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Alternative Therapies for Male and Female Sexual Dysfunction

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Abstract: Sexual dysfunction is prevalent in both men and women. Although new pharmaceutical agents have been identified for male erectile problems, sexual desire and orgasm disorders, individuals with sexual dysfunction often seek alternative therapies, including traditional Chinese medicine. This article reviews currently used alternative therapies, such as herbal medications, L-arginine, acupuncture, biofeedback and others. Potential herb-drug interactions are also presented.

Keywords: Sexual Dysfunction; Alternative Therapies; Traditional Chinese Medicine; Yohimbine; Ginkgo; Ginseng; Herbal Formulation; L-arginine; Acupuncture.

Introduction

Sexual dysfunction is characterized by disturbances in sexual desire and in the psychophysiological changes associated with the sexual response cycle (American Psychiatric Association, 1994). Prevalent in both genders, it ranges from 10–52% of men and 25–63% of women based on several studies (Frank *et al*., 1978; Spector and Carey, 1990; Rosen *et al*., 1993). It has been reported that the incidence of sexual dysfunction in the United States is greater in women (43%) than in men (31%) (Laumann *et al*., 1999).

Advances have occurred in the understanding of the neurovascular mechanisms of sexual response in both men and women (Rajfer *et al*., 1992; Burnett, 1995; Park *et al*., 1997). Several new classes of drugs have been identified that offer significant therapeutic potential for the treatment of male erectile disorder (Heaton *et al*., 1995; Morales *et al*., 1995; Boolell

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et al., 1996), while other agents are indicated for sexual desire and orgasm disorders (Rosen and Ashton, 1993; Segraves *et al*., 1993; Morales *et al*., 1995). In addition to conventional therapies, however, individuals with sexual dysfunction often seek alternative therapies.

Sexual Dysfunction in Men

Penile erection is mediated by the parasympathetic nervous system, which, when stimulated, can cause arterial dilation and relaxation of the cavernosal smooth muscle. Increased blood flow into the corpora cavernosa in association with reduced venous outflow results in penile rigidity. Nitric oxide (NO), a chemical mediator of erection, is released from nerve endings and vascular endothelium. This causes smooth muscle relaxation, resulting in venous engorgement and penile tumescence.

Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse (NIH, 1993), and has been estimated to affect 20–30 million men in the United States (Feldman *et al*., 1994; Benet and Melman, 1995). Erectile dysfunction can be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal or drug-induced), or mixed psychogenic and organic (Lue, 2000). Treatment options have progressed from psychosexual therapy and penile prostheses (1970s), through revascularization, vacuum constriction devices and intracavernous injection therapy (1980s), to transurethral and oral drug therapy (1990s). The discovery that the NO-cyclic GMP pathway affects erectile function and the development of sildenafil citrate (Viagra) are recent advances (Lue, 2000).

Herbal Medicines

Yohimbine

Yohimbine is an alkaloid derived from the bark of the central African tree *Corynanthe yohimbe*. It may cause penile vasodilatation via alpha-2-receptor antagonism. The results from a meta-analysis suggest yohimbine is effective for erectile dysfunction. No trials have been conducted to compare yohimbine with sildenafil citrate, but indirect comparison of placebo-controlled trials suggests that yohimbine is less effective but relatively safer (O'Leary, 1999). The combination of yohimbine and L-arginine is in early phase III development (Padma-Nathan and Giuliano, 2001). A double-blind cross-over trial of 4 weeks duration was used to evaluate the efficacy of yohmibine in reversing anorgasmia, 10–15 mg dosage did not cause any worsening of patients' obsessive compulsive (depression) symptoms (Segraves, 1993).

In addition, one case report showed that yohimbine is effective in the treatment of antidepressant-induced (e.g. selective serotonin reuptake inhibitors, clomipramine and tricyclic antidepressants) sexual dysfunction, anorgasmia and difficulty obtaining and maintaining an erection. It has been shown that clomipramine dosage of up to 150 mg/day inhibited the patient's orgasmic ability, and dosage of 200 mg/day inhibited to obtain erection (Price and Grunhaus, 1990).

Oral doses of 5–10 mg yohimbine three times daily are generally well tolerated. The side effects of yohimbine are clearly dose dependent (Tam *et al*., 2001), with doses over 30 mg occasionally causing small increases in blood pressure, and doses of 50 mg or higher associated with increased heart rate in normotensive subjects (Tam *et al*., 2001).

Ginkgo biloba

Ginkgo biloba or ginkgo facilitates microvascular circulation that may physiologically lead to an improvement in sexual function in animal studies (Welt *et al*., 1999). There is evidence that ginkgo extract may directly elucidate smooth muscle relaxation, likely via effects on the NO pathway. The extract has an effect in human and rabbit corpus cavernosum tissue using organ bath and electric field stimulation (Paick and Lee, 1996). An open label clinical trial used ginkgo extract to treat arterial erectile dysfunction. Sixty patients who had not improved with papaverine injections of up to 50 mg were treated with 60 mg/day ginkgo extract for 12 to 18 months. The penile blood flow was re-evaluated by duplex sonography every 4 weeks. Fifty percent of patients had regained potency (Richard *et al*., 1989).

Another open label trial showed that ginkgo is effective in treating antidepressant-induced sexual dysfunction. Ginkgo generally had a positive effect on all four phases of the response cycle (i.e. desire, excitement, erection and lubrication), orgasm and resolution (Cohen and Bartlik, 1998).

Ginseng

Ginseng has been an essential herb in traditional Chinese medicine for many years. The principle active constituents in ginseng are ginsenosides. Over 20 different ginsenosides have been identified from ginseng root extracts of different ginseng species. Ginseng is commonly used for the treatment of sexual dysfunction (Attele *et al*., 1999; Murphy and Lee, 2002).

Effects of American ginseng on copulatory behavior have been shown in adult male rats. Ginseng-treated rats demonstrated a significant decrease in mount, intromission and ejaculation latencies compared to vehicle controls. Hormone analyses revealed no difference in plasma luteinizing hormone (LH) or testosterone levels between ginseng- and vehicle-treated animals. However, plasma prolactin levels were significantly reduced by all doses of ginseng tested, suggesting ginseng-induced alterations in dopaminergic neurotransmission may play a role in the ability of ginseng to stimulate copulatory behavior (Murphy *et al*., 1998).

A recent study showed that both Asian ginseng and American ginseng enhance libido and copulatory performance. These effects of ginseng may not be due to changes in hormone secretion, but to direct effects of ginseng, or its ginsenoside components, on the central nervous system and gonadal tissues. Ginsenosides can facilitate penile erection by directly inducing the vasodilatation and relaxation of penile corpus cavernosum. In addition, the effects of ginseng on the corpus cavernosum appear to be mediated by the release and/or modification of release of nitric oxide from endothelial cells and perivascular nerves (Murphy and Lee, 2002).

Clinically, ginseng is believed to have aphrodisiac effects for patients with sexual dysfunction (Vogler *et al*., 1999). One placebo-controlled study assessed 90 patients for 3 months. Among them, 30 patients were treated with either Korean red ginseng extract (1.8 g), 30 were treated with placebo, and the remaining 30 patients received trazodone (25 mg). Although no intergroup differences were reported for frequency of intercourse, the results suggested superiority of ginseng for penile rigidity, girth, libido and satisfaction (Choi *et al*., 1995). Ginsenosides, have been shown to increase NO production in endothelial cells in *in vitro* studies, possibly due to upregulation of NO synthase activity by the compounds (Chen and Lee, 1995; Han and Kim, 1996). Thus, the effects of ginsenosides on NO production have implications for improved sexual function.

Ginseng was also demonstrated to increase spermatozoa count and motility in infertility patients. In a study with 66 participants, 30 were oligoastenospermic sine causa, 16 were oligoastenospermic with idiopathic varicocele, and the remaining 20 age-matched volunteers were used as controls. Ginseng extract showed an increase in spermatozoa number per ml and progressive oscillating motility, an increase in plasma total and free testosterone, dihydrotestosterone (DHT), follicle-stimulating hormone (FSH) and LH, but a decrease in mean prolactin. It is suggested that ginsenosides may have an effect at different levels of the hypothalamus-pituitary-testes axis (Salvati *et al*., 1996).

Tribulus terrestris/Protodioscin

Protodioscin is a phytochemical agent derived from the *Tribulus terrestris* plant, which has been clinically proven to improve sexual desire and enhance erection via the conversion of protodioscin to De-Hydro-Epi-Androsterone (DHEA) (Adimoelja, 2000). In a double-blind placebo-controlled multicenter study of 45 subfertile couples with idiophatic oligo-astheno-terato-zoosperma, the husbands were treated with 500 mg/day Tribestan (protodioscin phytochemical compound) for 12 weeks. Eight pregnancies were noted after 4 months (Moeloek *et al*., 1994). Another controlled study enrolled 40 subjects (20 in the DHEA group and 20 in the placebo group) of ages ranging from 43 to 68 years for 24 weeks. Daily dose of 50 mg DHEA has been found to be effective in increasing fertility in subfertile males and improve erectile dysfunction in both diabetic and non-diabetic men (Moeloek *et al*., 1994; Morales *et al*., 1994).

Damiana

Damiana (*Turnera diffusa and Turnera aphrodisiaca*) has been traditionally used as a tonic for the central nervous system and hormonal system in Latin America (Foster, 1991). It has been shown that damiana has progestin receptor-binding activity and is considered a phyto-progestin, the progesterone from plant (Zava *et al*., 1998). In an *in vivo* study, high progestin-binding activity of damiana has been demonstrated, based on their effect on alkaline phosphatase, an end-product of progestin action (Zava *et al*., 1998). Sexually impaired rats treated with damiana increased their rates of copulatory performance (Arletti *et al*., 1999).

Others

Eurycoma longifolia, Pimpinella pruacen and *Muara puama* are also believed to enhance sexual functions (Adimoelja, 2000). In addition to botanicals, vitamins and minerals may also possess abilities to enhance sexual function (Bayer, 1960; Sandler and Faragher, 1984; Kumamoto *et al*., 1988; Mohan *et al*., 1997; Robinson *et al*., 1998). More research studies are needed to prove their efficacy.

Herb Formulations

Herbal formulations constitute an important aspect of traditional Chinese medicine treatment. Individual herbs are organized into broad therapeutic categories according to the principal action observed by the administration of the herb. Each herb has a primary effect on one or more organ system (Crimmel *et al*., 2001).

Gosyajinki-gan

Gosyajinki-gan is a traditional Chinese medicine formulation composed of ten herbs (Sato *et al*., 1997). One study compared the effect of limaprost, an oral prostaglandin E1 (PGE1) derivative, to the gosyajinki-gan. The study comprised 50 patients with mild erectile dysfunction who showed a good erectile response to intracavernosal injection of 20 mg PGE1. Limaprost was administered to the first 25 patients (30 mg three times daily) and gosyajinki-gan (7.5 g three times daily) to the next 25 patients for 8 consecutive weeks. Patients were evaluated by their ability to achieve vaginal penetration and by a subjective assessment of erectile functions (i.e. penile rigidity and maintenance of erection) before and after the treatment, using a self-administered questionnaire. Objective measurements (e.g. nocturnal penile tumescence) were also evaluated. Four of the 24 taking gosyajinki-gan succeeded in vaginal penetration. However, these positive responders did not experience a full erection (Sato *et al*., 1997).

Ryu-wei-ti-huang-wan

Ryu-wei-ti-huang-wan is a Chinese herbal formulation composed of extracts from six plants (Tong *et al*., 1996). It was used in clinical treatment of male diabetic impotence. On evaluation of diabetic impotence, adult male rats were divided into three groups: (1) rats rendered diabetic with a single intraperitoneal injection of streptozotocin (60 mg/kg body weight); (2) rats with streptozotocin-induced diabetes treated with 30 mg/day ryu-wei-ti-huang-wan powder twice a day; and (3) control rats. Each male rat was caged with an adult ovariectomized female rat during the dark cycle. Infrared-illuminated video recording was utilized to evaluate the sexual performance. The diabetic rats exhibited depressed mounting activity and no intromission or ejaculation. After ryu-wei-ti-huang-wan treatment either for 1 day or 2 weeks, the diabetic rats showed significant improvement in mounting performance with preservation of intromission and ejaculation. No significant difference in the blood sugar level was noted between the treatment and non-treatment groups (Tong *et al*., 1996).

A Chinese herbal medicine mixture

This formulation composed of 18 herbs including ginseng, dioscoreae and *Paeoiae alba* (Bakircioglu *et al*., 2000). The formulation showed an effective response in hypercholesterolemic erectile dysfunction male rats. In the study with 32 rats, eight control animals were fed a normal diet and the remaining 24 were fed cholesterol diet for 4 months. After 2 months, herbal medicine was added to the drinking water of the treatment group of 16 rats but not the cholesterol only group. Serum cholesterol levels were measured at 2 and 4 months. At 4 months, erectile function was evaluated with cavernous nerve electrostimulation in all animals. Penile tissues were collected for electron microscopy, and to perform Western blot for endothelial NO synthase, neuronal NO synthase, basic fibroblast growth factor (bFGF) and caveolin-1. Erectile response was significantly better in the Chinese herbal-treated group. High levels of bFGF and caveolin-1 expression in the treated group may protect the cavernous smooth muscle and endothelial cells from the harmful effect of high serum cholesterol (Bakircioglu *et al*., 2000).

Mustong

An uncontrolled study assessed the potential of mustong, an Oriental herbal preparation containing mainly *Mucuna pruriens* and *Withania somnifera*, as an option for male sexual dysfunction (Ojha *et al*., 1987). The report suggests improvement of sexual function in 16 out of 25 diabetic patients with impotency. Mustong was given in two tablets twice daily for 7–8 weeks. After mustong administration, there was an increased desire to have sexual intercourse, strong erection, hardness, and increased duration of coitus (Ojha *et al*., 1987). No adverse effects were observed.

L-arginine

L-arginine is an amino acid that functions as a precursor to the formation of NO, which mediates the relaxation of vascular and non-vascular smooth muscle. In a double-blind, placebo-controlled study, a high oral dose of L-arginine (5 g/day) was given for 6 weeks, and the treatment induced significant improvement in sexual function in men with organic erectile dysfunction (Chen *et al*., 1999). A combination of L-arginine and yohimbine was used for individuals with sexual dysfunction (Berman *et al*., 1999). One controlled, three-way crossover clinical trial was conducted to compare the efficacy and safety among 6 g L-arginine plus 6 mg yohimbine, 6 mg yohimbine alone and placebo, for the treatment of erectile dysfunction. The primary endpoint was changed in the Erectile Function Domain score of the International Index of Erectile Function. The secondary endpoints were patient and investigator assessments of treatment success. Forty-five patients were enrolled in this 2-week crossover study, and the drug was orally administered 1 to 2 hours before intended sexual intercourse. This study showed that administration of L-arginine plus yohimbine is effective in improving erectile function in patients with mild to moderate erectile dysfunction (Lebret *et al*., 2002). However, data from another controlled study reported that, compared

to placebo, low-dose oral L-arginine (1.5 g/day) for 17 days did not have any improvement in the mixed type of erectile dysfunction (Klotz *et al*., 1999).

Acupuncture

One randomized controlled trial evaluated acupuncture as a treatment for patients with non-organic erectile dysfunction (Aydin *et al*., 1997). Nine patients were treated with acupuncture points and six received placebo acupuncture twice weekly for 6 weeks. Improvements in sexual function were reported in the treatment group, but were not significantly different from the control group. Data from uncontrolled studies indicate some positive effects on the quality of erection and sexual activity in erectile dysfunction due to non-organic (Kho *et al*., 1999) and mixed (Yaman *et al*., 1994) etiologies. In another study with 52 patients, improvement of impotence was seen in majority of the cases (Zhu and Ni, 1997).

Biofeedback

A controlled trial of biofeedback training assessed 30 patients with psychogenic erectile dysfunction. There were ten patients in each group. The first group received feedback plus the viewing of segments of erotic film. The second group viewed film segments without feedback, and the third group received no feedback and no film. There were no intergroup differences in erectile functioning during a 1-month follow-up period (Reynolds, 1980). It was concluded that the therapeutic value of erectile feedback remains undemonstrated.

Hypnotherapy

A randomized controlled trial assessed the effects of hypnotic suggestions on sexual function in patients with sexual dysfunction with no detectable organic cause (Aydin *et al*., 1996; Aydin *et al*., 1997). In the study, the first group received testosterone, the second group received trazodone, the third group underwent hypnosis therapy, and the last group served as control. After 4, 6 and 8 weeks, the effects were verified by interviewing their partners. The study found some obvious improvements in sexual function by hypnosis therapy.

Pelvic Floor Exercise

Pelvic floor exercises apply pressure on the glans penis to trigger reflex contractions of the ischiocavernosus and perineal muscles. The exercise may reinforce the strength of perineal muscles and facilitate penile rigidity during erection (Lavoisier *et al*., 1988). One controlled trial compared a pelvic floor exercise program with surgery (Claes and Baert, 1993). One hundred and fifty patients with erectile dysfunction and with leakage from corpora cavernosa as diagnosed by dynamic infusion cavernosometry were included; 78 randomized to the training program. Prior to the study, pelvic floor exercises were demonstrated to the patients, who also underwent general muscle consciousness training to help them differentiate between

abdominal, gluteal, femoral adductor and pelvic floor muscles. Patients were also instructed in a home exercise program in the prone, sitting and standing positions. Training was given in five once-weekly sessions and supervised by a trained physiotherapist. In this context, the mechanism of penile erection focused on muscular and vascular role, for increasing in arterial inflow and restricting of venous outflow (Newman and Northup, 1981; Wagner, 1981; Junemann *et al*., 1986). The study data suggested that in mild-to-moderate cases of venous leakage, pelvic floor exercise might provide benefits and eliminate the need for surgery. However, surgical intervention was recommended for severe venous leakage cases.

Sexual Dysfunction in Women

Female sexual response consists of a three-phase model: desire, arousal and orgasm (Kaplan, 1974). In female sexual function, neurotransmitter-mediated vascular smooth muscle relaxation results in increased vaginal lubrication, vaginal wall engorgement and vaginal luminal diameter expansion, as well as increased clitoral length and diameter (Goldstein and Berman, 1998). Female sexual dysfunction is characterized by decreased libido, vaginal dryness, pain and discomfort with intercourse, decreased genital sensation, decreased arousal, and difficulty in achieving orgasm. These dysfunctions are due to vasculogenic, neurogenic, hormonal or psychogenic etiologies (Berman *et al*., 1999). For example, atherosclerotic vascular disease can result in conditions such as insufficient vaginal engorgement and clitoral erectile syndromes.

In the rat, vaginal atrophy and decreased sexual interest often occurs during menopause. It is believed that NO is involved in both of these conditions (Berman *et al*., 1998), as estrogen withdrawal appears to play a role in the regulation of vaginal NO synthase expression and apoptosis in nerves, smooth muscle, vascular endothelium and epithelium of the vagina, implying an NO-related mechanism in female sexual function. As an NO precursor, L-arginine has been shown to be essential to sexual maturation in the female rat (Pau and Milner, 1982).

Female sexual dysfunction is a complex result of psychological and physiological factors and no efficacious pharmaceutical therapies are currently available. Administration of sildenafil citrate to 30 post-menopausal women did not significantly improve sexual function, although there was some increase in vaginal lubrication and clitoral sensitivity (Kaplan *et al*., 1999).

Herbal Therapies

Some herbal medicines have been tested for treating sexual dysfunction in women. In a study of women with low sex drive, yohimbine had no significant effect on improving sexual desire, although it increased plasma 3-methoxy-4-hydroxyphenylglycol, the major central nervous system metabolite of norepinephrine, to a plasma level similar to that seen in men (Newman and Northup, 1981; Piletz *et al*., 1998).

In an open label trial, ginkgo seemed efficacious in the treatment of antidepressant-induced sexual dysfunction, particularly in women (Cohen and Bartlik, 1998). In the study

with 33 women and 30 men, subjects were given an average dose of 207 mg per day for 4 weeks. After 4 weeks, over 80% women had symptom relief in antidepressant-induced sexual dysfunction. The data also showed that women were more responsive to sexually enhancing effects of gingko than men with relative success rates of 91% versus 76% (Cohen and Bartlik, 1998).

A nutritional supplement containing ginseng (30% ginseng extract), ginkgo (24% flavone glycosides and 6% terpene lactones), damiana leaf, L-arginine, along with vitamins A, B6, B12, biotin, folate, niacin, pantothenic acid, riboflavin, thiamin, antioxidant vitamins (C and E), calcium, iron, and zinc, was tested in a double-blind placebo-controlled trial for enhancement of female sexual function. The study enrolled 77 women over the ages of 21 years with an interest in improving their sexual function. In these subjects, 34 receive the nutritional supplement and 43 received placebo. After 4 weeks, 74% of the nutritional supplement group experienced an improvement in satisfaction with their sex life. Notable improvements were observed in sexual desire, reduction in vaginal dryness, frequency of sexual intercourse and orgasm, and clitoral sensation without significant side effects (Ito *et al*., 2001).

Summary

There is convincing evidence for the effectiveness of yohimbine for male erectile dysfunction from organic or non-organic causes. Comparative studies with conventional oral medication, such as sildenafil citrate, are not available at present, but it has been suggested that yohimbine is less effective but probably safer. Whether yohimbine is safe for long-term use remains to be tested in future controlled studies. There are some data supporting ginkgo's use for impotency due to arterial insufficiency and selective serotonin reuptake inhibitors. However, patients on blood thinners, such as warfarin and aspirin, should be cautious in using ginkgo as it may potentiate the blood thinning effects. Despite the huge popularity of ginseng for centuries, there is lack of solid data to support its use for sexual concerns. Since L-arginine is a precursor to the formation of NO, it may play a role in treating male and female sexual dysfunction. Other approaches, such as hypnotherapy, although the evidence is not compelling, may be beneficial for some patients.

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