

## **Female Sexual Dysfunction Potential for Pharmacotherapy**

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### **Abstract**

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The act of sex includes a woman's sexual self and self-image, intimate relationships, family, society and culture. The complexities of her environment, sexual and partner history, past relationships, mental health status, current medical problems and hormonal status all play a role. An interdisciplinary consensus conference panel expanded the former Diagnostic and Statistical Manual of Mental Disorders-IV classifications of female sexual dysfunction to include psychogenic and organic causes of desire, arousal, orgasm and sexual pain disorders that cause personal distress. The US FDA Guidance paper details the recommendations for the clinical development of drugs for the treatment of female sexual dysfunction. In this document, great emphasis is placed on orgasm as a clinical trial endpoint and it would appear that satisfactory sexual intercourse is of secondary importance to the Agency. However, there is no evidence to suggest that the majority of women correlate their sexual enjoyment and satisfaction with numbers of orgasms or even the likelihood of orgasm during a given sexual interaction. Nonetheless, any drug coming through the regulatory agency in the US will need to follow these recommendations. Currently, there are six major pharmaceutical therapeutic paths being pursued for treatment of female sexual disorders and/or postmenopausal symptoms. These include dopaminergic agonists and related substances, melanocortin-stimulating hormones, adrenoceptor antagonists, nitric oxide delivery systems, prostaglandins, and androgens. A number of compounds that target these pathways are undergoing development for female sexual dysfunction. The array of pharmacological agents that are being developed for female sexual dysfunction must prove to be efficacious and have a good safety profile at a time when there are increasing worries that hormonal replacement with estrogen and progestogens are not safe. It is unclear if any of these pharmaceutical pathways will prove to be both safe and effective for the treatment of female sexual disorders; however, studies investigating this area will provide important scientific data for the future.

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**Table I.** Potential treatments being developed for female sexual dysfunction

Drug mechanism of action	Probable indication	Product Name	Developing company (phase of development)
Dopamine receptor agonist	Desire	Intranasal apomorphine	Nastech/Pharmacia (phase II)
Nonselective $\alpha$ 1- and $\alpha$ 2-adrenoceptor antagonist	Arousal	Oral phentolamine	Zonagen (phase I)
Nitric oxide system Phosphodiesterase IV inhibitor	Arousal Arousal	Sildenafil Tadalafil	Pfizer (phase II) Lilly/ICOS (phase II)
Other nitric oxide donors	Arousal	Arginine + yohimbine	NitroMed
$\alpha$ -Melanocyte stimulating hormone analogue	Desire and Arousal	PT-141	Palatin (phase I)
Prostaglandins (smooth muscle relaxant)	Arousal Arousal	Alprostadil topical gel Alprostadil topical	Vivus (phase II) NexMed
Androgens Testosterone	Desire Desire	Transdermal testosterone Testosterone gel	Watson/Proctor & Gamble (phase III) Cellegy
Estrogen/androgen combination	Desire	Esterified estrogen/methyltestosterone <sup>a</sup>	Solvay
Androgenic dietary supplements	No claims for an indication (NRR)	Multiple androgen substances	Multiple sources
<b>Natural Products</b>	<b>No claims for an indication (NRR)</b>	<b>Zestra<sup>TMb</sup> for Women<sup>c</sup></b>	<b>QualiLife</b>

a Indicated for the management of moderate to severe vasomotor symptoms associated with menopause in patients who do not respond to estrogens alone.

b Use of tradenames is for product identification only and does not imply endorsement.

c This product has been deemed as 'generally recognised as safe' and is available via the internet.

**NRR** = no regulatory review.

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### Herbal Remedies

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Compounds that are made up of 'generally recognised as safe' (GRAS) substances require no regulatory review. One such product, Zestra for women (Qualilife Pharmaceuticals) is an oil that contains natural botanical ingredients (borage seed oil, evening primrose oil, special extracts of angelica, coleus forskolin, antioxidants and vitamin E) with natural fragrances. It has entered the internet market and featured at the October 2001 Female Sexual Function Forum of the International Society for the Study of Women's Sexual Health in Boston, Massachusetts, USA.<sup>[76]</sup> Before market entry of Zestra the sponsor conducted a small, randomised, double-blinded, crossover study in 20 women, of whom, 10 had female sexual arousal disorder. Diary questions regarding satisfaction with arousal were used as primary efficacy endpoints. Secondary endpoints included diary questions. The study reported improvements relative to placebo in levels of arousal, desire, satisfaction and sexual pleasure. Zestra is meant to be applied (0.5–1 mL) with gentle massage to the external female genitalia, clitoris, labia and vaginal opening at least 3–5 minutes prior to vaginal intercourse for enhanced sexual experience.

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### Conclusion

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The development of a drug that can be safely used in the treatment of female sexual dysfunction continues to be complicated. The array of neurotransmitter agonists and antagonists (e.g. dopaminergic agonists, adrenoceptor antagonists), nitric oxide delivery systems, smooth muscle relaxants (e.g. prostaglandins), and new hormonal formulations (e.g. melanocortin-stimulating hormones, prostaglandins and androgens) that are being developed for female sexual dysfunction must prove to be effective and have a good safety profile at a time when there are increasing worries that hormonal replacement with estrogen and progestogens are not safe. The field is further complicated by the interaction between the categories of sexual response (e.g. desire, arousal and orgasm) adding variance to outcomes that may be additionally magnified by learned behaviour (or placebo response) in clinical trials. It is unclear whether any of the major pharmacological paths currently being investigated in the treatment of female sexual dysfunction will result in safe and effective treatments. If it is possible to identify subpopulations who respond to a therapeutic regimen, the question will remain whether such regimens may be applied to the entire population. While the mechanisms underlying female sexual dysfunction still remain unclear, additional research will further elucidate the complexity of the female sexual repertoire, which will hopefully lead to safe pharmacological therapy.

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The text and tables in this document are selected excerpts from the referenced *Drugs* publication.

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