

## Pharmacological Advances in the Management of Sexual Dysfunction

### INTRODUCTION

Sexuality in men and women is a complex phenomenon involving biological, psychological, social, and according to some, spiritual domains of life. Since time immemorial, there was a search for aphrodisiacs to improve sexual functioning and well-being.

Sexual revolution, which became a social movement in 1960s, had its antecedents in early 20<sup>th</sup> century Freudian and certain French social theories.<sup>[1]</sup> Sexual discourse and expression ever since have turned toward a highly charged political and rights-based movement. On the other hand, sexual revolution helped people seek professional help for their intimate relationship issues and thereby receive help for much related psychological suffering.

Kinsey reported<sup>[2]</sup> initially and the Masters and Johnson<sup>[3]</sup> after that spear-headed the branch of sexual disorders management and have contributed a lot through the behavioral approach. Later, Kaplan<sup>[4]</sup> brought in a balanced perspective in the management of the sexual disorders by combining behavioral and psychodynamic approaches. Sexual research has made much progress since then and helped us understand gender differences of sexual experience and the effect of factors such as age, media, culture, religion, and medical diseases on the function and experience of sex.

Medical revolution in this area had a delayed inauguration in 1998 when the US Food and Drug Administration (FDA) approved a phosphodiesterase type-5 inhibitor (PDE5I) called, sildenafil which was originally designed for hypertension, for the management of male erectile dysfunction. Marketed as Viagra, it took not only the pharmaceutical industry but also the black market by storm where it is known variously as Vitamin V, Blue pill, Blue diamond, etc., It became popular due to its good efficacy for many people suffering from erectile dysfunction. However, side effects such as headache, dizziness, and visual disturbances poor response in people with comorbidities such as diabetes mellitus, hypertension, and hindrance to the spontaneity in the sexual intercourse due to its on-demand nature of dosing – have limited its use. Other phosphodiesterase

inhibitors approved by FDA are vardenafil, tadalafil, and avanafil.

Need for newer medication with less side effects, which will be effective even in people with medical comorbidities and the need for medication for hypoactive sexual desire disorder (HSDD), especially in women, is widely felt and current pharmacological research is being carried out in these directions.

### EMERGING AGENTS FOR MALE SEXUAL DYSFUNCTION

PDE5Is have been effective and thereby became popular medication in the area of male erectile dysfunction, so much so that it overtook the use of other effective, albeit invasive options such as intracavernosal injections and medicated urethral system for erections. Daily dose and on-demand selective serotonin reuptake inhibitors have been effective for the management of premature ejaculation. However, as mentioned above, various reasons require the development of better medication with broader applications.

Current research in drug development is working in these directions:

1. Improving the selectivity, efficacy, and drug delivery of phosphodiesterase inhibitors
2. Targeting alternate pathways involved in the physiological process of erection to develop drugs for those with penile neurologic and vascular damage
3. Gene-related therapies
4. Testosterone therapy in people with hypogonadism and erectile dysfunction
5. Stem cell therapy in people with
6. Post-radical prostatectomy-related erectile dysfunction.

#### Better phosphodiesterase type-5 inhibitors

Sildenafil, tadalafil, and vardenafil have been formulated as oro-dispersible tablets or coated films for faster drug delivery.<sup>[5]</sup> Newer drugs such as Udenafil and Mirodenafil are found to be effective even in patients with diabetes mellitus and hypertension (on multiple antihypertensive agents). These drugs, when combined

with  $\alpha$ -1 blockers, produced better erections and reduced lower urinary tract symptoms. Udenafil has the dual advantage of faster onset and longer duration of action while mirodenafil is ten times more selective to PDE5 than sildenafil. Other agents such as lodenafil and SLx-2101 are also under development, and they promise lesser side effects and longer duration of action.

#### Alternate mechanisms of action

Drugs acting on alternate pathways can be divided into those acting on central mechanisms such as melanocortin receptors, dopamine, and serotonin and those acting peripherally on Rho-kinase system and upstream to nitric oxide (NO)-dependent activation of guanylate cyclase.<sup>[6]</sup> Melanocortins modulate sexual signaling in the brain, spine, and the penis by acting through dopaminergic neurons and stimulating the release of oxytocin. Melanocortin receptor agonists such as Melanotan II and bremelanotide have been studied for their proerectile potential. While Melanotan II was effective in producing significant erection even in the absence of any visual sexual stimulus, bremelanotide was efficacious in people with diabetes mellitus and those not responding to PDE5Is. The combination of low-dose bremelanotide and PDE5I had higher efficacy and lower side effects than either drug alone. Bremelanotide when tried through the intranasal route caused nausea and increased blood pressure, so a low dose through subcutaneous route is being preferred.

Dopamine is known to have a significant role in the sexual signaling in the brain.<sup>[7]</sup> This is being explored through the D4 selective agonists such as ABT-724. In animal studies either the drug alone or the low-dose combination with sildenafil showed good efficacy and had no side effects such as nausea or emesis as D3 receptor was not involved. Similarly, clavulanic acid, commonly used in combination with antibiotics, when studied for its antianxiety action suggested good efficacy in sexual arousal and erection in Phase-IIa research. This works through upregulation of serotonin and dopamine.

Myosin light chain phosphatase (MLCP) helps in relaxing the smooth muscle, Rho-kinase inactivates MLCP and thereby maintaining the smooth muscle in a contracted state.<sup>[8]</sup> Rho-kinase inhibitors have been studied in the diabetic population with erectile dysfunction where usually RhoA/Rho-kinase pathway increases smooth muscle contractility. Fasudil, Y-27632, and SAR-407899 are few Rho-kinase inhibitors which showed promise in the diabetes rat and rabbit models. SAR-407899 showed good efficacy even when NO synthase inhibitor was added to the animal model.<sup>[5]</sup>

In a healthy man, NO-dependent guanylate cyclase activation leads to the production of cyclic guanosine

monophosphate which is needed for the action of PDE5I drugs.<sup>[8]</sup> In diabetic and postprostatectomy patients, this process is deficient at the level of NO-dependent guanylate cyclase activation, therefore, the potential role for non-NO dependent guanylate cyclase activation either through heme-dependent activation which synergizes with NO activity or through heme-independent activation which works on pathological form of guanylate cyclase formed as a result of oxidative stress. Heme-dependent activators such as BAY 60-4552 have been studied in animal models and *in vivo* human corpus cavernosal tissue which showed efficacy alone or in combination with vardenafil and even in people with PDE5I nonresponse.

#### Gene-related, hormone, and stem cell therapies

Gene-related therapy, wherein maxi-K ion channels, are transferred to the penile tissues because penis is easily accessible for the procedure, and tunica albuginea has slow turnover rate facilitating the study of prolonged gene action. Maxi-K ion channel activators increase potassium currents and thereby increasing the relaxation of smooth muscles.<sup>[6]</sup> A recent meta-analysis<sup>[9]</sup> concluded that testosterone therapy was found useful in treating mild erectile dysfunction in hypogonadal men while the combination of testosterone and PDE5I was suggested for hypogonadal men with severe erectile dysfunction. Stem cell therapy<sup>[10,11]</sup> with autologous bone marrow mono nuclear cells (BN-MNCs) in people with postradical prostatectomy-related erectile dysfunction (surgery done for the treatment of prostate cancer, because of which penile neurovascular bundles are damaged) shows promise. In rat models, BN-MNC intracavernous injection reduced cell apoptosis, improved erectile function, and penile vascularization. It also accelerated the recovery of neural and endothelial NO synthase levels.

#### EMERGING AGENTS FOR FEMALE SEXUAL DYSFUNCTION

After the popularity of Sildenafil in male sexual dysfunction, Pfizer conducted research of its usefulness in other populations such as women, people with spinal injury, multiple sclerosis and those with antidepressant-induced erectile dysfunction and found no consistent results. Researchers commented that increase in genital engorgement was not useful for the treatment of female sexual dysfunction.<sup>[12]</sup> Tadalafil showed response in both daily dose form and on-demand form in few reports; however, these studies had small samples and were without any objective measures and placebo control.<sup>[13]</sup>

In women with vulvovaginal atrophy, vaginal dryness and dyspareunia, various treatments such as vaginal moisturizers or lubricants, systemic or low-dose vaginal estrogen therapy, and oral ospemifene, which is an estrogen-receptor modulator with selective estrogen agonism in vagina with nil breast or endometrial action, are available.<sup>[14]</sup>

### Hypoactive sexual desire disorder management

HSDD was noted to be a major concern in women with about 31%–36% of them reporting it in the USA.<sup>[14]</sup> Hence, the research focus was on the factors associated with HSDD. Bupropion which has dopamine agonism was found to be helpful in both depressed and nondepressed women with or without antidepressant-induced reduced libido. Melanocortin receptor agonist, bremelanotide, was also found to be useful when used in low-dose subcutaneous form.<sup>[15]</sup>

Topical testosterone is in off-label use in many countries for HSDD. There are possible side effects such as increase in lipids and cardiovascular or thromboembolic events, increase in body hair when >300 µg testosterone was used, increased risk of breast cancer, and adverse effects on endometrium.<sup>[14]</sup> However, many women with surgical or natural menopause showed significant improvement in low sexual desire irrespective of whether they were on estrogens or not.<sup>[16]</sup> This being supported by the American Endocrine Society 2014 guidelines,<sup>[17]</sup> which based on evidence, comments that there are short-term efficacy and safety of high physiological doses of testosterone therapy in postmenopausal women with HSDD.

Combinations of testosterone and other agents are available which work by reducing the inhibitory processes and increase excitatory processes of desire according to the dual control model of sexuality. Lybrido which has sublingual testosterone and sildenafil combination aims to increase excitatory processes, and Lybridos which have testosterone and bupropion combination aim to reduce sexual inhibitory processes. These two combinations were useful in women with low sensitivity to sexual cues wherein they improved preconscious attention to sexual cues and increased genital response to sexual fantasies.<sup>[16]</sup> Other agents such as bupropion and trazodone were also combined with testosterone for HSDD management.

### Flibanserin for hypoactive sexual desire disorder

Flibanserin is the first drug approved by US-FDA for the management of female HSDD. Flibanserin is a centrally acting agent with postsynaptic 5HT<sub>1A</sub> agonism and 5HT<sub>2A</sub> antagonism. Through these receptors, it increases the action of dopamine and norepinephrine and reduces the action of serotonin. It

is contraindicated in people with hepatic failure and in people concurrently taking alcohol and moderate to strong CYP3A4 inhibitors such as erythromycin, ketoconazole, and nefazodone.<sup>[15]</sup>

Since its approval in 2015, there is a debate about its efficacy. First, meta-analysis<sup>[18]</sup> presented positive picture of its efficacy, however, two latter meta-analyses<sup>[19,20]</sup> presented a less optimistic picture and even commented that its efficacy is only marginally better than placebo and that the efficacy cannot be translated into relevant clinical improvement. These two latter meta-analyses are more robust and include the analysis of unpublished studies.

Contraindication in people who take alcohol is due to the fact that it causes significant hypotension, syncope, and dizziness. The particular study which prompted such a drug warning was done on 23 men and had only two women.<sup>[21]</sup> Hence, it is being debated that the drug warning is not founded on good evidence and that it shows the ongoing gender bias in the sexual research.

## COMBINED MEDICAL AND PSYCHOLOGICAL MANAGEMENT

Above mentioned new options in the management of sexual dysfunction for both men and women expand the pharmacological armamentarium of the clinician and help to better plan the combined psychological and pharmacological management. Anxiety management, various kinds of couples therapy, sensate focus, and other behavioral therapies can be combined with the newer options to provide a balanced care.

## PROBLEMS AND OPPORTUNITIES WITH PHARMACOLOGICAL SEX RESEARCH

1. The success and share of market of PDE5Is influences the research agenda and funds are mostly used to develop faster or longer acting PDE5Is with low side effects and not for developing medications with alternate mechanisms for people with medical comorbidities<sup>[5]</sup>
2. Animal research though useful, is not appropriate, as human sexuality is more complex and varied than the sexual changes in animals. More studies should be done using *in vivo* human tissues such as (corpus cavernosum)
3. Research in women and people with medical comorbidities continues to be a problem, and currently, most of Phase II and III research is done on healthy adult men
4. Effectiveness of combined psychological and pharmacological sex therapy has to be investigated.

## CONCLUSION

Pharmacological research for sexual dysfunction has made progress over the last decade and is offering new options not only for the management of male sexual dysfunction but also for the female sexual dysfunction. We discussed mechanisms of action, promising efficacy, and side effects of emerging drugs and outlined few areas of problems and opportunities in pharmacological research. Clinicians working with people suffering from sexual dysfunction in the specialties of psychiatry, gynecology, general medicine, geriatrics, urology, venerology, and endocrinology have to be aware of these pharmacological advances and use them for their patients' benefit.

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