

Sexual dysfunction in the peri- and postmenopause

Status of incidence, pharmacological treatment and possible risks
A secondary publication

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Conflicts of Interest: Hired and paid as a consultant by Pfizer, Annamaria Giraldi has been project coordinator and chief responsible in medical trials conducted on the effect of a new selective estrogen receptor modulator and sildenafil on female sexual dysfunction in postmenopausal women. Subsequent teaching of general practitioners, for which Ms. Giraldi has also been responsible was organized and paid for by Pfizer. Similarly, Pernille Jensen received payment as a consultant in the same medical trials.

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ABSTRACT

The frequency of female sexual dysfunction increases with age, and the menopausal transition has a negative effect on the sexuality. Pharmacological treatment options for female sexual dysfunction during the peri- and postmenopause include hormone therapy or sildenafil. A limited number of randomized, controlled trials have been conducted and evidence suggests that systemic hormone therapy with estrogen, estrogen/progesterone, estrogen/testosterone and tibolone have a positive impact on sexual dysfunction during the peri- and postmenopause. Further, there is evidence that treatment with local estrogen relieves vaginal dryness and dyspareunia. Recent knowledge on side effects related to hormone therapy necessitates careful evaluation of the indication for hormone therapy and the duration of postmenopausal hormone therapy should be as short as possible. Long-term side effects of testosterone have not yet been fully investigated. A positive effect of sildenafil has been observed in a limited group of women; those with arousal problems but with no desire problems. The results suggest an intensified focus on new pharmaceutical products for the treatment of female sexual dysfunction in the postmenopause. For the time being the effect of testosterone therapy and tibolone on female sexual dysfunction is being investigated.

Sexual dysfunction in women (Female Sexual Dysfunction, FSD) is multi-factorial and influenced by physiological, psychological, social and emotional factors. FSD is defined in four diagnostic groups: desire-, arousal-, orgasm- and pain problems. Recently, it has been suggested that the woman herself should assess the dysfunction as distressful to be diagnosed as having a sexual dysfunction [1]. There are only a limited number of well-conducted population surveys on the prevalence of FSD. Further, relatively few randomized, controlled trials of pharmacological treatment of FSD have been carried out.

METHODS

A computer-based search in PubMed was conducted with the key words: *Sexual function, female sexual dysfunction, sexual dysfunction, sexuality, postmenopausal [women], androgen deficiency syndrome, menopause, dyspareunia, vaginal atrophy, vaginal dryness, hormone replacement therapy (HRT), estrogen, tibolone, sildenafil, Viagra, testosterone and androgen*. Papers through 2004-2005 were selected and reviewed for design and content, further using their references to locate other relevant papers. It was decided to focus on randomized, controlled trials with regard to the effect of pharmacological treatment of sexual problems during the peri- and postmenopause.

INCIDENCE OF SEXUAL DYSFUNCTION DURING THE PERI- AND POSTMENOPAUSE

From the literature it appears that the prevalence of sexual problems in women is high, that the prevalence increases with age, and that the menopausal transition has a negative influence on sexuality [2-8]. The prevalences of sexual dysfunctions may be underestimated in several of the surveys cited in the present paper as only sexually active women are included in the surveys. Hypoactive sexual desire is the most frequently reported sexual problem in women, ranging from 15-25% in the premenopausal women to 40-50% in the postmenopausal women. Lubrication problems are reported in 10-15% of the premenopausal women increasing to 25-30% of the postmenopausal women. Problems with orgasm occur in approximately 20% of all age groups; however, there is a tendency towards a higher frequency among the youngest women. Dyspareunia is rare among younger women (approximately 5%), it increases with age but fluctuates greatly among the postmenopausal women. The reported prevalence of dyspareunia in the latter group varies between 12%-45% [3, 6-8].

Thus, there is an association between the menopausal transition, age and an increasing prevalence of FSD. However, it remains unclear which factors related to the menopause that contribute the most to the observed increase. It is known from several studies that multiple factors influence female sexuality: The general health of the woman, hormonal changes, the woman's previous sexual function, partner's erectile dysfunction, changed life- and partner status, the woman's expectation to her sexual life during the peri- and postmenopause and her acceptance of physiological and psychological changes [4, 7, 9-11].

During the menopausal transition there is a sudden drop in the endogenous estrogen level, whereas a gradual decline in the androgen level starts around the age of 25 resulting in a low level around the menopause. It is well known that the postmenopausal low estrogen level produces vaginal atrophy, which predisposes to lubrication problems. Few studies have elucidated the prognostic significance of a drop in the endogenous hormone level for the occurrence of FSD in the postmenopause. Dennerstein et al have in their prospective, observational population-based study demonstrated that a drop in serum estradiol is correlated to reduced sexual desire and sexual responsiveness, defined as arousability, orgasm and sexual pleasure. In the same study there was no correlation between serum androgen levels and FSD [4, 10]. Minor studies on both pre- and postmenopausal women as well as women with surgically induced menopause have demonstrated a correlation between reduced sexual desire and low androgen levels [12-15].

PHARMACOLOGICAL TREATMENT

FSD is traditionally treated with sexological counselling and/or hormones. However, within the past years, the successful development of new pharmacological treatments of erectile dysfunction in men has resulted in an increasing focus on the development of new pharmacological treatment options for FSD. Pharmacological treatment options of FSD in postmenopausal women can be hormonal (estrogen, estrogen/progesterone, estrogen/testosterone, and tibolone) or non-hormonal (sildenafil). Several uncontrolled studies of the effect of these products on FSD in postmenopausal women have been conducted. However, as previously mentioned, we have decided to focus on the limited number of randomized, blinded, placebo controlled trials (Table 1).

SYSTEMIC ESTROGEN

Estrogen is fat-soluble and exerts its effect on intracellular receptors. The estrogen-receptor complex penetrates to the nucleus of the cell where it is bound reversibly to the DNA, and then induces mRNA synthesis, protein synthesis and mitosis activity. This leads to the effects of estrogen, among these the proliferation of the vaginal mucous membrane. In addition, estrogen receptors are present in other

Table 1. Overview of randomized, controlled studies of pharmacological treatment of sexual dysfunction in postmenopausal women.

Reference	Design	Preparation	N	Results				
				desire	lubrication	orgasm	dyspareunia	other
Dennerstein L et al 1980 (16) . . .	RCT, DB, PC, CO	Estrogen vs. placebo	36	↑	↑	↑	NA	Sexual pleasure ↑
Nathorst-Böös J et al 1993 (17).	RCT, DB, PC	Estrogen vs. placebo	239	↑	↑	→	↓	Sexual pleasure and activity ↑
Kökcü A 2000 (18)	RCT, SB	Tibolone vs. E+P	24	↑	NA	↑	↓	Sexual activity ↑
Nathorst-Böös J et al 1997 (19).	RCT, DB	Tibolone vs. E+P	315	→*	→*	→*	→*	Sexual activity, pleasure and satisfaction ↑
Wu MH et al 2001 (20)	RCT, SB	Tibolone vs. E+P	43	↑	↑	↑	↓	Sexual satisfactor ↑
Suckling J et al 2003 (21)	RCT, DB Cochrane Review	Local estrogen vs. placebo	2129	→	(↑)	NA	↓	Lubrication not measured directly, but vaginal dryness reduced
Sarral P et al 1998 (22)	RCT, DB	E+T vs. Estrogen	20	↑	→	NA	→	Sexual activity →
Lobo RA et al 2003 (23)	RCT, DB	E+T vs. Estrogen	218	↑	NA	NA	NA	Sexual responsivity ↑
Flöter A et al 2002 (24)	RCT, DB, CO	E+T vs. Estrogen	44	↑	→	→	→	Sexual pleasure ↑
Shifren JL et al 2000 (25)	RCT, DB	E+T vs. Estrogen	65	→	→	↑	NA	Sexual activity ↑
Buster JE et al 2005 (26)	RCT, DB, PC	E+T/ Estrogen	533	↑	NA	↑	NA	Personal distress ↓ Sexual arousal, total satisfying sexual activity, pleasure, responsiveness ↑
Simon J et al 2005 (27)	RCT, DB, PC	E+T/ Estrogen	562	↑	NA	↑	NA	Personal distress ↓ Sexual arousal, total satisfying sexual activity, pleasure, responsiveness ↑
Laan E et al 2001 (28)	RCT, DB, PC, CO	Tibolone vs. placebo	38	↑	↑	→	↓	–
Palacios S et al 1995 (29)	RCT, SB, PC	Tibolone vs. placebo	24	↑	↑	↑	→	Sexual activity ↑
Basson R et al 2002 (30)	RCT, DB, PC	Sildenafil vs. placebo	204	NA	→	NA	NA	Sexual pleasure and satisfaction →, Genital sensitivity →
Berman J et al 2003 (31)	RCT, DB, PC	Sildenafil vs. placebo	192	→	↑	↑	→	Genital sensitivity and sexual satisfaction ↑ Predominantly effective in women with no desire problems
Basson R and Brotto L 2003 (32)	RCT, DB, PC, CO	Sildenafil vs. placebo	34	NA	→	→	NA	–

RCT = Randomized, controlled study; DB = Double blind; SB = Single blinded; PC = Placebo controlled; CO = Cross-over study; E+T = Estrogen + testosterone; E+P = Estrogen-progesterone; NA = Not Available; ↑: Increase/Improvement; ↓: Decrease; →: No change
 * A positive effect of tibolone was found on all measured goals, but compared to estrogen-progesterone treatment the only additional effect of tibolone was measured on sexual activity, pleasure and satisfaction.

tissues, e.g. in the central nervous system (CNS), the pituitary gland and the hypothalamus.

Whether hormone therapy using estrogen/estrogen combined with progesterone actually does alleviate FSD has been debated for many years and remains controversial. Clinical experience and the results of several studies have shown that urogenital discomforts arising in relation to the menopausal transition can be alleviated with estrogen. Postmenopausal women treated with estrogen report less vaginal irritation, vaginal dryness and pain during intercourse. However, only a limited number of studies have investigated this in a randomized design. A study from 1980 on 36 women with surgically induced menopause demonstrated that estrogen-only treatment, compared with placebo or levonorgestrel, significantly improved the women's sexual desire, lubrication, orgasm frequency and overall sexual pleasure [16]. Nathorst-Böös et al demonstrated in a large study from 1993 of 239 naturally postmenopausal women that estrogen-only treatment significantly increased the frequency of sexual activity and sexual fantasies, improved the level of sexual pleasure and vaginal lubrication, and decreased dyspareunia compared to placebo [17]. Hence, only a limited number of randomized trials have investigated the effect of estrogen treatment on the sexual function in comparison to placebo. However, both studies show a positive effect. The positive effect of estrogen on FSD is further sup-

ported by studies in which the effect of estrogen has been compared to other hormone treatments [18-20].

LOCAL ESTROGEN

Estrogen can be administered vaginally as creams, pessaries, tablets or estradiol releasing ring. The local administration results in a considerable local effect but a minimal systemic effect.

A Cochrane review from 2003 of local estrogen treatment of vaginal atrophy analyzed 16 studies of 2129 surgically induced or naturally postmenopausal women. Evidence pointed towards that local estrogen treatment has a positive effect on vaginal dryness and dyspareunia regardless of application form. However, the tablets demonstrated significantly better effect compared to either creams or the vaginal ring/pessary. None of the treatments altered the sexual desire [21].

SYSTEMIC ESTROGEN AND ANDROGEN

Like estrogen, testosterone is a steroid which crosses the cell membrane and is bound to intracellular receptors after being transformed into dihydrotestosterone. Subsequently, the receptor-hormone complex penetrates the nucleus of the cell resulting in protein synthesis. Like estrogen receptors, testosterone receptors are present both in peripheral tissues and in the CNS.

Results from several studies suggest that testosterone may have a positive effect on FSD in the postmenopause. There are currently no registered hormone products with a combination of estrogen and testosterone or testosterone-only, for the treatment of menopausal symptoms. Despite this, estrogen/testosterone combinations have been used off-label for some years (e.g. in the United Kingdom, the USA and Australia).

Currently, there is an on-going discussion about the existence of an androgen deficiency syndrome, particularly in women with menopause induced by surgery, radiotherapy, or chemotherapy. Clinical observations suggest that the initial positive effect of estrogen treatment on FSD decreases with time. Based on these observations several studies have been conducted, to investigate the effect of estrogen and testosterone in different administration forms on FSD.

In 1998 Sarrel conducted a study of 20 surgically induced or naturally postmenopausal women. Despite estrogen/estrogen-progesterone treatment, all women still had menopausal symptoms, lubrication problems, dyspareunia and reduced sexual desire. Following a two week wash-out placebo period, the effect of estrogen-only treatment versus estrogen + testosterone treatment was investigated. Compared to the group receiving the estrogen-only treatment, the group receiving the combination of testosterone and estrogen treatment reported a significant improvement in sexual desire. However, there was no effect on lubrication and dyspareunia suggesting that these are primarily influenced by estrogen [22]. In a recent, double-blind randomized study of 218 surgically or naturally induced postmenopausal women with hypoactive sexual desire, it was found that estrogen and methyltestosterone treatment significantly increased both the level and frequency of the women's sexual desire compared to the estrogen-only treatment. These findings suggest a positive effect of the androgen component of the combination treatment [23]. A randomized cross-over study of 44 surgically induced menopausal women showed that treatment with estrogen-testosterone significantly improved sexual desire and pleasure compared to estrogen treatment only [24]. Finally, a randomized cross-over study of 65 surgically induced menopausal women, continually receiving estrogen treatment, demonstrated that transdermal testosterone treatment significantly improved sexual activity and pleasure/orgasm while sexual desire and arousability were not significantly improved [25]. Two large studies of 562 and 533 surgically induced menopausal women with hypoactive sexual desire disorder have recently been reported. They showed that women receiving testosterone (300 µg/day) as a transdermal patch together with concomitant oral estrogen experienced a statistically significant increase in the frequency of total satisfying sexual activity, as well as a statistically significant increase in sexual desire when compared to estrogen-only therapy. Significant improvements were also seen in arousal, orgasm, pleasure, responsiveness, concerns, self-image and distress levels for women using the female testosterone patch. Overall, adverse events were similar in the testosterone and placebo groups. Although the overall incidence of androgenic adverse events was low, the incidence was slightly higher in the testosterone group [26, 27].

TIBOLONE

Tibolone is a synthetic steroid with estrogenic- and gestagenic effects as well as a weak androgenic effect. The effect of tibolone on FSD has also been tested. Two minor, randomized placebo controlled trials have demonstrated a positive effect of tibolone regarding sexual desire, lubrication and orgasm, whereas only one of the studies has demonstrated a positive effect on dyspareunia [28, 29]. To investigate whether the androgenic effect of tibolone makes it superior to estrogen/estrogen-progesterone treatment regarding FSD, Nathorst-Böös & Hammar conducted a randomized controlled study in 315 naturally postmenopausal women. An improvement was observed in the tibolone arm regarding all measured endpoints: Sexual desire, lubrication, orgasm, pain and overall sexual satisfaction. However, comparing tibolone to estrogen-progesterone, tibolone

was only superior regarding sexual satisfaction and pleasure [19]. Two minor randomized studies have demonstrated that tibolone compared to estrogen-progesterone treatment incurs better results on sexual desire and dyspareunia [18, 20].

SILDENAFIL

Sildenafil is a phosphodiesterase 5 inhibitor (PDE5-inhibitor), which relaxes smooth muscle cells through the nitric oxide/cyclic guanosine monophosphate (cGMP) system. Sildenafil increases the vaginal blood flow leading to increased lubrication. At this background sildenafil can theoretically be expected to increase sexual pleasure and satisfaction in women with lubrication problems.

A randomized study of 204 naturally postmenopausal women, who were experiencing sexual problems and not receiving any hormone supplements, demonstrated that sildenafil treatment compared to placebo did not result in improved sexual function regarding lubrication, genital sensitivity, sexual pleasure or satisfaction with sexual life [30]. The lack of effect of sildenafil in this particular study can be attributed to the fact that the test group was very heterogeneous: All included women were complaining of arousal problems, but this was only the primary problem in approximately 50% of the women. Subsequent studies with sildenafil were conducted on women primarily experiencing arousal and orgasm problems. Berman et al observed the effect of sildenafil on FSD in 192 surgically induced or naturally postmenopausal women. The women were receiving HRT in the form of estrogen/estrogen-progesterone. Moreover, women with low levels of plasma testosterone, received testosterone treatment. The study showed that in women with arousal problems but no concomitant desire problems sildenafil improved genital sensitivity, lubrication, subjective arousal, orgasm and satisfaction with intercourse, whereas there was no effect on those women who also experienced desire problems. The same study showed no effect on desire and dyspareunia [31]. Basson & Brotto investigated 34 naturally postmenopausal women receiving estrogen-progesterone treatment for diagnosed arousal and orgasm problems. The study demonstrated that sildenafil did not improve orgasm and subjective sexual arousal, even though it was objectively measured that sildenafil increased the blood flow to the vagina during sexual stimulation [32].

In conclusion, the above studies only demonstrate a positive effect of sildenafil in a selected group of women, i.e. those with arousal problems and no concurrent desire problems. The manufacturers of the product have decided to no longer test sildenafil for treatment of sexual problems in women. It therefore remains uncertain whether there would be any beneficial effects in women experiencing sexual problems due to diseases like depression, diabetes or adverse events in connection with cancer treatment.

RISKS RELATED TO PHARMACOLOGICAL TREATMENT

Recently, adverse events to HRT have been evaluated in several large studies [33-37]. They found that HRT increased the risk of ischemic heart disease, breast cancer, stroke and pulmonary embolism. The duration of the treatment as well as socio-economic status and the presence of diabetes were significant prognostic factors regarding these complications. Treatment with tibolone seems to be associated with a lower risk of developing breast cancer compared to HRT with estrogen and progesterone but a higher risk than treatment with estrogen-only [33]. However, recently a multicenter study investigating the use of tibolone for treatment of osteoporosis in elderly women have been terminated as there were indications of a higher risk of stroke in the tibolone group compared to placebo [38]. These studies have prompted a revised official recommendation from the Danish Medicines Agency advising that short-term hormone therapy in relation to substantial discomforts experienced during and after the menopausal transition is still well-founded. Clinical recommendations from the Danish Society of Obstetrics and Gynaecology state that hormone supplements can be applied to release

FSD after the menopause [39]. The need for hormone treatment must be carefully assessed on an individual basis, taking into account possible risks relating to the individual woman. The lowest possible dose should be used and the treatment duration should be as short as possible [39, 40].

Adverse events related to local estrogen treatment are rare, but no studies have evaluated long-term effects beyond six months. One study has demonstrated that the use of estrogen cream was correlated with a significant increase in vaginal bleedings, breast tension and perianal pain compared to vaginal estradiol tablets [21].

Treatment with testosterone is based on the principle that serum levels of testosterone should be kept within upper normal range; thereby unwanted adverse events are believed to be minimized. Potential adverse events are acne, weight gain, hirsutism, voice changes and serum lipid changes. Few adverse events have been reported in those controlled studies published on testosterone treatment, given that the serum testosterone has been kept within the normal physiological level [26, 27, 41]. However, future studies are to evaluate possible long-term adverse events.

The adverse event profile of sildenafil is similar in women and men: Headache, facial flushing, dizziness, rhinitis, upper dyspepsia and visual disturbances. The adverse events are described as mild and transient in the present cited studies [30-32].

CONCLUSION

The prevalence of FSD increases with age and menopause is an independent

prognostic factor for developing FSD. The causal relations have not yet been documented, but it is suggested that hormonal factors such as reduced serum estrogen- and androgen levels are of importance.

The treatment of FSD in postmenopausal women should be based on an individual assessment where the points of reference are the woman's subjective discomforts, risk factors and potential underlying causes of the problem. If pharmacological treatment of FSD is deemed indicated, several randomized studies have demonstrated a positive effect of systemic hormone therapy with estrogen/estrogen-progesterone, combined estrogen and androgen as well as with tibolone. Moreover, local estrogen therapy has demonstrated a positive effect on vaginal dryness and dyspareunia. One study has demonstrated a significant effect of sildenafil on lubrication problems in women who are not also experiencing hypoactive sexual desire disorder.

The known side effects of hormone therapy and the comparatively sparse effect of sildenafil necessitate an intensified focus on new areas in the field of pharmacological treatment options of FSD. Internationally, most research is being conducted with testosterone but the risk of potential side effects demands long-term follow-up. In addition ongoing studies investigate the effect of tibolone on hypoactive sexual desire and lubrication problems in postmenopausal women.

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