Female sexual dysfunction in postmenopausal women: Systematic review of placebo-controlled trials

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OBJECTIVE: This systematic review includes all randomized and placebo-controlled trials (RCTs) of treatment for female sexual dysfunction (FSD) in postmenopausal women published since 1990.

STUDY DESIGN: Electronic database and manual bibliography searches were conducted to identify all relevant publications.

RESULTS: Only six RCTs have been done to assess the effects of different therapies on sexual function in postmenopausal women: one with sildenafil citrate (Viagra), three with hormone replacement therapy, and two with tibolone.

CONCLUSIONS: In women with FSD, many treatments that are used in practice are not supported by adequate evidence. Although an improvement of sexual function was reported with tibolone and the combination of estrogen-androgen therapy, it still remains unclear which groups of postmenopausal women with FSD would benefit most from these therapies. The adverse effects of testosterone replacement therapy should be assessed against the effects of placebo in RCTs with larger sample sizes and longer duration. (Am J Obstet Gynecol 2003;188:286-93.)

Key words: Postmenopausal women, female sexual dysfunction, sildenafil citrate, tibolone, hormone replacement therapy

Female sexual dysfunction (FSD) is a common clinical condition that affects the quality of life of many women.[1-4] FSD is defined as persistent or recurring reduction of sex drive or aversion to sexual activity, difficulty becoming aroused, inability to reach orgasm, and pain during sexual intercourse.[5,6] The causes of FSD are multifactorial and include hormonal changes in postmenopausal women, as well as psychologic problems such as stress, fatigue, and depression. On the basis of the National Health and Social Life Survey, nearly 50% of women in the United States have FSD.[7]

However, until recently, little clinical research has been done on FSD; therefore, our knowledge and understanding of this disorder are limited. The measurement of sexual function in women has never been an easy task. It has taken several years of different experimental approaches to establish the physiologic and subjective end points relevant to diagnose FSD. Three years ago, a new classification and diagnostic system was established by the American Foundation of Urologic Disease Consensus Panel.[5] Since then, this improved and expanded system has been used by both gynecologists and psychiatrists to diagnose women with FSD. Because of the complex nature of FSD, it is often difficult to clearly define the factors primarily responsible for the disorder, as well as to establish the meaningful steps in treatment.

Recent interest in women's health issues together with advances in modern technology and diagnostics have brought new insight to the endocrinologic, cardiovascular, neurologic, and genital changes in women in regard to their sexual response. Several investigators have discovered that the female sexual response cycle is initiated by neurotransmitter-mediated vascular and nonvascular smooth muscle relaxation that results in increased pelvic blood flow, vaginal lubrication, and clitoral and labial engorgement.[6,8] It has been proved that these mechanisms are mediated by a combination of neuromuscular and vasocongestive events, all of which are crucial in maintaining normal sexual function.[8] Therefore, all of the physiologic and psychologic impairments that interfere with the normal sexual response may lead to FSD.

FSD is a multicausal disease with many determinants. In all women, despite biological age, any chronic medical illness, specifically hypertension,[9,10] diabetes,[11] coronary artery disease, atherosclerosis and vascular

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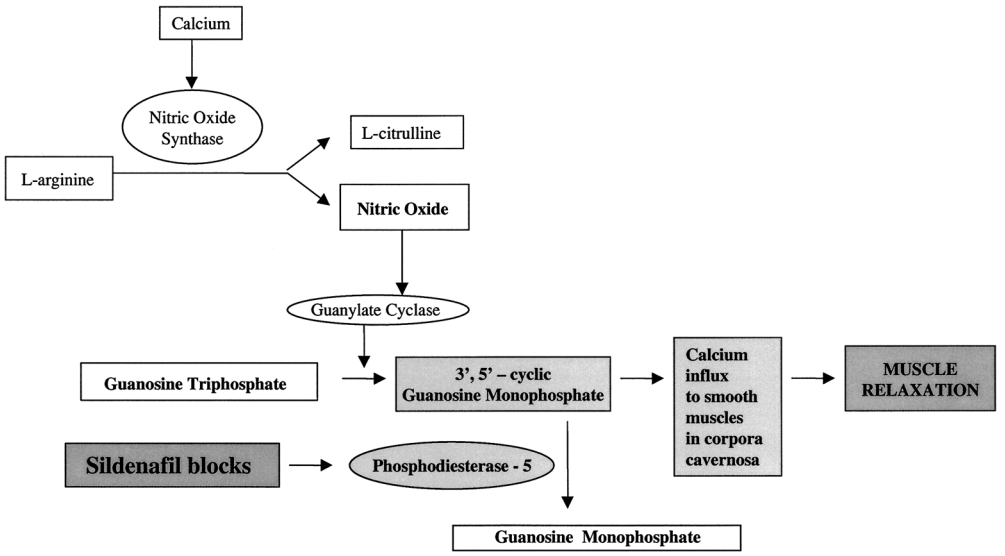

Fig 1. Sildenafil citrate mechanism of action. Sildenafil citrate blocks the activity of PDE-5, causing the accumulation of 3´,5´-cyclic guanosine monophosphate in the corpora cavernosa, which leads to muscle relaxation.

diseases,[12-16] depression,[17-19] prior pelvic trauma, current abdominal injuries,[20,21] neurologic disorders,[22] immunologic and endocrinologic disorders,[23-25] spinal cord injury,[26-28] and multiple sclerosis[29] may lead to FSD. Not forgotten is the negative impact of the use of medication to treat the above conditions. In addition, sexually transmitted diseases, particularly those associated with pain, may cause a decrease in sexual function.[30] Women with breast, cervical, or endometrial cancer may have decreased sexual function.[31-35] Women with pelvic malignancies may have fibrosis of the vaginal or bladder walls, therefore having diffuse urogenital symptoms as well as sexual function complaints related to fibrosis and vascular insufficiency.[32] Finally, women who are exposed to radiation and chemotherapy for an existing malignancy, as well as women with decreased ovarian function or premature ovarian failure, may have FSD.[36]

We performed a systematic review of randomized and placebo-controlled trials (RCTs) of treatment for FSD. We aimed to determine the effects of sildenafil citrate, different combinations of hormone replacement therapy (HRT), and tibolone on sexual function in postmenopausal women with FSD. We included only randomized and placebo-controlled trials in this review because we think these study designs are most valuable for the clinical investigation of FSD. The measurements of the effects of the different pharmaceutical compounds on frequency of sexual activities, satisfaction, and orgasm should be calculated against "the effects" of placebo because women with FSD have a high placebo response.[37] Randomization is also very important because there are many possible confounding variables among postmenopausal women with FSD, which include age (early and late postmenopausal women), general health status, use or nonuse of HRT, social status, educational level, and cultural and spiritual differences and beliefs.

This review is divided into three sections. The first section discusses the clinical effects of sildenafil on sexual function in postmenopausal women. The second section addresses the effects of "non-sildenafil" pharmacologic agents on sexual function in postmenopausal women. In this section, we have included several RCTs of the combination of estrogen-progesterone and estrogen-androgen replacement therapy, which have been used in postmenopausal women with FSD. There are no RCTs of the effects of estrogen-only replacement therapy on the sexual function in postmenopausal women. Finally, the third section discusses the effects of tibolone on sexual function in postmenopausal women with FSD.

Material and methods

A computerized search of the published literature in MEDLINE/Health STAR, PubMed@UCSF, Gallen II, and EMBASE was conducted using the following key words: sexual function, sexual dysfunction, sexuality, postmenopausal women, cancer, cardiovascular diseases, sildenafil, Viagra, nitric oxide, arginine, oxytocin, prolactin, neuroendocrine response, estrogen, testosterone, androgen, and tibolone. Journal articles published from January 1990 to February 2002 were retrieved and reviewed for content, and their references were used to identify other articles of interest. Additionally, we manually searched conference proceedings and bibliographies of published articles.

Because the aim of this review is to summarize the effects of different therapies on postmenopausal women

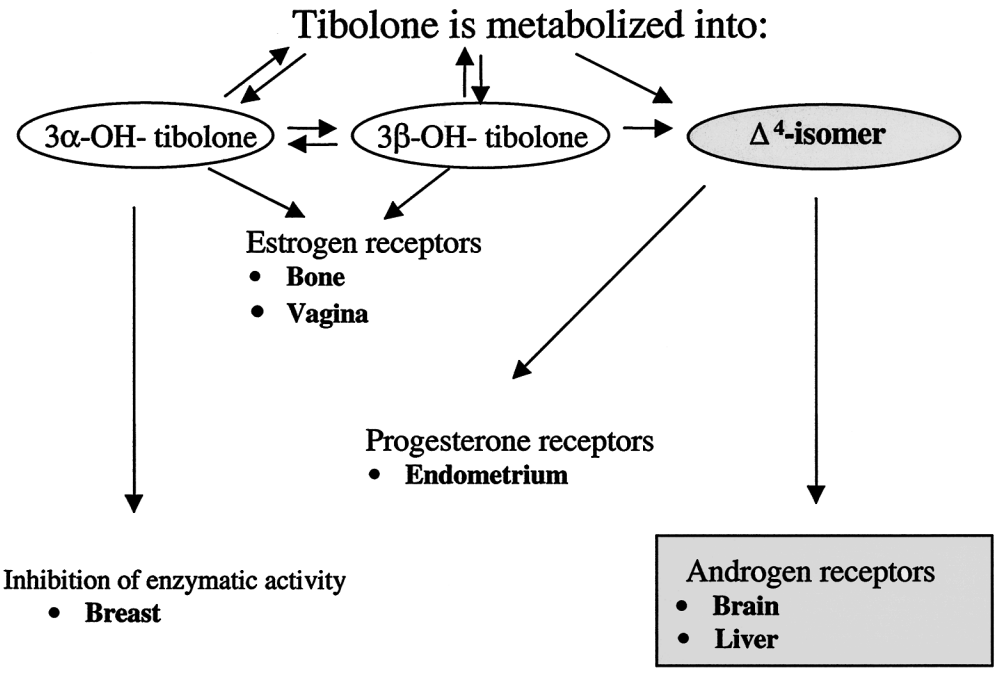

Fig 2. Tissue-specific effects of tibolone's metabolites. Tibolone is metabolized into 3α-OH-tibolone, 3β-OH-tibolone, and a Δ4-isomer. The 3α- and 3β-OH-metabolites bind to the estrogen receptors, whereas the Δ4-isomer binds to the progesterone and androgen receptors.

with FSD, we have excluded trials involving premenopausal women, nonrandomized and open-labeled studies, retrospective analyses, and trials in which the use of a placebo was not specifically stated. We also have excluded nonpharmacologic therapy, clitoral-stimulating devices, moisturizers, and lubricants.

Sildenafil citrate in postmenopausal women with FSD

Sildenafil citrate has been prescribed to more than 10 million patients for treatment of sexual dysfunction.[38-40] Sildenafil is the first selective inhibitor of phosphodiesterase 5 (PDE-5). The cellular mechanism of action of sildenafil is presented in Fig 1. The first messenger molecule, nitric oxide (NO), is produced in the nerve terminal after the influx of calcium and activation of NO synthase. NO is released from either vascular endothelium or from certain types of nonadrenergic, noncholinergic nerves. Then, NO diffuses from the nerves to the postjunctional cells and acts primarily through guanylate cyclase to trigger a rise in cyclic guanosine monophosphate (cGMP), which is the second messenger molecule. Elevated levels of cGMP cause calcium influx to smooth muscles in the corpora cavernosa (which is present in both the glans penis and the glans clitoris) and thereafter relaxation of the muscles. Sildenafil promotes erection by blocking the activity of PDE-5, which causes 3´,5´ cGMP to accumulate in the corpora cavernosa. Specifically, sildenafil competes with cGMP for binding to the catalytic site on the enzyme. In this way, sildenafil promotes relaxation by further increasing levels of cGMP in cavernous smooth muscle in response to NO or nitrates.[41-43] Peak serum levels of sildenafil after oral intake are achieved within 1 hour and the half-life of the compound is 4.5 hours.[44] Therefore, sildenafil should be taken 30 to 60 minutes before intercourse.

Several trials have shown the effectiveness of sildenafil in men with erectile dysfunction (ED) associated with prostatectomy, radiation therapy, diabetes mellitus, or certain neurologic and vascular disorders.[40,45-48] Although there have been almost 800 publications on sildenafil and sexual function, we found only one RCT of sildenafil in postmenopausal women with FSD (Table I).[49]

Six additional trials of sildenafil in women did not qualify for our review because they were either done in premenopausal women[26,52] or were open labeled and nonrandomized.[53-56] These trials concluded that sildenafil improved vaginal lubrication and clitoral sensitivity,[53] arousal, and frequency of sexual fantasies, sexual intercourse, and orgasm.[52] One trial suggested that sildenafil may partially reverse FSD in women with spinal cord injuries.[26] Another trial found that sildenafil is beneficial in reversing FSD induced by selective serotonin reuptake inhibitors.[55] In addition, another trial concluded that sildenafil causes an improvement in sexual function in men and women with antidepressant-induced sexual dysfunction.[56]

Only one trial on the effects of sildenafil qualified for our review.[49] This trial was done to evaluate the efficacy

Table I. Effects of sildenafil citrate and HRT on sexual function in postmenopausal women

Reference	*Study design*	*No. (age)*	*Duration (wk)*	*Characteristics of subjects/therapy*	*Methods of measurements*	*Change in sexual function*
Sildenafil citrate						
Basson et al (2000)[49]	Random, placebo controlled	583 (18-55 y)	12	Women with FSAD; sildenafil (10, 50, or 100 mg) vs placebo	Sexual Function Questionnaire, Life Satisfaction Checklist, and event log of sexual activity	Sildenafil did not improve sexual response in women with FSAD
HRT (estrogen-progesterone)						
Sherwin et al (1991)[50]	Random, placebo controlled	48 (47-57 y)	48	Healthy postmenopausal women assigned to 4 groups: groups A and C received 0.625 or 1.25 mg of CEE (days 1-25) and 5 mg of progesterone acetate (days 15-25); groups B and D received 0.625 or 1.25 mg CEE, respectively (days 1-25) and placebo (days 15-25)	Questionnaires (Daily menopausal rating scale, including sexual desire, menopausal index)	Significant increase in sexual desire ($P < .05$) and arousal ($P < .02$) in all women on HRT (first 2 wk of the treatment cycle) vs week 4 when no hormone was taken ($P < .05$)
HRT (estrogen-androgen)						
Sarrel et al (1998)[51]	Random, double-blind, after single-blind, placebo-controlled period	20 (45-55 y)	12	Healthy postmenopausal women; esterified estrogens 1.25 mg alone or combined with 2.5 mg methyltestosterone once daily vs placebo	Yale Midlife Survey Questionnaire	Significant improvement of sexual desire ($P < .05$) and in frequency of sexual intercourse ($P < .01$) with estrogen-androgen therapy vs estrogen alone and vs placebo baseline. No changes in orgasm, vaginal lubrication, and dyspareunia with any treatment
Shifren et al (2000)[37]	Random, double-blind, placebo-controlled trial	75 (31-56 y)	12	Women after oophorectomy and hysterectomy; estrogens (0.625 mg/d) and transdermal testosterone (150 mg/d or 300 mg/d) vs placebo	Brief Index of Sexual Functioning for Women, Psychological General Well-Being Index	Testosterone (300 mg/d) increased frequency of sexual activity and pleasure-orgasm ($P = .03$) for both comparisons with placebo. Testosterone (300 mg/d) improved the score for problems affecting sexual function vs placebo ($P = .07$)

FSAD, Female sexual arousal disorder; *CEE,* conjugated equine estrogen.

and safety of sildenafil (10, 50, or 100 mg) versus placebo in women with female sexual arousal disorder (FSAD). The results of this trial were based on several questionnaires, and they have shown that sildenafil does not improve the sexual response among women with FSAD (Table I). However, the treatment was well tolerated and there were no serious adverse events reported. Definite conclusions with regard to the effects of sildenafil on the sexual response in women with FSD need to be established in other large RCTs using the psychologic and the physiologic measurements of response to the therapy versus the effects of placebo.

HRT in postmenopausal women with FSD

Decreased sexual function in postmenopausal women is due in part to both estrogen and androgen depletion after menopause. The estrogen decline associated with menopause is a major cause of climacteric symptoms, such as vaginal atrophy, hot flushes, dyspareunia, and nocturnal awakening. Several clinical trials reported that estrogen replacement therapy (ERT) has improved sexual desire in postmenopausal women.[57-60] However, only one such trial was randomized and placebo controlled and therefore qualified for inclusion in this review.[50] This trial investigated the effects of estrogen and progestin on sexual desire, arousal, and mood in healthy postmenopausal women against placebo (Table I). Sherwin[50] has found that postmenopausal women had significantly improved sexual desire and arousal during the weeks on ERT compared with the time when no therapy was administered. However, assessments of frequency of sexual activity and orgasm were not made in this trial. The absence of a pure placebo group (the comparison was made between the "estrogen-progesterone" and "estrogen-placebo" subgroups) prevents conclusions about the effect of estrogen on sexual function in postmenopausal women.

Table II. Effects of tibolone on sexual function in postmenopausal women

Reference	*Study design*	*No. (age)*	*Duration (wk)*	*Characteristics of subjects/therapy*	*Methods of measurements*	*Change in sexual function*
Nevinny-Stickel (1983)[73]	Random, double-blind, placebo-controlled, crossover trial	35 (48-69 y)	16 wk/ period	Healthy post-menopausal women; tibolone (2.5 mg/d) vs placebo	Menopausal symptoms score (0-3 points), also measured loss of libido	No significant differences in libido vs placebo
Laan et al (2001)[74]	Random, double-blind, placebo-controlled, crossover trial	38 (>65 y)	12	Healthy post-menopausal women; tibolone (2.5 mg/d) vs placebo	VPA, sexual function questionnaires and daily diaries	Tibolone increased VPA levels ($P < .001$), arousability ($P < .01$), sexual fantasies ($P < .03$), sexual desire ($P = 0.08$), vaginal lubrication ($P < .001$) vs placebo. No change in frequency of sexual intercourse, initiation of sexual activity, and orgasm vs placebo

VPA, Vaginal pulse amplitude.

The androgen decline associated with menopause may contribute to muscle wasting, osteoporosis, loss of energy, changes in mood and depression, decreased libido, and finally impaired sexual function. After menopause, there is a decline in the adrenal and ovarian androgen production, including dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, and testosterone.[61-65] In addition, postmenopausal women who are treated with ERT have an increase in sex hormone–binding globulin (SHBG), which reduces the amount of free testosterone.

Several investigators have reported improvement in sexual function in postmenopausal women treated with the combination of estrogens and exogenous testosterone over the effects achieved with estrogen alone.[51,65-69] However, we have found only two trials of the effects of estrogen-androgen replacement therapy in postmenopausal women that qualified for inclusion into this review[37,51] (Table I). In the first trial, the combined estrogen-androgen replacement therapy significantly increased sexual sensation, desire, and frequency of sexual intercourse versus estrogen alone but did not change the frequency of sexual fantasies, vaginal lubrication, and pain during intercourse.[51] The small sample size (n = 20) has limited the power to detect significant differences in all variables that are important to assess sexual function. Also, the adverse effects and dropout rate were not reported in this trial.[51] In the second trial, there was a significant improvement in sexual function in women who were treated with transdermal testosterone (150 μg/d and 300 μg/d) versus placebo.[37] The higher testosterone dose resulted in a further increase in scores for frequency of sexual activity and orgasm. Interestingly, there was an extremely strong response in sexual function in women on placebo compared with women who received testosterone.[37] Treatment-related adverse effects of testosterone replacement, such as hirsutism, facial acne, agitation, and nipple discharge, led 24% of study participants to withdraw from this trial.[37]

The effects of tibolone on sexual function in postmenopausal women

Tibolone is a synthetic steroid that has taken a special role in the prevention of postmenopausal osteoporosis and in the treatment of climacteric symptoms, including reduced sexual function. Tibolone (Livial, Org OD14), produced by Organon (West Orange, NJ) has been used in Europe over the last 20 years. It is not yet available in the United States, but currently an RTC on the effects of tibolone in postmenopausal women is being conducted. Tibolone has tissue-specific estrogenic, progestagenic, and androgenic properties.[70-72] Specifically, after administration, tibolone is quickly metabolized into 3α-OH-tibolone and 3β-OH-tibolone compounds, which are also present in an inactive, sulfated form in the breast tissue (Fig 2).[70] The 3α- and 3β-OH-metabolites bind solely to the estrogen receptors, whereas the Δ4-isomer has affinity for progesterone and androgen receptors, but not estrogen receptors. The Δ4-isomer of tibolone is formed either from tibolone directly or from the 3β-OH-metabolites (Fig 2). This isomer stimulates androgen receptors and may play an important role in improving sexual function in postmenopausal women. This is plausible because testosterone has been shown to increase libido and frequency of sexual activities, and tibolone may have intrinsic androgenic activities.[70]

We have found two trials in which the effects of tibolone on sexual function in postmenopausal women were compared with the effects of placebo[73,74] (Table II). Nearly 20 years ago, Nevinny-Stickel[73] reported that there was no significant difference in libido in postmenopausal women on tibolone versus placebo. However, sexual function was

not the main objective of this trial; only libido was assessed. In addition, the sample size of this trial was small (n = 35), there was no washout period, and a dropout rate was not reported. Because of too many limitations of this trial, the interpretation of the final result in regard to sexual function is not meaningful. The recent placebo-controlled trial was undertaken specifically to measure sexual function in healthy postmenopausal women treated with tibolone versus placebo for 3 months.[74] According to the results of this trial, tibolone significantly improved the physiologic aspects of sexual function, such as vaginal blood flow and lubrication, as well as the subjective measures, such as sexual desire and arousability. However, the frequency of sexual function, initiation and rejection of sexual activity, and orgasm were unchanged when compared with placebo. The small sample size in the subgroups (n = 38) may have diminished the power to detect statistical differences between the groups.

The other two trials we have found on the effects of tibolone on sexual function did not qualify for this review because tibolone was compared with the combination of estradiol and noresthisterone acetate (E2/NETA).[75,76] In the first trial, Nathorst-Böös and Hammar[75] randomly assigned 437 women to receive tibolone or E2/NETA. The improvement of sexual function in regard to "frequency, satisfaction, and enjoyment" was measured in both groups. Almost 30% of the subjects dropped out and the reasons for discontinuation were unreported. In the second trial, Dören et al[76] reported that women treated with tibolone had higher free testosterone levels and lower serum SHBG levels in comparison with women treated with E2/NETA. However, sexual function was not assessed in this trial. The main problem with the interpretation of these trials is that exogenous estrogen increases SHBG and there were no placebo-controlled groups.

Finally, a recently published trial in Taiwanese postmenopausal women has reported that tibolone affected sexual function to a further extent than the combination of conjugated equine estrogen (Premarin, 0.625 mg/d) and medroxyprogesterone acetate (Provera, 5 mg/d).[77] However, this trial did not qualify for the inclusion in this review because it was an open-label, prospective, single-blind study. In addition, there was no placebo-controlled group used.

In conclusion, the effects of tibolone on sexual function in postmenopausal women versus the effects of HRT need to be assessed in other randomized and placebo-controlled trials. It will be important to determine whether tibolone improves sexual function by increasing free testosterone in women with very low testosterone concentrations and significantly decreased libidos.

Comment

Nearly 50% of postmenopausal women in the United States have FSD, and many of these women seek medical consultation.[1,7,78] Although the prevalence of FSD among postmenopausal women is very high, information about treatment is very limited. In addition, many treatments that are used in practice are not supported by adequate evidence. Our search did not only include RCTs done on postmenopausal women treated with sildenafil, HRT, or tibolone therapy; we also sought evidence concerning the impact of other medications approved to treat FSD. Surprisingly, we have not found any other trials that were randomized, double-blinded, and placebo-controlled in design, therefore qualifying for inclusion in our review.

There are several hypotheses about the effects of different drugs on sexual function in postmenopausal women. First, several studies have shown that the selective estrogen receptor modulators (SERMs), such as raloxifene or tamoxifen, improve the health-related quality of life.[79-81] Therefore, it is plausible that SERMs may also improve libido and sexual function in postmenopausal women.[82] However, we have not found any published RCTs on the effects of SERMs on sexual function in postmenopausal women. Another hypothesis is that any compounds that increase NO synthesis, such as L-arginine, may also improve sexual function because several studies in men have shown that NO is an important messenger in sexual function.[83,84] (Fig 1). We have not found any RCTs on the effects of L-arginine on sexual function in postmenopausal women with FSD. In addition, α-adrenergic receptor modulators, such as phentolamine, clonidine,[85] and mitrazapine,[86] may affect sexual function by increasing pelvic blood flow, arousal, and sexual satisfaction. Again, we have not found any RCTs on these compounds that assess sexual function in postmenopausal women with FSD. Finally, studies have shown that prostaglandin E_1 (PGE_1) stimulates cyclic adenosine monophosphate production and intracellular calcium ion concentration (Fig 1) and may therefore increase sexual function. PGE_1 was tested in men with ED,[87] but there are no published RCTs to assess the use of PGE_1 in postmenopausal women with FSD.

The limitation of this review is the fact that we did not attempt a meta-analysis because there were substantial methodological differences between the few RCTs we included. The measurements of sexual function (changes in desire, arousal, frequency of intercourse, orgasm) were done using different scores and different scales. In addition, the trials differed in regard to patient age (naturally vs. surgically menopausal women), methods of measurements, demographics, and inclusion and exclusion criteria.

In summary, only six RCTs have been conducted to assess the effects of different therapy regimens in postmenopausal women with FSD.[37,49-51,73,74] However, because of the many limitations of these trials, it is still unknown which group of postmenopausal women with FSD would benefit most from the therapy with sildenafil, HRT, or tibolone. In addition, the adverse effects of testosterone replacement therapy should also be assessed against the effects of placebo in larger RCTs. Finally, de-

finitive conclusions about the treatment of women with FSD need to be established in additional RCTs with larger sample sizes and longer duration. Currently, a number of investigators have trials underway to determine the effects of different compounds on sexual function in postmenopausal women. Perhaps they will provide guidance and new proven approaches in the treatment of postmenopausal women with FSD.

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