Pharmacotherapy of Sexual Dysfunctions: Current Status

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ABSTRACT
The sexual dysfunctions are one of the most prevalent conditions. Sexual dysfunctions can have profound effect on the psychological well-being of an individual and the psychosexual relationship of a couple. Management of the sexual dysfunction should be preceded by an accurate diagnosis reached after a complete medical and sexual history and physical examination. Current focus of researchers has been on understanding the pathophysiology of erectile dysfunction, premature ejaculation and other sexual dysfunctions that can help in developing newer pharmacological cures for these conditions.

Recently, a number of clinical trials have studied the potential effectiveness of the phosphodiesterase (PDE)-5 inhibitor sildenafil in the treatment of Erectile Dysfunction (ED) and Premature Ejaculation (PME). The introduction of PDE-5 inhibitors like sildenafil, vardenafil and tadalafil has revolutionized the treatment of sexual dysfunctions.

This review focuses on the recent pharmacological advances in the treatment of common sexual dysfunctions like ED and PME with special focus on the role of PDE-5 inhibitors. Also discussed is the pharmacological treatment of other less prevalent and recognized disorders like female sexual dysfunction, drug induced sexual dysfunction etc.

Key words: Erectile dysfunction, premature ejaculation, sildenafil, PDE-5 inhibitors, sexual dysfunction.

Introduction
Satisfactory sex life is an important influencing factor for a harmonious marriage. Sexual dysfunction deeply affects personal life by causing isolation, frustration and decreased self-esteem, which may extend into their job performance and interaction with others. Despite the pervasiveness of this problem, not until two decades ago were sexual dysfunctions clearly defined and clinically evaluated. Management of sexual dysfunctions should be preceded by an accurate diagnosis after a complete medical and sexual history and physical examination. It is also important to quantify the magnitude of the problem as much as possible. It is also important to determine the expectations of the patient and his partner regarding the frequency and the duration of the sexual act. A careful psychological evaluation is also indicated to determine if a concomitant psychosexual issue exists.

The pharmacological treatment of Erectile Dysfunction (ED) has taken central importance amongst therapeutic approaches for this increasingly recognized and widely prevalent disorder. Although the pharmacological treatment of Premature Ejaculation (PME) includes a wide array of drugs like topical anaesthetic agents, antipsychotics, α-adrenoceptor antagonists, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), an approved treatment does not exist. Besides their success in treatment of ED, phosphodiesterase (PDE)-5 inhibitors have also been evaluated in a few clinical trials to investigate their efficacy in treatment of PME.

This review highlights the pharmacological treatment of various sexual dysfunctions primarily ED and PME. The review also highlights the rationale between the use of PDE-5 inhibitors and other agents in the treatment of sexual dysfunctions, presents data from the clinical trials of agents used in these conditions, and looks at the current knowledge explaining the possible mechanisms of action of various pharmacological agents.

Male Sexual Dysfunctions

Erectile Dysfunction (ED)

Definition: Erectile dysfunction (ED), a more precise term for impotence, has been defined as the persistent or repeated inability for at least 3 months to attain and/or maintain an erection sufficient for satisfactory sexual performance (Rosen et al., 1998; NIH Consensus Development Panel on Impotence, 1993).

Since erection is a vascular event, an intact endothelium is necessary for erection. The regulation of penile tumescence inside the corpus cavernosum (CC) involves the balance between contracting and relaxing factors, which regulate
the functional state of smooth muscle cells. In the last few years, the pathophysiological mechanisms of erection have been partially clarified, and the molecular machinery of the cellular components of the corpus cavernosum (CC) has been widely investigated (Aversa et al., 2004). Recent studies have highlighted the importance of local factors (i.e. phosphodiesterases, rho-kinases and endothelins) and that most pharmacological agents modulate the function of these mediators of erection (Chitaley et al., 2001).

Various studies have shown that ED can have multiple etiologies including organic, psychogenic and a combination of both. Amongst organic causes neurogenic, arterial, endocrinologic and cavernosal causes are prominent (Krane et al., 1989; Burnett, 1998; Lue, 1995). Psychogenic causes may include anxiety, depression, religious inhibitions, ‘widower syndrome’ and sexual phobias (Seftel et al., 2004). Aging (Althof & Seftel, 1995), drugs (Rosen et al., 1998) and systemic diseases (Lue, 1992; 1995) may also cause ED. Nocturnal penile tumescence monitoring is one of the most effective methods to differentiate between organic and psychological cause of ED.

Researchers in the last decade or so have tried to find a pharmacological agent that fulfills the criteria of a first line therapy for ED. A first line therapy for ED is one which is easy to administer, reversible, non-invasive, low risk and which is appropriate for a broad range of patients (Padma-Nathan, 1999).

A) Oral Erectogenic Agents

Oral therapy with vasoactive agents has emerged as the first line treatment and has transformed the manner in which the general public views erectile dysfunction and even the way health care professionals deliver care.

(i) Efficacy of PDE (Phosphodiesterase) -5 inhibitors in ED

Sildenafil citrate is the first oral PDE-5 inhibitor approved by the FDA for treatment of ED. PDE-5 inhibitors are competitive and selective inhibitors of cGMP specific phosphodiesterase type 5, thus, inhibiting cGMP hydrolysis (Sadovsky et al., 2001).

On sexual stimulation (CNS or sensory), the non-adrenergic non-cholinergic neurons (NANC) produce nitric oxide (NO). This nitric oxide activates guanylate cyclase in the vascular smooth muscle cells increasing the synthesis of cGMP, which in turn leads to smooth muscle relaxation. This leads to the dilatation of the helicine arterioles allowing the relaxation of the trabecular smooth muscles of corpus cavernosum (CC) thus leading to inflow of arterial blood. The increased blood oxygen tension in CC (from 25-40 → 90-100 mm of Hg) as well as the shear effect contributes to endothelial nitric oxide synthase production, which further increases the cGMP (Nehra et al., 2001). The PDE-5 inhibitor sildenafil increases the cGMP by inhibiting its hydrolysis.

Short-term efficacy trials: Results in all the 21 placebo controlled, flexible dose-escalation studies done so far showed that PDE-5 inhibitor sildenafil produced greater improvement in erectile functioning than placebo when evaluated on International Index of Erectile Function (IIEF) regardless of the cause, baseline severity and age of the patients (Levine, 2000). In all the 2nd and 3rd phase trials, sildenafil was found to be safe and well tolerated. The overall discontinuation rates caused by adverse events were low and statistically non-significant when compared to placebo (Levine, 2000). All the side effects at 50-100 mg dose were mild to moderate and related to the vasodilatory property of sildenafil.

Long-term efficacy trials: The earliest open label, long-term trial (1 year) found 88% of patient of ED to show significant improvement (Guiliano et al., 1997). Subsequently two long-term (2 years) randomized double blind, placebo-controlled trials of sildenafil found that it had good safety and tolerability; incidence rates of severe CVS side-effects were comparable for patients receiving sildenafil or placebo (Hackett & Gingell, 1999; Padma-Nathan et al., 1998). Post FDA approval field experience update in Nov 1998 showed efficacy rates similar to those in short and long-term trials. Of the 128 deaths reported, 70% had one or more risk factors for cerebrovascular disease and none of the deaths were attributed to sildenafil alone (Viagra monologue,1999). Three retrospective studies of patients of ED with comorbid cardiac disorders have suggested that the incidence of myocardial infarction / unstable angina in PDE-5 inhibitor, sildenafil and placebo group was comparable (Conti et al., 1999; Jackson et al., 1999; Herrmann et al., 2000). In a meta-analysis on tolerability of sildenafil, Kloner and his co-workers (Kloner & Jarow, 1999; Kloner et al., 2001) found incidence rates of myocardial infarction (MI) to be 1.7 and 1.4 per 100 patient years with treatment in sildenafil and placebo group respectively. Other side effects include headache, hot flushes (Moreira et al., 2000; Morales et al., 1998) blue green-colour vision (Wallis et al., 1998) and premature acrosomal reaction leading on to failed fertilization (Cuadra et al., 2000; Burger et al., 2000). Most
researchers suggest that sildenafil is contraindicated in patients using organic nitrates and can lead to fall in BP of greater than 30 mm of Hg if taken within 24 hours of each other (Webb et al., 2000). Important drug interactions have been seen with CYP P450 3A4 isoenzyme inhibitors, which tend to increase the plasma levels of sildenafil (Muirhead et al., 2000).

Sildenafil has been found to be efficacious in ED following radical prostatectomy (Zagaja et al., 2000; Montorsi et al., 2004), spinal cord injury (Derry et al., 1998), ED with diabetes mellitus (Rendell et al., 1999; Hirsh et al., 1999), ED with chronic renal failure (Chen et al., 2001), Parkinson’s disease (Hussain et al., 2001; Zesiewicz et al., 2000) and in elderly males (Wagner et al., 1998).

A short-term, randomized, double blind study (Seidman et al., 2001) found sildenafil to be efficacious in patients with comorbid mild to moderate depressive disorders. Improvement in ED was also associated with improvement in depressive symptoms and quality of life. Erectile dysfunction and associated sexual dysfunction secondary to antidepressant therapy may occur up to 90% of men (Rosen & Marin, 2003). Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCA) are amongst the drugs, which cause maximum sexual dysfunction. Mixed mediators, non-serotonergic antidepressants that block post-synaptic serotonin type 2 receptors (nefazodone, mitrazapine) or those that primarily increase dopamine or norepinephrine levels (bupropion) were thought to be good choices for avoiding antidepressant induced sexual dysfunction. However, most of these studies have methodological flaws, which make the claims difficult to substantiate. Augmentation with these agents to TCAs or SSRIs has not shown clear evidence of any improvement in sexual dysfunction. Therefore, few proposed treatment options apart from avoidance of offending drugs have proved effective for antidepressant associated sexual dysfunction. (Labbate et al., 2003).

There are other PDE-5 inhibitors under various stages of development (Pryor & Redman, 2000) like vardenafil, which is a highly selective PDE-5 inhibitor. Four randomized, placebo-controlled, double-blind, multicenter studies have found it to be effective in ED especially in sexual functioning, confidence, orgasmic functioning and overall satisfaction (Keating & Scott, 2004; Crowe & Streetman, 2004; Kendirci et al, 2004; Porst et al, 2001). Another PDE-5 inhibitor, tadalafil’s clinical trials have shown it to significantly enhance erectile functioning across a wide range of ED cases including those with psychogenic, organic and mixed etiologies (Kloner et al., 2003; Padma-Nathan, 2003). However, no head to head trials have been undertaken to compare these newer generation PDE-5 inhibitors with sildenafil.

ii) Other Oral Erectogenic Agents

One of the earliest drugs used in erectile dysfunction was trazodone. Trazodone and its active metabolite mCCP, both have antagonistic effect on 5HT2c receptors and may also have adrenoceptor antagonistic action (Monsma et al., 1993; Krege et al., 2000). One of the more recent double-blind, placebo-controlled, randomized studies in non-organic ED found trazodone to be more efficacious (Enzlin et al., 2000). A systematic review and metaanalysis of 6 trials of trazodone treatment of ED proved that trazodone was more efficacious than placebo in mixed and psychogenic ED (Fink et al., 2003).

Yohimbine is an alpha-2-adrenergic blocker. Before introduction of sildenafil, yohimbine was the most widely used oral treatment of ED. Two initial studies (Vogt et al., 1997; Mann et al., 1996) produced inconsistent results, which prompted American Urologic Association for Erectile Dysfunction Guidelines (1996) to declare yohimbine as ineffective in treatment of erectile dysfunction (Padma-Nathan, 1999; Montague et al., 1996). Later, a meta-analysis of 7 randomized placebo controlled trials by Ernst and Pittler (Ernst & Pittler, 1998) found yohimbine to be superior to placebo. Some researchers now recommend yohimbine to be a reasonable initial treatment option as its benefits outweigh its risks (Ernst & Pittler, 1998).

Apomorphine is a dopamine agonist (D1 & D2 receptors) and its sublingual form (Apo-SL) is a new central initiator of erection and has been found to be effective in various types of ED (Dula et al., 2000; Heaton, 1997). When used in conjunction with a psychosexual counseling strategy, it can prove as an effective and safe pharmacological therapy for ED (Costa, 2003). Recent studies show that Apo-SL has a safe and favourable cardiovascular profile thus making it a new treatment option for patients with concomitant diseases including CVS disorders and diabetes mellitus (Montorsi, 2003).

Oral phentolamine mesylate (Vasomax), which has a faster onset, readily absorbed drug, is a competitive inhibitor of alpha-adrenergic receptors. Two double blind placebo-controlled multicenter trials (Mitka, 1998; Goldstein et al., 2001) showed better penetration rates and successful intercourse rates in the test group. It also has the advantage...
of lack of interaction with nitrates and hence has been suggested as an alternative to treatment of ED with cardiac illness (Padma-Nathan et al., 2002).

Other oral pharmacological agents like opioid antagonist Naltrexone (endogenous opioids modulate orgasmic response and peripheral intensity of sexual arousal and orgasm) (van Ahlen et al., 1995; Sathe et al., 2001), adrenocorticotropic hormone, melanocortin receptor agonists (Wessells et al 1998; 2000) and antihypertensive agent losartan (Llisterri et al., 2001) are also under study for treatment of ED and inhibited sexual desire.

B) Vasoactive Intracavernous Injections

Since early 1980’s, till advent of sildenafil, intracavernous injections were the mainstay of the treatment of erectile dysfunction (Brindley, 1983; Virag, 1982).

Phentolamine mesylate, an a-adrenoceptor antagonist acts via increasing cAMP and decreasing intracellular Ca\(^{2+}\) and also possibly via nitric oxide synthase (NOS) activation (Traish et al., 1998). Clinical efficacy and safety of intracavernosal mesylate has been well documented. (Anderson, 1995).

Papavarine is a non-selective inhibitor of phosphodiesterase (PDE) and acts by increasing cAMP thus decreasing intracellular Ca\(^{2+}\) leading to relaxation of trabecular smooth muscle. It is used in PIPE test (Papvarine Induced Penile Erection) to distinguish between psychogenic and organic ED. However, it has limited efficacy so it is used with other agents such as phentolamine (bimix) and with phentolamine and prostaglandin E\(_1\) (trimix) (Padma-Nathan, 1999).

Vasoactive Intestinal Peptide (Dinsmore & Alderdice, 1998; Mac Mohan, 1996) and Forskolin (Mulhall et al., 1997), which increase cAMP, have been found to be efficacious in moderate to severe ED resistant to monotherapy and polypharmacotherapy.

Alprostadil—a synthetic prostaglandin E\(_1\) is an adenylate cyclase activator and is now the drug of choice for intracavernosal pharmacotherapy (Padma-Nathan, 1995). Due to its synergistic action, it is often used with phentolamine and papavarine (Govier et al., 1993). Some studies demonstrated that patients of erectile dysfunction preferred trimix (Phentolamine +papavarine + prostaglandin E\(_1\)) to sildenafil, regardless of the etiology (Bella & Brock, 2004; Sommer & Engelmann, 2004).

A metaanalysis of 25,000 patients (Steers, 2000) showed that the advantage of mixing above agents is that lower doses of drugs are required thus leading onto synergistic effects with lesser side effects. Prominent side effects are priapism, pain, corporal fibrosis and scar tissue formation. Also, being an invasive procedure, many patients find it inconvenient to inject repeatedly (Linet & Ogrinc, 1996). Procedural complicacy, bleeding and injury to urethra (Porst, 1995; Purvis et al., 1999) caused higher attrition rates at 1 year follow-up of patients being treated with intracavernosal vasoactive drugs.

C) Intraurethral Therapy

Medicated urethral system for erection (MUSE), which contains 500-1000ug of alprostadil, has shown success rates varying from 43%-69% in efficacy studies (Porst, 1997; Padma-Nathan et al; 1997). It has advantages that self-administration had little systemic and local side effects.

D) Topical Therapy

Nitroglycerine, a nitric oxide donor (Cavallini, 1994), testosterone (Yap & McVary, 2002) and minoxidil ointments (Cavallini, 1994) have met with only minimal success. Although, still under investigation. But these agents could act as another tool in the armamentarium of physicians treating erectile dysfunction.

II) Premature Ejaculation

Premature (rapid) ejaculation (PME) has been described as the commonest form of male sexual dysfunction and implies that a man is unable to exert voluntary control over the ejaculatory reflex, with the result that once he is sexually aroused orgasm is achieved rapidly, which leads to dissatisfaction of patient and his partner. This condition is most common amongst young adults and men who lack sexual experience and frequency. In its severe form, it can lead to secondary erectile dysfunction (Abdel-Hamid, 2004). Premature ejaculation may be primary or secondary to an underlying disease. Treatment of PME has primarily focused on behaviour therapy, topical anaesthetic agents, tricyclic antidepressants and selective serotonin reuptake inhibitors. However, an approved treatment regime does not exist.

A study comparing fluoxetine monotherapy with fluoxetine and local lidocaine ointment application found the latter group to have longer orgasmic latency (Atan et al., 2000). Three trials using newer SSRI’s like paroxetine have found it to
be more efficacious in both long-term as well as on demand trials (Ludovico et al., 1996; Mac Mohan & Touma, 1999; Balachandra, 2001). Although, initially it was thought that different SSRI’s don’t have any advantages over the other (Murat Bashar et al., 1999) but in a recent systematic review and meta-analysis of treatment of PME with SSRIs (Waldinger et al., 2004), it was found that paroxetine appeared to be more effective in increasing the intra-vaginal ejaculatory latency time (IELT).

Recently, a number of clinical trials have studied the potential effectiveness of phosphodiesterase (PDE-5) inhibitor sildenafil in treatment of PME and have found it to be beneficial either as a single agent (Abdel-Hamid et al., 2001; Lobik et al., 2002) or in combination with SSRIs like Paroxetine (Salonia et al., 2002; Chen et al., 2003) and Sertraline (Lozano & Castane, 2003).

Available data indicate that there is clinical, anatomical, physiological, pharmacological and genetic evidence to explain the efficacy of PDE-5 inhibitors in PME. The rationale for use of PDE-5 inhibitors in treatment of PME could be due to peripheral and central mechanisms. Possible peripheral ejaculation retarding capabilities may include modulation of the contractile response of the vas deference (VD), seminal vesicles (SV), prostate and urethra; induction of a state of peripheral analgesia and prolongation of the total duration of erection (Abdel-Hamid, 2004). Possible central mechanisms may involve lessening of the central sympathetic output. Furthermore, there is evidence from animal studies regarding efficacy of PDE-5 inhibitors in PME (Abdel-Hamid, 2004). Mice lacking the gene for endothelial nitric oxide synthase develop a condition similar to PME (Kriegsfeld et al., 1999). Role of Chinese herbs like S-S cream, which are used as topical agents have good efficacy and favorable side effect profile (Choi et al., 1999; 2000).

Female Sexual Dysfunctions

Female sexual dysfunction is one of the less researched areas and pathophysioloogy is not clearly understood. There are no clear diagnostic criteria for diagnosing these conditions. Both central nervous system as well as sympathetic nervous system plays a vital role in both sexual desire and arousal in females. Nonadranergic noncholinergic neurotransmitters (NANC) eg. Vasoactive intestinal polypeptide and nitric oxide are involved in arousal. Female sex hormones like estrogen has role in smooth muscle relaxation and enhancement of genital blood flow. Androgens primarily affect sexual desire, arousal, orgasm and overall sense of well-being. Like men, in women the sexual dysfunctions may be caused by organic (arteriosclerosis, neurological, diabetes mellitus, hormonal changes and drug induced), psychogenic or mixed etiologies.

In a placebo-controlled study Apomorphine SL has been found to be effective in both hypoactive sexual desire and arousal disorders (Caruso et al., 2004). Medical management of female sexual dysfunction so far is primarily based on hormone replacement therapy. Several trials have been conducted using testosterone replacement (Warnock et al., 1999), yohimbine (Piletz et al., 1998), trazodone, fenfluramine but with no convincing results. Bupropion (sustained release) has been found to show moderate response in non-depressed patients of hyposexual desire disorders (Segraves et al., 2004). In a single-blind, sequential order treatment of 3 weeks each of placebo, bupropion-SR 150 mg/day, bupropion 300mg/day, non depressed women with sexual orgasmic and arousal disorders responded favourably thus indicating that bupropion-SR may be an useful agent for treating orgasmic delay and inhibition and possibly disorders of sexual arousal (Modell et al., 2000).

Conclusion

Erectile dysfunction and premature ejaculation are one of the most prevalent sexual dysfunctions. The scene in the treatment of erectile dysfunction and PME has been revolutionized by the introduction of sildenafil and other newer PDE-5 inhibitors. The clinical utility of PDE-5 inhibitors in the treatment of PME and ED may be improved through focusing on the exact PDE isoform expressed in the human vas deference and seminal vesicles. The various neurotransmitters like rho-kinases, changes in the central NO/cGMP signaling pathways should be further studied to understand exact pathophysiology of erection and ejaculatory response. The effective and approved treatment of PME has still not been developed and efforts should be made to develop such a regime. Other sexual disorders like female sexual disorders are less understood and less researched. Greater efforts should be made to understand female sexual pathophysiology and develop effective pharmacological treatment for the same.

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