS, coupled with a surplus of NO-donors (L-arginine and L-citrulline), delivers a high quantity of NO following neural stimulation of e-NOS. Result is a long lasting vasodilation in female organs after arousal. The vasculogenic effect of PACR on female sexual orgasm is in perfect agreement with the effect of Prelox®, consisting of Pycnogenol and L-arginine, on erectile dysfunction (ED) in men. Two randomized, double-blind, placebo-controlled, cross-over studies with patients suffering from ED demonstrated a tremendous, significant ($p<0.01$) improvement of erectile function [45,46].

The positive effects on desire could be related to the general enhancement of cognitive functions by Pycnogenol. The pine bark extract promotes learning and memory in animal experiments as well as in clinical studies [47-48]. The mechanisms for these neurogenic effects could be an improved blood circulation in brain as result of vasodilatation or an increase of neuronal activity by a NO-mediated biochemical reaction.

Pycnogenol does not influence hormonal secretion in women, as plasma concentrations of estradiol, follicle-stimulating hormone or dehydro-epiandrosterone are not significantly changed following intake of Pycnogenol [49,50]. Therefore, the improvement of FSD by PACR does not relate to hormonal effect.

The benefits of PACR result most probably from the combined action of the vasculogenic effects, mediated by NO, and the neurogenic effects.

LIMITATIONS AND FUTURE RESEARCH

Although the studies with PACR seem to offer an option for women looking for a non-hormonal, natural alternative to hormone therapy or pharmacotherapy with drugs, more well designed double-blind, placebo-controlled studies are needed to extend the basis of knowledge about PACRs actions and clinical effects. Studies on other non-caucasian populations or on women with defined problems as diabetes, hypertension or depression are needed to enlarge the data base for safety and efficacy.

In conclusion, the clinical studies with Pycnogenol and PACR suggest that PACR offers a safe and non-hormonal option for relieving FSD in pre-menopausal, peri-menopausal and post-menopausal women.

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