Orgasm - a psychophysiology-based approach to hormonal and non-hormonal medical strategies to manage orgasmic disorders in women

Johannes Bitzer

University Hospital Basel, Department Obstetrics and Gynecology, Switzerland

ABSTRACT

Background: Orgasm is a complex psychophysiological component of the human sexual response that involves different organ systems and central nervous system regulatory processes.

As part of the human sexual response, it is strongly linked to sexual desire and arousal.

With regard to hormonal and non-hormonal pharmacological approaches, most studies reporting treatment effects on orgasmic dysfunction are in women with concomitant desire and arousal disorders. On the basis of their action, these approaches can be divided into the following types.

- *Enhancement of the afferent part of the spinal orgasmic reflex by improving the intensity of the sexual stimulus and/or increasing the receptivity to the stimulus (this demands structural integrity of vulva and vagina, blood flow to the vulva and the vagina)*

These effects are provided by local estrogens, testosterone, Dihydroepiandrosterone (DHEA), non-hormonal lubricants, medicaldevices.

- *Enhancement of the efferent pathway by noradrenergic/cholinergic activation and/or enzymatic action on the guanosine monophosphate (GMP) system.*

Drugs acting at this level are mainly PDE-5 inhibitors, vasodilators, specific prostaglandins

- *Medical interventions (drugs) targeting brain centers which either increase central excitation or decrease nervous inhibition*

Systemic estrogen/androgens act via central nervous receptors directly and indirectly through activation of neurotransmitters; centrally-acting drugs include bupropion, buspirone, flibanserin and melanocortin

These approaches can also be used in women without desire and arousal disorder.

In addition to these approaches, for women experiencing sufficient arousal but reporting inhibition at the plateau level, medical devices like Eros and Fiera have shown pro-orgasmic effects.

KEYWORDS

Female orgasm disorder, neurophysiology, medical treatment.

Introduction

Orgasm can be understood as a complex summation reflex that is regulated by both the somatic and autonomic nervous systems linked to central nervous processing regions.

On the basis of this concept two major approaches in research and clinical practice can be distinguished, which serve as the basis for diagnosis and therapy. One sees orgasm as a biological process involving different organ systems and networks, while the other sees it as a subjective experience.

a) Orgasm as a biological process involving different organ systems and networks [1-4]

Afferent pathways

The pudendal nerve relays sensory stimuli from the external genitals, the perineum, clitoris and urethra, and the pelvic floor musculature. The pelvic and hypogastric nerves mediate sensory information from the internal pelvic organs. Light touch, noxious and/or chemical stimuli of the vulva, vagina, cervix, and uterus are primarily mediated via the pelvic nerve. Another afferent pathway in animal research is the vagus nerve which conveys sensory information from female pelvic organs to nuclei in the brainstem.

It is important to note that these main afferents are sensitive to the levels of steroid hormones.

Spinal centers

The pudendal nerve afferents enter the spinal cord through the superficial dorsal horn of segments L6-S1 (in humans S2-S4) and travel through the medial dorsal horn to the dorsal gray

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Contact
Johannes Bitzer; johannes.bitzer@hin.ch
Department of Obstetrics and Gynecology University Hospital Basel, Basel, Switzerland

commissure which is located in the medial cord. The hypogastric nerve afferents terminate in the medial dorsal horn and medial gray of spinal segments T13-L3. The spinothalamic and spinoreticular pathways relay sensory information to the brain. Descending pathways travel through the same structures.

Efferents mediating genital responses

The efferent fibers of the pudendal nerve provide innervation of the pelvic floor and anal and urethral sphincters. The pudendal motor neurons are located in the ventral horn of the lumbar spinal cord in Onuf's nucleus. The pelvic nerve is composed of parasympathetic preganglionic neurons (the sacral parasympathetic nucleus), located primarily in the lumbosacral spinal cord.

The hypogastric nerve is composed of sympathetic preganglionic neurons in the upper lumbar spinal cord. The preganglionic neurons arise from the medial and intermediolateral cell columns.

Supraspinal control

- Inhibition

  The nucleus paragigantocellularis (NPGC) exerts inhibition of spinal sexual reflexes in males and females. The NPGC projects directly to pelvic efferent neurons. Serotonin is the main neurotransmitter in this system with an inhibitory action.
- Stimulation

  The medial preoptic area (MPOA) plays an important role especially in males but also in females. Stimulation of this nucleus and injection of galanin into the MPOA facilitates some female sexual behaviors in animal research. There is no direct connection between the MPOA and the lumbosacral centers, but the MPOA sends information through a relay to hypothalamic and brainstem nuclei.

The endocrine environment

Sex steroids, interacting with receptors in the brain, provide the endocrine milieu. Estrogens (mainly estradiol) have central nervous system effects which seem to increase receptivity to sexual stimuli and facilitate permissive behavior in animal research. Peripheral effects of estrogens are important in maintaining vulvovaginal structural integrity and facilitating blood flow to the vagina. Testosterone has a central excitatory and activating effect on the limbic system, including brain centers linked to sexual motivation. In animal research this is related to proactive search for sexual clues. The role of progesterone is still not completely elucidated, but it seems to be directed mainly towards reproductive function. Circulating levels of prolactin, vasopressin, oxytocin, adrenalin and vasointestinal polypeptide have been reported to increase with orgasm. Prolactin increases with orgasm are maintained for approximately 60 minutes after orgasm.

Central modulatory input

Several nuclei in the brainstem including the NPGC , the raphe nuclei pallidus and the locus ceruleus project to pelvic efferent neurons and interneurons in the lumbosacral spinal cord, most likely to modulate lumbosacral spinal cord reflexes.

The periaquaductal gray matter of the midbrain is heavily interconnected with the brainstem and hypothalamic sites related to sexual behavior, seemingly serving as a relay center. Within the hypothalamus, the medial preoptic area, nucleus paraventricularis and the ventromedial nucleus are believed to have major roles in female sexual function. During orgasm, activation of the mesodiencephalic transition zone can be observed. Serotonin, dopamine, epinephrine, opioids are neurotransmitters and neuropeptides that modulate female sexual function. In the context of dual control of human sexual behavior, these molecules act either as excitatory signals (epinephrine, dopamine) or as inhibitory signals (serotonin, opoids)

b) Orgasm as a subjective experience

According to Mah and Binik, [5] the subjective experience of orgasm can be broken down into three elements: sensory, evaluative and affective.

- Sensory components are the build-up of tension, release of tension, spreading sensations, whole body involvement, ejaculatory sensations, rhythmic sensations, thermal sensations, miscellaneous.
- Evaluative components are the feeling of inevitability, temporal evaluation, intensity, physical effects, depth, global pleasure, sensual pleasure, satisfaction and excitement.
- Affective items are emotional intimacy, joy-peacefulness, joy-elation, emotional excitation, emotional fusion, unreality, lack of awareness of surroundings, suspension, miscellaneous.

Orgasmic disorders

Female orgasmic disorders (FOD) are absence of orgasm, difficulty experiencing orgasm, or decreased intensity of orgasm during all or most episodes of sexual activity. [6] The symptoms can be lifelong or acquired. Difficulty reaching orgasm might be isolated to specific sexual activities, situations or partners. The symptoms must be distressing to the individual.

A few subtle but important differences distinguish the diagnostic criteria for FOD as reported in the DSM-IV-TR and DSM-5. A significant change in the DSM-5 was the removal of the criterion requiring that difficulty with orgasm occur despite "a normal excitement phase." [6]

The diagnosis is thus based mainly on the subjective experience. The objective criteria are summarized by Meston *et al*. [7]

Medical treatment of orgasmic disorders

With regard to the medical treatment of orgasmic disorders, clinical situations can be divided into two types:

- medical treatment of orgasmic disorder in the context of desire/arousal disorders
- medical treatment of orgasmic disorder in women without desire/arousal disorders

In clinical practice the hormonal and non-hormonal pharmacological treatment of orgasmic disorders is based on studies that fail to differentiate clearly between these groups. Therefore treatment strategies and options overlap.

Medical treatment of orgasmic disorders in the context of desire/arousal disorders.

Most of the drugs summarized below are studied in the context of desire and arousal disorders. In this setting, orgasmic function is measured as a secondary outcome looking for an increase in orgasmic capacity (frequency, intensity).
The following approaches can be distinguished:

Enhancement of the afferent part of the spinal orgasmic reflex by improving the intensity of the sexual stimulus and/or increasing the receptivity to the stimulus (structural integrity of vulva and vagina, blood flow to the vulva and the vagina).

- Local estrogen therapy
  Local estrogen therapy (LET) increases blood flow in the microcirculation of the vagina, leading to vasocongestion (experimental studies) [8] LET improves vulvovaginal integrity in menopausal women with vulvovaginal atrophy syndrome (VVA) and VVA-related sexual arousal and pain symptoms (RCTs, guidelines) [9-11]. The extent to which pain symptoms contribute to orgasmic dysfunction may not be easy to discern.
- Local estrogen and testosterone
  A clinical trial [12] showed improvement in all domains of the Female Sexual Function Index (FSFI) in women receiving local estrogen or testosterone compared to placebo lubricant.
- Dihydroepiandrosterone DHEA
  Randomized controlled trials (by one group) [13,14] showed improvement of the integrity of the mucosa and the connective tissue and showed a positive effect on arousal. In a review Davis *et al*. [15] found no clear evidence suggesting a prosexual effect in postmenopausal women.

Enhancement of the efferent pathway by noradrenergic/cholinergic activation and or enzymatic action on the guanosine monophosphate (GMP) system.

- Phentolamine
  Phentolamine is an a1 and a2 adrenergic agonist tested in a small pilot study with a low level of evidence. [16] The participants were postmenopausal women with a lack of lubrication and with sexual arousal difficulties of at least 6 months' duration. All subjects received a single dose of oral phentolamine (40 mg) and placebo in a single-blind, dose-escalation design. Dependent variables for the study included vaginal pulse amplitude, measured by means of vaginal photoplethysmography, self-report measures of sexual response, and patient- and physician-based assessments of adverse events. The results indicated a mild, positive effect of phentolamine across all measures of arousal, with significant changes ($p < .05$) in self-reported lubrication and pleasurable sensations in the vagina.
- Cholinergic drugs
  Betanechol is a cholinergic agonist. It was investigated in male patients with depression treated with an SSRI (clomipramine) and suffering from ejaculatory delay. [17] 12 fully remitted panic disorder patients, complaining of severe clomipramine-induced ejaculatory delay, were randomly assigned to either bethanecol chloride tablets (20 mg, as needed) or placebo according to a randomized, double-blind, placebo-controlled, two-period crossover design. A visual analog scale was used to assess severity of the orgasmic dysfunction. A clear improvement was observed in the active treatment period. No placebo or carry-over effects were observed. To date, there are no published studies in females.
- PDE-5 inhibitors
  These drugs increase vaginal blood flow via the GMP system (see above). One RCT, a randomized cross over study with sildenafil, showed improvement in arousal and orgasmic function. [18] The authors of a larger study reviewed a total of 16 studies. Studies using self-reported measures of sexual functioning showed mixed results whereas ones examining physiological effects of Phosphodiesterase-5 inhibitors PDE-5 on genital vasocongestion consistently reported significant effects on genital sexual response. [19]
- Topical alprostadil
  This drug acts on vasodilation and vasocongestion in the vagina. A review found that in-clinic application of alprostadil increased genital vasocongestion, vaginal erythema, transudates, and some patient-assessed indices of sexual arousal; however, these effects were not consistently superior to placebo. Three out of 4 trials investigating at-home use of topical alprostadil demonstrated improvements in achievement of satisfactory levels of sexual arousal and successful sexual encounters in patients with female sexual arousal disorder (FSAD). [20]

Medical interventions (drugs) targeting brain centers that either increase central excitation or decrease central inhibition

- Systemic estrogen and testosterone therapy
  Systemic estrogen, systemic testosterone, and combined estrogen and testosterone therapy decrease arousal dysfunction, increase desire and improve orgasmic function in premenopausal and postmenopausal women and in women after unilateral or bilateral oophorectomy. These effects are due, on the one hand, to the permissive and receptive central nervous system effects and the positive effects on vulvovaginal structure and function of estrogens, and on the other to the activating and excitatory effect of testosterone on the limbic system of the brain (RCTs, level of evidence 1). [21-34]
- Tibolone
  Combined estrogenic, progestogenic and androgenic action (RCTs, level of evidence 1), [35-38] increasing desire, arousal and orgasm.
- Bupropion
  Buproprion acts via dopamine and norepinephrine reuptake inhibition and does not have a direct serotoninergic effect (RCTs, mild to moderate effect). [39- 41]
- Flibanserin
  5-hydroxytryptamine (5-HT)1A agonist and 5-HT2A antagonist, binding also with moderate affinity to 5-HT2B, 5-HT2C and dopamine D4 receptors. RCTS and reviews show significant effect. [42-51]
- Buspirone
  5-HT1 agonist possibly producing some oxytocin activation. Some evidence of prosexual effects in patients treated with SSRIs for depression. [52]
- Vilazodone
  Partial HT1A agonist. (see above)
- Melanocortin agonists [53]
  Bremelanotide is a melanocortin-3 and 4 agonist with an activating effect on arousal pathways (basic science studies, dose-finding studies, RCTs). Preliminary studies are ongoing;

these show prosexual effects in men and women (Phase II studies) [54- 58]

- Apomorphine

  Apomorphine is a non-selective dopaminergic receptor agonist (1 RCT showing prosexual effects) [59]. However, the occurrence of significant nausea and vomiting have prevented its further development.

Drugs with unspecific effects

- Lady Prelox

  20 mg Pycnogenol® pine bark extract, 200 mg L-arginine, 200 mg L-citrulline and 50 mg Rosvita® rose hip extrac (2 observational studies showing small group prosexual effects, low level of evidence). [60,61]

  Lady Prelox is a dietary supplement which was given to 100 women in a healthy lifestyle intervention where sexual function was evaluated using the FSFI in part of the sample (30 women). This is an uncontrolled observation with very low level of evidence.

- Gingko biloba

  Gingko biloba may have an effect on blood flow (central, peripheral). An RCT failed to show a significant effect if when was applied alone but supportive effect in the context of counseling. [62]

- ArginMax

  This is a blend of Ginseng, Ginkgo biloba, damiana leaf and vitamins. (1 RCT showed it to be superior to placebo, but the difference was not statistically significant). [63]

Short-acting drugs for "on demand" treatment

- Oxytocin

  Oxytocin (OXT) may work synergistically with sex hormones to facilitate muscle contractions during orgasm. Oxytocin is secreted by the paraventricular nucleus of the hypothalamus into the bloodstream during arousal and orgasm, and it is thus considered a facilitator of arousal and orgasm. [64]

A study involving 29 healthy heterosexual couples (n=58 participants), studied in a naturalistic setting, explored the effects of intranasally administered OXT (24 IU) on sexual drive, arousal, orgasm and refractory aspects of sexual behavior together with partner interactions. Data were assessed using psychometric instruments (Acute Sexual Experiences Scale, Arizona Sexual Experience Scale) as well as biomarkers, such as cortisol, α-amylase and heart rate.

Intranasal OXT administration did not alter "classical" parameters of sexual function, such as sexual drive, arousal or penile erection and lubrication. However, analysis of variance and a hierarchical linear model (HLM) revealed specific effects related to the orgasmic/post-orgasmic interval as well as parameters of partner interactions. According to HLM analysis, OXT increased the intensity of orgasm, contentment after sexual intercourse and the effect of study participation. According to ANOVA analysis, these effects were more pronounced in men. Men additionally indicated higher levels of sexual satiety after sexual intercourse with OXT administration. Women felt more relaxed and subgroups indicated better abilities to share sexual desires or to empathize with their partners. The effect sizes were small to moderate. [65] Thus, OXT can be considered a facilitator of arousal and orgasm. [64, 65] The compound's instability at room and body temperature severely limits its utility under real-world conditions.

Combination of short-acting drugs on demand

This therapeutic concept is based on the different prosexual actions of testosterone (central effect), sildenafil (peripheral effect) and buspirone (dopaminergic and specific 5HT receptor action). Treatment combinations have been tested based on the dual control model, looking into differential effects of drug combinations in women with low and high inhibition. [66, 67] The combination of testosterone sublingually (0.5mg) with buspirone (10mg) showed a prosexual effect in women most probably by reducing inhibition. [68] The combination of testosterone sublingually (0.5mg) with the PDE5-inhibitor sildenafil 50mg) also showed prosexual effects significantly over placebo, most probably mediated by activation of the peripheral response (excitatory effect). [69]

Medical treatment of orgasmic disorder in women with subjectively sufficient arousal

These treatments are based on studies performed in women with the main complaint of not being able to experience/attain an orgasm despite the fact that they feel desire and subjective excitement and arousal. There are very few studies that include women with an isolated orgasmic difficulty.

The underlying pathophysiology can be described as an interruption of or decline in the process of growing intensity of arousal towards the development of the orgasmic response beyond what has been described as plateau phase. Physiological treatments targets therefore consist of:

- Intensification of the arousal stimulus (strength, frequency, additional stimuli) through lubricants and moisturizers and specific sexual response-enhancing topical products. Zestra, for example, is an over-the-counter massage oil of a blend of borage seed oil, angelica extract, evening primrose oil, coleus extract and vitamins C and E, and it was designed to increase blood flow to the clitoris, labia and vaginal opening. Borage oil and evening primrose oil both contain high amounts of gamma-linolinic acid, which is metabolized to prostaglandin E1, angelica root contains osthole, which increases cGMP and cAMP, and the components of coleus extract are adenylate cyclase stimulants. In a small, randomized, double-blind placebo controlled, two-way crossover study [70] of 10 women with FSAD and 10 women without FSAD, this topical application was associated with increases in levels of arousal, desire, ability to have orgasm, and sexual pleasure and satisfaction, in both the normal and the FSAD-affected women when compared with placebo. Women with FSAD showed a greater response than women without the condition, and women using SSRIs had the same improvement as women not using antidepressants
- PDE5-inhibitors and prostaglandins. (as decribed above). The drug most used in studies is siledenafil and alprostadil (see above)

• Medical devices

Medical devices may work through vibratory stimulation or by causing clitoral vascular engorgement using a vacuum system. While a number of vibratory stimulating devices are available, only one U.S. Food and Drug Administration (FDA) cleared-to-market device is available by prescription to treat FSD: the Eros® Therapy device (UroMetrics, Inc., St. Paul, Minn., USA). Eros® is a small, battery-powered appliance used to gently apply direct vacuum over the clitoris causing the clitoral erectile chambers and labia to fill with blood. The vibration from the suction pump may also aid in stimulation.

• Fiera™

Fiera Arouser for Her™, abbreviated as simply-- Fiera™ (Nuelle, Inc.) is the first wearable "intimacy enhancer". The device consists of a small, rechargeable, battery operated, vibrating device which "adheres" to a woman's clitoris by gentle suction (i.e. it is hands free). It is worn in preparation for sexual activity. The device is meant to decrease the time to orgasm by providing added stimulation time before foreplay.

Conclusions

Hormonal and non-hormonal pharmacologic strategies for managing orgasmic disorders in women are based on an understanding of the psychophysiology of the orgasmic phase of the human sexual response.

These strategies include enhancement of the afferent stimulatory signals of the orgasmic reflex through facilitation of the tissue and neurovascular response (local hormonal and non-hormonal treatments, medical devices), enhancement of the efferent action of neurovascular and neuromuscular activation (vasodilatation), modulation of the central processing response by increasing excitatory neurotransmission and decreasing inhibitory signals by means of centrally acting drugs (e.g. systemic estrogen and testosterone therapy and drugs interacting with serotonin, dopamine, noradrenaline, melanocortin, oxytocin and neurosteroid pathways).

There is good evidence that effective medical treatment of desire/arousal disorder increases the chances of orgasmic response in the individual woman.

With regard to the medical treatment of isolated orgasmic dysfunction more research and clinical trials are needed.

References

1. Salonia A, Giraldi A, Chivers ML, et al. Physiology of women's sexual function: basic knowledge and new findings. J Sex Med. 2010;7:2637-60.
2. Levin RJ. The pharmacology of the human female orgasm - its biological and physiological backgrounds. Pharmacol Biochem Behav. 2014;121:62-70.
3. Maravilla KR, Yang CC. Magnetic resonance imaging and the female sexual response: overview of techniques, results, and future directions. J Sex Med. 2008;5:1559-71.
4. Pfaus JG. Pathways of sexual desire. J Sex Med. 2009;6:1506-33.
5. Mah K, Binik Y The nature of human orgasm: a critical review of major trends. Clin Psychol Rev. 2001;21:823-56.
6. Kingsberg SA, Althof S, Simon JA, et al. Female sexual dysfunction-medical and psychological treatments, committee 14. J Sex Med. 2017;14:1463-91.
7. Meston CM, Levin RJ, Sipski ML, Hull EM, Heiman JR. Women's orgasm. Annu Rev Sex Res. 2004;15:173-257.
8. Nappi RE, Polatti F. The use of estrogen therapy in women's sexual functioning. J Sex Med. 2009;6:603-16.
9. Sturdee DW, Panay N; International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric. 2010;13:509-22.
10. Rees M, Perez-Lopez FR, Ceasu I, et al. EMAS clinical guide: low-dose vaginal estrogens for postmenopausal vaginal atrophy. Maturitas. 2012;73:171-4.
11. NAMS. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause. 2013;20:888-902.
12. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med. 2014;11:1262-70.
13. Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause. 2009;16:923-31.
14. Labrie F, Archer D, Bouchard, et al. Lack of influence of dyspareunia on the beneficial effect of intravaginal prasterone (dehydroepiandrosterone, DHEA) on sexual dysfunction in postmenopausal women. J Sex Med. 2014;11:1766-85.
15. Davis SR, Panjari M, Stanczyk FZ. Clinical review: DHEA replacement for postmenopausal women. J Clin Endocrinol Metab. 2011; 96:1642-53.
16. Rosen RC, Phillips NA, Gendrano NC III, Ferguson DM. Oral phentolamine and female sexual arousal disorder: a pilot study. J Sex Marital Ther. 1999;25:137-44.
17. Berni M, Vieira AHG, Nunes PV. Bethanol chloride for treatment of clomipramine- induced orgasmic dysfunction in males. Rev Hops Clin Fac Med S Paulo. 2004 ; 59:357-60.
18. Chivers ML, Rosen RC. Phosphodiesterase type 5 inhibitors and female sexual response: faulty protocols or paradigms? J Sex Med. 2010;7:858-72.
19. Caruso S, Intelisano G, Farina M, Di Mari L, Agnello C. The function of sildenafil on female sexual pathways: a double-blind, cross-over, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2003;110:201-6.
20. Kielbasa LA, Daniel KL. Topical alprostadil treatment of female sexual arousal disorder. Ann Pharmacother. 2006;40:1369-76.
21. Gast MJ, Freedman MA, Vieweg AJ, De Melo NR, Girão MJ, Zinaman MJ; Dyspareunia Study Group. A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women.. Menopause. 2009;16:247-56.
22. Davis SR, Braunstein GD. Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. J Sex Med. 2012;9:1134-48.
23. Somboonporn W, Davis S, Seif MW, Bell R. Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev. 2005;4:CD004509.
24. Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:3489-510.
25. Kingsberg S, Shifren J, Wekselman K, et al. Evaluation of the clinical relevance of benefits associated with transdermal testosterone treatment in postmenopausal women with hypoactive sexual desire disorder. J Sex Med. 2007;4:1001-8
26. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. Obstet Gynecol. 2005;105:944-52.
27. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab. 2005;90:5226-33.
28. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause. 2006;13:770-9.

29. Davis SR, Moreau M, Kroll R, et al. APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008;359:2005-17.
30. Panay N, Al-Azzawi F, Bouchard C. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. Climacteric. 2010;13:121-31.
31. Davis S, Papalia MA, Norman RJ, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. Ann Intern Med. 2008;148:569-77.
32. Fooladi E, Bell RJ, Jane F, et al. Testosterone improves antidepressant emergent loss of libido in women: findings from a randomized, double blind, placebo-controlled trial. J Sex Med. 2014;11:831-9.
33. Nastri CO, Lara LA, Ferriani RA, et al. Hormone therapy for sexual function in perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2013;6:CD00967.2
34. Alexander JL, Kotz K, Dennerstein L, et al. The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. Menopause. 2004;11:749-65.
35. Biglia N, Maffei S, Lello S, Nappi RE. Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials. Gynecol Endocrinol. 2010;26:804-14.
36. Davis SR. The effects of tibolone on mood and libido. Menopause. 2002;9:162-70.
37. Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric. 2001;4:28-41.
38. Nijland EA, Weijmar Schultz WC, Nathorst-Boos J, et al. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. J Sex Med. 2008;5:646-56.
39. Modell JG, May RS, Katholi CR. Effect of bupropion-SR on orgasmic duysfunction in non deperessed subjects; a pilot study J Sex Marital Ther. 2000; 26:231-40.
40. Safarinejad MR, Hosseini SY, Asgari MA, et al. A randomized, doubleblind, placebo-controlled study of the efficacy and safety of bupropion for treating hypoactive sexual desire disorder in ovulating women. BJU Int. 2010;106:832-9.
41. Clayton AH, El Haddad S, Iluonakhamhe JP, et al. Sexual dysfunction associated with major depressive disorder and antidepressant treatment. Expert Opin Drug Saf. 2014;13:1361-74.
42. Flibanserin Clayton AH, Dennerstein L, Pyke R, Sand M. Flibanserin: a potential treatment for Hypoactive Sexual Desire Disorder in premenopausal women. Womens Health (Lond). 2010;6:639-53.
43. Simon JA, Kingsberg SA, Shumel B, et al. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. Menopause. 2014;21:633-40.
44. Thorp J Jr, Palacios S, Symons J, et al. Improving prospects for treating hypoactive sexual desire disorder (HSDD): development status of flibanserin. BJOG. 2014;121:1328-31.
45. Reviriego C. Flibanserin for female sexual dysfunction. Drugs Today (Barc). 2014;50:549-56.
46. DeRogatis LR, Komer L, Katz M, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET study. J Sex Med. 2012;9:1074-85.
47. Thorp J, Simon J, Dattani D, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012;9:793-804.
48. Jayne C, Simon JA, Taylor LV, et al. SUNFLOWER study investigators. Open-label extension study of flibanserin in women with hypoactive sexual desire disorder. J Sex Med. 2012;9:3180-8.
49. Katz M, Derogatis L, Ackerman P, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med. 2013;10:1807-15.
50. Nappi R, Dean J, van Lunsen H, et al. Efficacy of continued flibanserin as a potential treatment for Hypoactive Sexual Desire Disorder in European pre-menopausal women: results from the ORCHID trial. J Sex Med. 2009;6(Suppl 5):409.
51. Goldfischer E, Cotton D, Miki J, et al. Efficacy of continued flibanserin treatment on sexual desire and satisfying sexual events in premenopausal women with Hypoactive Sexual Desire Disorder: results from the ROSE study. J Sex Med. 2008;5(Suppl 3):174.
52. Belkin ZR, Krapf JM, Goldstein AT. Drugs in early clinical development for the treatment of female sexual dysfunction. Expert Opin Investig Drugs. 2015;24:159-67.
53. Pfaus J, Giuliano F, Gelez H. Bremelanotide: an overview of preclinical CNS effects on female sexual function. J Sex Med. 2007;4(Suppl 4):269-79.
54. Safarinejad MR. Evaluation of the safety and efficacy of bremelanotide, a melanocortin receptor agonist, in female subjects with arousal disorder: a double blind placebo-controlled, fixed dose, randomized study. J Sex Med. 2008;5:887-97.
55. Portman DJ, Edelson J, Jordan R, et al. Bremelanotide for hypoactive sexual desire disorder: analyses from a phase 2B dose-ranging study. Obstet Gynecol. 2014;123(Suppl 1):31S.
56. Derogatis LR, Edelson J, Jordan R, et al. Bremelanotide for female sexual dysfunctions: responder analyses from a phase 2B dose-ranging study. Obstet Gynecol. 2014;123(Suppl 1):26S.
57. Kingsberg S, Derogatis LR, Edelson J, et al. Distress reduction in female sexual dysfunctions: a dose-ranging study of subcutaneous bremelanotide. Obstet Gynecol. 2014;123(Suppl 1):29S-30S.
58. Bechara A1, Bertolino MV, Casabé A et al A double-blind randomized placebo control study comparing the objective and subjective changes in female sexual response using sublingual apomorphine.. J Sex Med. 2004;1:209-14.
59. Bottari A1, Belcaro G, Ledda A, et al Lady Prelox® improves sexual function in post-menopausal women. Panminerva Med. 2012;54(1 Suppl 4):3-9.
60. Bottari A, Belcaro G, Ledda et al: Lady Prelox® improves sexual function in generally healthy women of reproductive age Minerva Ginecol. 2013;65:435-44.
61. Meston CM1, Rellini AH, Telch MJ.Short- and long-term effects of Ginkgo biloba extract on sexual dysfunction in women. .Arch Sex Behav. 2008;37:530-47.
62. Ito TY, Trant AS, Polan ML: A double-blind placebo controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. J Sex Marital Ther. 2001;27:541-9.
63. Magon N, Kalra S. The orgasmic history of oxytocin: Love, lust, and labor. Indian J Endocrinol Metab. 2011;15 (Suppl 3):S156-61.
64. Behnia B, Heinrichs M, Bergmann W, et al. Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. Horm Behav. 2014;65:308-18.
65. Bloemers J, van Rooij K, Poels S, et al. Toward personalized sexual medicine (part 1): integrating the "dual control model" into differential drug treatments for hypoactive sexual desire disorder and female sexual arousal disorder. J Sex Med. 2013;10:791-809.
66. van Rooij K, Poels S, Worst P, et al. Efficacy of testosterone combined with a PDE5 inhibitor and testosterone combined with a serotonin (1A) receptor agonist in women with SSRI-induced sexual dysfunction. A preliminary study. Eur J Pharmacol. 2015;753:246-51.
67. van Rooij K, Poels S, Bloemers J, et al. Toward personalized sexual medicine (part 3): testosterone combined with a Serotonin1A receptor agonist increases sexual satisfaction in women with HSDD and FSAD, and dysfunctional activation of sexual inhibitory mechanisms. J Sex Med. 2013;10:824-37.
68. van der Made F, Bloemers J, Yassem WE, et al. The influence of testosterone combined with a PDE5- inhibitor on cognitive, affective, and physiological sexual functioning in women suffering from sexual dysfunction. J Sex Med. 2009;6:777-90.
69. Ferguson DM, Steidle CP, Singh GS, Alexander JS, Weihmiller MK, Crosby MG. Randomized, placebo-controlled, double blind, crossover design trial of the efficacy and safety of Zestra for Women in women with and without female sexual arousal disorder. J Sex Marital Ther. 2003;29(Suppl 1):33-44.
70. Ferguson DM, Hosmane B, Heiman JR: Placebo controlled double blind parallel design trial of the efficacy and safety of Zestra in Women with mixed desire, interest, arousal, orgasm disorder JSMT. 2010;36:66-86.