



In Focus

Flibanserin for Low Sexual Desire in Women: A Molecule From Bench to Bed?

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Flibanserin, a drug with mixed effects on serotonergic and dopaminergic neurotransmitter systems, has recently been recommended for FDA approval, albeit with many restrictions, for the treatment of low sexual desire in premenopausal women. The sexual side effects of antidepressants with at least partially known mechanisms of action indicate that flibanserin should enhance sexual response. Rather than illustrating translation of knowledge from bench to bedside, the reality is less dramatic – as is flibanserin's efficacy.

Ineffective as an antidepressant, but noted to have pro-sexual side effects, flibanserin was trialed for this new indication in the early 2000's. The FDA denied Boehringer Ingelheim's application for approval of flibanserin for hypoactive sexual desire disorder (HSDD) in women in 2010 as two phase 3 trials failed to show statistically significant benefit on one of two co-primary endpoints – a daily diary assessment of desire. Sprout Pharmaceuticals reapplied in 2013 with data from a third trial which used a different co-primary endpoint – a retrospective assessment of desire over the previous 4 weeks. Due both to safety concerns, which include hypotension, syncope, somnolence, fatigue, and potential carcinogenicity and to the short duration of studies and questionable accuracy of 4 week recall along with marginal efficacy, approval was denied and additional safety studies recommended. Benefit across all phase 3 studies averaged a placebo-corrected increase of 'satisfactory sexual events' by 0.5 to 1 per month and an increase of 0.3 on the retrospective desire scale (range 1.2–6.0). Surprisingly, despite lack of additional efficacy data, but with data ruling out driving impairment and assessing alcohol's enhancement of side effects in 23 men and 2 women, on June 4, 2015, an FDA advisory committee voted 18 to 6 to accept flibanserin's approval, but with reservations. Fifteen members endorsing its approval declared their reluctance to do so.

An additional concern is that trial participants had no clear diagnosis of sexual disorder as is currently understood. Growing concern that HSDD criteria are not appropriate for women led to interim definitions of low desire in 2003, and to an officially changed definition in 2013 (American Psychiatric Association, 2013). A state of ongoing sexual desire between sexual experiences is de-emphasized. Responsive desire triggered by sexual stimuli including those received during sexual encounters is now recognized (Both et al., 2007; Stoléru et al., 2012). Beginning partnered sexual activity for reasons other than 'desire' has been clearly documented as the most common scenario in both young (Meston and Buss, 2007) and older women (Cain et al., 2003). Pathology now focuses on the inability to trigger desire and arousal during sexual experiences. Participants in flibanserin studies, however, reported 2 to 3 rewarding sexual experiences each month at baseline.

Backwards translation of sexual side effects of medications identifies neurotransmitters involved in the brain's sexual response system, the sensitivity of which is highly variable. There is robust evidence that sexual and non-sexual distractions, fatigue, low self-image, depressive thoughts, anxiety and stress (Cyranski et al., 2004; de Jong, 2009; Nelson and Purdon, 2011; Nobre and Pinto-Gouveia, 2008) can lessen that sensitivity to inhibit sexual arousal, pleasurable physical sexual sensations and orgasms. Sexual activity is not rewarding and sexual motivation fades: satisfactory sexual experiences cease. Women with this most common type of dysfunction (Brotto, 2010), a muting of all phases of sexual response, were not the cohort recruited for the flibanserin trials.

To date there is no example of 'bench to bed' knowledge translation of drugs to benefit sexual dysfunction. Sildenafil's success in managing erectile dysfunction (ED) resulted from capitalizing on a pro-sexual side effect of a putative antihypertensive drug that failed for that indication. The activity of nitric oxide (NO), a major neurotransmitter underlying the vaso-dilatation of erection, can be prolonged by inhibiting phosphodiesterase type 5. The latter inhibits cGMP whose production is initiated by NO from autonomic nerve terminals in the penile sinusoidal spaces in response to sexual arousal. Providing a man is sexually excited and that the signaling from his brain through the spinal cord to autonomic nerve endings in cavernosal tissue is relatively intact, the erectile mechanism is enhanced. Phosphodiesterase type 5 inhibitors cause similar increase in neurogenic vasodilatation in clitoral tissue, but with minimal impact on women's sexual concerns: reduced clitoral engorgement rarely underlies women's sexual dysfunction. The degree of genital congestion correlates poorly with women's subjective arousal, and is not typically the pleasant reassurance of and contributor to subjective arousal as it is for men.

Future medications for ED may emerge from lab-based discovery of other players additional to NO. The age-related increase in rho kinase, which modulates the sensitivity of cavernosal smooth muscle to intracellular calcium, may allow inhibitors of rho A/rho kinase signaling to benefit ED. Translating knowledge of genes coding for the various molecules affecting cavernosal smooth muscle relaxation allows exploration of gene therapy for ED.

Backwards translation of medications' sexual side effects allows choice of more sex-friendly antidepressants to improve compliance. Drugs which are not 5HT_{2C} or 5HT_{2A} agonists but activate 5HT_{1A} receptors minimize sexual harm. Examples include trazodone, a 5-HT_{2A} receptor antagonist and 5-HT_{1A} partial agonist, and mirtazapine, a

noradrenergic and specific serotonergic antidepressant. Unlike SSRIs, SNRIs, and MAOIs, mirtazapine does not activate 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ receptors, benefiting sleep, appetite and sexual function. Gepirone and a new SSRI, vilazodone, both with 5-HT_{1A} partial agonist action, may also prove sex-friendly. Neither bupropion, which prevents reuptake of noradrenaline and dopamine, nor meclizolam, a reversible monoamine oxidase inhibitor, nor agomelatine, a MT1 and MT2 agonist, typically harm sexual response.

Conversely, medications which activate 5HT_{2C} and/or antagonize 5HT_{1A} receptors are used off label to delay ejaculation: dapoxetine (an unsuccessful antidepressant), is approved for this indication.

Further research into the neuroendocrinology of sexual response is needed. This would include the aspect that women so frequently find dysfunctional – namely pleasurable and relatively intense psychological and physical arousal such that desire for more of the same is triggered to allow orgasms and pleasurable outcomes. Rewarding sex provides its own incentive for its repetition: no ‘desire drug’ needed.

Conflicts of Interest

Drs Basson, Driscoll and Correia report no conflicts of interest.

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