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Late-stage clinical development in lower urogenital targets: sexual dysfunction

*,[1]Usman Azam

[1]Johnson & Johnson Pharmaceutical Research & Development, PO Box 300, 920 Route 202 South, Raritan, NJ 08869, U.S.A.

In recent years, late-stage clinical drug development that primarily focuses on urogenital targets has centered around four areas of medical need (both unmet need and aiming to improve on existing therapies). These include male sexual dysfunction (MSD), female sexual dysfunction (FSD), prostatic pathology (neoplastic, pre-neoplasitic, and non-neoplastic), and improvement in lower urinary tract symptoms. Despite the regulatory approval of compounds to treat erectile dysfunction (ED), benign prostatic hyperplasia, a number of treatments for overactive bladder, and stress urinary incontinence, there remains a deficiency in addressing a number of conditions that arise out of pathophysiological dysfunction resulting in lower urogenital tract sexual conditions. In terms of late-stage clinical development, significant progress has most recently been made in MSD development, especially in understanding further a common and complex sexual dysfunction – that of premature ejaculation. The search also continues for compounds that improve ED in terms of better efficacy and superior safety profile compared to the currently marketed phosphodiesterase-5-inhibitors. Whilst there are no approved medications to treat the subtypes of FSD, there has been significant progress in attempting to better understand how to appropriately assess treatment benefit in clinical trial settings for this difficult to diagnose and treat condition. This review will focus on late-stage human clinical development pertaining to MSD and FSD.
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Abbreviations: AEs, adverse events; BPH, benign prostatic hyperplasia; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders – fourth edition – text revision; ED, erectile dysfunction; FSAD, female sexual arousal disorder; FSD, female sexual dysfunction; HSDD, hypoactive desire disorder; IELT, intravaginal ejaculatory latency time; LUTS, lower urinary tract symptoms; MSD, male sexual dysfunction; OAB, overactive bladder; PDE5is, phosphodiesterase-5-inhibitors; PE, premature ejaculation; PRO, patient reported outcomes; SSRI, selective serotonin reuptake inhibitors; SUI, stress urinary incontinence

Male sexual dysfunction

Premature ejaculation

Premature ejaculation (PE), also sometimes referred to as rapid or early ejaculation, is one of the most common male sexual dysfunctions (MSDs). The prevalence of PE has been estimated to range from 21 to 32.5% in men aged 18–59 (Laumann *et al*., 1999a, b; Rosen *et al*., 2004a; Rowland *et al*., 2004a). PE has no universally accepted definition, its etiology is not completely understood, and its treatment varies widely (Metz *et al*., 1997). The impact of PE on men who suffer from the condition is shadowed by their reluctance to discuss their sexual dysfunction; all too often, healthcare professionals assume that patients will discuss an issue if it is a problem for them. The distress associated with PE can affect the individual, his partner, the relationship as a whole, and other areas of the individual's life (Symonds *et al*., 2003; Rosen *et al*., 2004a; Rowland *et al*., 2004a). Furthermore, men with PE may avoid pursuing relationships because of the embarrassment and social stigma associated with PE (Waldinger *et al*., 1998a; Symonds *et al*., 2003; Rosen *et al*., 2004a; Rowland *et al*., 2004a).

*Author for correspondence; E-mail: uazam@prdus.jnj.com

The ejaculatory reflex is a complex process that arises out of interplay between central serotonergic and dopaminergic neurons, with secondary involvement of adrenergic, cholinergic, oxytocinergic, and GABAergic neurons. From the aspect of neurotransmitter modulation, there has been extensive focus on the role of dopamine and 5-hydroxytryptamine (5-HT, serotonin) in the human ejaculatory process. It is postulated that dopamine exerts an effect by promoting seminal emission/ejaculation *via* D2 receptors, whereas serotonin has an inhibitory role on ejaculation (Gessa & Tagliamonte, 1974). It is on this basis that selective serotonin reuptake inhibitors (SSRIs) have been used as off-label pharmacotherapy in the treatment of PE. Currently, 14 different 5-HT receptor subtypes have been identified (Peroutka & Snyder, 1979; Tork, 1990).

Historically, the causes of PE were considered to be purely psychological, and therefore early approaches to treatment consisted primarily of behavioral therapy (Masters & Johnson, 1970). Behavioral and cognitive therapies have shown initial success (Masters & Johnson, 1970); however, many patients do not maintain benefits over the long term, and PE typically returns (De Amicis *et al*., 1985; Waldinger, 2002). Conventional pharmacotherapy for PE involves off-label use of SSRIs and other antidepressants, which are known to cause delayed ejaculation as a common side effect (Rosen *et al*., 1999; Keltner *et al*., 2002; Scharko, 2004). Drugs for erectile

dysfunction (ED), such as phosphodiesterase (PDE)-5 inhibitors, have shown modest success when used off-label for the treatment of PE (Goldstein *et al*., 1998; Damis *et al*., 1999; Salonia *et al*., 2002). Topical anaesthetics may also be prescribed, but their use is much less common in the United States than in Europe.

One of the earliest definitions of PE, proposed by Masters & Johnson (1970), focused on the man's inability to delay ejaculation long enough for the woman to achieve orgasm at least 50% of the time. Kaplan later suggested that PE is primarily a problem of voluntary control over timing of ejaculation (Kaplan, 1974). The Diagnostic and Statistical Manual of Mental Disorders – fourth edition – text revision (DSM-IV-TR) defines PE as 'the persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it' (American Psychiatric Association, 2000). The definition requires that the condition 'must also have marked distress or interpersonal difficulty,' and states that it 'is not due exclusively to the direct effects of a substance.' The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) defines PE as 'the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction' (WHO, 1992). The American Urological Association (AUA) Guideline on the Pharmacologic Management of Premature Ejaculation recently defined PE as 'ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners' (Montague *et al*., 2004). Regardless of the definition, it appears that a number of clinical domains emerge that can be used as both assessment tools for the condition and for potential treatment and outcome assessments.

These outcome assessments for PE may be considered patient reported outcomes (PROs). Such PROs include assessments of time to ejaculation using stopwatch (the so-called intravaginal ejaculatory latency time (IELT), introduced as a concept by Waldinger *et al*. (1998a), self-reports on the ability of control over ejaculation, severity of the PE problem, distress about timing of ejaculation, and satisfaction with sexual intercourse. As men with PE typically recognize and identify their problem by self-diagnosis (Symonds *et al*., 2003), IELT used in isolation may not be the best way to diagnose or assess PE. Time to ejaculation and ejaculatory control are only a part of the condition; the degree of satisfaction with sexual intercourse, psychological well-being, and well-being of the relationship should also be assessed for both the individual and the partner (Althof, 1998). The guidelines recommend that the diagnosis of PE be based on sexual history alone, and that a detailed sexual history be obtained from all patients with ejaculatory complaints (Montague *et al*., 2004).

Since the publication in 2004 of the Standards for Clinical Trials in Male Sexual Dysfunction (Hirsch *et al*., 2004), where the need for developing standards in clinical trials and outcomes assessments was highlighted, substantial progress has been made in the arena of PE in applying validated instruments in the assessment of treatments in development for PE.

One main challenge researchers in the field have faced is attempting to discriminate what is normal and abnormal in the setting of men and their partners suffering with PE and the relevant contribution of various components of characteristics that could be used to assess diagnosis and treatment for the condition. Two recent studies have attempted to examine this issue in detail. The first study by Patrick *et al*. (2005) was undertaken to help characterize PROs of men and their partners with PE and those without PE. This observational study examined 207 PE men and 1380 non-PE men, all in stable heterosexual relationships of at least 6 months duration prior to enrollment in the study. Patients were diagnosed as suffering with PE or not suffering with PE using the DSM-IV TR criteria. IELT, control over ejaculation, sexual satisfaction (partner and subject), personal distress, and interpersonal difficulty were assessed at screening, baseline, and 2-weekly followup visits. No pharmacotherapy was administered in this study. The findings from this study showed that PE subjects reported significantly shorter IELTs than their non-PE counterparts (1.8 min in the PE subjects (range 0–41) and 7.3 min in the non-PE subjects (range 0–53)). The study also highlighted that while there was overlap of these two populations in terms of IELT, this measure alone does not fully capture the impact of PE. Examination of the PROs pertaining to control over ejaculation, satisfaction with sexual intercourse, interpersonal difficulty, and personal distress allows for further clarification of the key characteristics that will allow healthcare practitioners to further help identify the appropriate population of men suffering with PE.

Waldinger *et al*. (2005a) conducted an IELT-based cohort study in five nations – U.K., Netherlands, Turkey, Spain, and U.S.A. They did not define men as suffering with PE or non-PE using any diagnostic framework or criteria, but rather attempted to establish a distribution of IELT from the population of men they examined. Subsequent to this study, Waldinger *et al*. (2005b) have gone on to establish a proposal for a definition of lifelong PE based on their IELT findings. Their initial cohort study found that the mean stopwatch IELT in the population of apparently normal men is 8 min and 4 s. This is in relative agreement with findings by Patrick *et al*. in their non-PE population findings. In contrast, Waldinger *et al*. argue that epidemiological studies would infer that only those of the population who are 2.5 standard deviations from the population mean they have identified can be classified as suffering with PE. From the cohort study conducted by Waldinger *et al*., this equates to an IELT of 1.3 min. They suggest that an IELT of less than 1 min is 'definite' PE, while an IELT of less than 1.5 min is 'probable' PE.

Debate continues in the field as to the emphasis that should be placed on any one assessment tool, such as IELT, control over ejaculation, or sexual satisfaction, but the role of all key patient-reported outcomes cannot be ignored for the purposes of development of investigational pharmacologic agents where patient and partner assessments may become requirements for gaining regulatory approval for such agents to treat sexual dysfunction, such as PE.

The role of serotonergic modulating agents has been evaluated in a number of human clinical studies, but with a few exceptions, many studies were conducted with suboptimal clinical designs, small patient numbers, and lack of validated instruments assessing PE (Waldinger *et al*., 1994; 1998b; 2001; 2003; 2004; Althof *et al*., 1995; Kara *et al*., 1996; Montejo-Gonzalez *et al*., 1997; McMahon, 1998; Kim & Paick, 1999; McMahon & Samali, 1999; McMahon & Touma, 1999; Rowland *et al*., 2004b; Kilic *et al*., 2005).

While daily and situational (PRN) dosing of antidepressants is often used, a period of daily dosing is typically required

prior to situational dosing for better efficacy compared with situational dosing alone with nonapproved antidepressants and SSRIs.

This is not the case for a new agent currently being developed as the first oral agent specifically designed to treat PE – dapoxetine hydrochloride, (ALZA Corporation, Mountain View, CA, U.S.A.).

Dapoxetine is a serotonin transport inhibitor that has been developed specifically for PE as an on-demand oral treatment. Dapoxetine has been shown to have a high affinity for the serotonin (5-HT) reuptake transporter. Dapoxetine has been shown to compete in a concentration-dependent manner for specific [^{3}H]citalopram-binding sites on the 5-HT reuptake transporter, with a corresponding pK_i value of 9.5 (Gengo *et al*., 2005). Unlike conventional SSRI antidepressants, which may require time to reach maximum serum concentrations (Hiemke & Hartter, 2000), dapoxetine has a pharmacokinetic profile characterized by peak plasma concentrations approximately 1 h after administration and an initial half-life of approximately 1.4 h (Dresser *et al*., 2005). By 24 h, plasma dapoxetine concentrations are approximately 5% of peak values. These pharmacokinetic findings make dapoxetine an ideal agent for treating a condition such as PE, a condition that intuitively lends a preference for on-demand treatment by patients who suffer from the condition, thereby avoiding the unnecessary usage of a daily dosed regimen of off-label SSRIs and possible related adverse events (AEs). Results of two recent large identical, randomized, double-blind, placebo-controlled studies in 2614 men suffering from severe PE have shown that dapoxetine is effective for the treatment of PE on the first dose, when taken 1–3 h prior to sexual intercourse (Pryor *et al*., 2005). In these studies, men with DSM-IV-TR criteria diagnosed with PE, with the mean IELT $\leqslant$2 min, were randomized 1 : 1 : 1 to placebo, 30 mg dapoxetine, and 60 mg dapoxetine. Each cohort had a 2-week baseline period and a 12-week treatment period. and were instructed to take the study drug 1–3 h prior to the anticipated intercourse. The primary efficacy end point was IELT, as measured by a stopwatch held by the female partner. Secondary end points (subject perception of Control Over Ejaculation and Satisfaction With Sexual Intercourse) were assessed at baseline, 4, 8, and 12 weeks, and rated on 5-point scales of 0 = very poor to 4 = very good.

Preliminary results showed significant differences between placebo and each active treatment group in mean IELT, control over ejaculation, and satisfaction with sexual intercourse ($P<0.0001$ for all end points *versus* placebo). Changes from baseline to the study end point for mean IELT were 0.90–1.75 min (placebo), 0.92–2.78 min (30 mg), and 0.91–3.32 min (60 mg). Changes from baseline to the study end point in percentage of subjects giving ratings of fair, good, or very good for control over ejaculation were 3.5–26.4% (placebo), 2.5–51.8% (30 mg), and 3.3–58.4% (60 mg), and for satisfaction with sexual intercourse, 51.8–55.2% (placebo), 52.4–70.9% (30 mg), and 56.7–79.2% (60 mg). Both dapoxetine 30 mg ($P=0.0006$) and 60 mg ($P<0.0001$) were more effective than placebo in increasing IELT on the first dose. Overall safety findings from these studies indicated that the most common treatment-related AEs (incidence $\geqslant$5%) with both 30 and 60 mg were nausea (8.7%, 20.1%) and headache (5.9%, 6.8%), and with 60 mg only, diarrhoea (6.8%) and dizziness (6.2%). Discontinuation rates due to AEs for placebo, 30 mg, and 60 mg were reported as 0.9, 4, and 10%, respectively.

These initial findings from the largest studies ever undertaken in men suffering with severe PE demonstrate the promising nature of dapoxetine as a viable, efficacious, and tolerable on-demand treatment option for that condition.

Candidates in mid-stage development include UK 390957 (Pfizer Inc., NY, U.S.A.). While no data are available on this new entity, it is being described as a serotonin modulator, which is rapidly acting and is in effect a short acting SSRI. LI-301 (Enhance Biotech, NC, U.S.A.) is being developed as a combination of an unknown SSRI and mu-opiod receptor agonist. VI-0162 (Vivus Inc., Mountain View, CA, U.S.A.) is a 5-HT_3 receptor antagonist also in early development for PE. Topical agents undergoing development for PE include NM-100061 (NexMed Inc., NJ, U.S.A.) and PSD-502 (Plethora Solutions Inc., London, U.K.), which is a formulation of two proprietary local anaesthetics – lidocaine and prilocaine.

Erectile dysfunction

There are currently two classes of oral treatments for treating male ED. The first are the phosphodiesterase-5-inhibitors (PDE5is), such as Viagra® (sildenafil citrate), Levitra® (vardenafil hydrochloride), and Cialis® (tadalfil).

These agents have not only transformed development thinking within male sexual medicine and helped dispel some of the stigma and taboos patients once encountered when seeking treatment for ED, but have also provided the impetus to researchers and regulators alike to examine the need for development of appropriate validated instruments, such as the International Index of Erectile Function (Rosen *et al*., 2002), for assessing ED.

The other class of product (approved in the EU, but not available in the U.S.) is Uprima® (apomorphine), which is a dopamine D2 agonist administered sublingually.

The role of PDE5is as a safe and effective treatment option in men with comorbid cardiovascular disease has gone far to allay fears arising from the earlier inappropriate use of such agents with concomitant medications such as nitrates (Webster & Michelakis, 2004). It is unlikely that any new mechanism of action will be superior in terms of efficacy to PDE5is in the immediate to mid-term landscape. Despite the widespread acceptance of PDE5is in mainstay urological practice, new entities and new mechanisms to treat ED continue to be explored, especially with a view to improved tolerability and safety. Avanafil (Vivus Inc.) is a PDE5i in phase II development. While no data on efficacy are published at the time of print, avanafil is being evaluated for the possibility of demonstrating a lower magnitude of hypotension when given in conjunction with vasodilators such as nitrates (no data have yet been published in this regard and currently all marketed PDE5is are contraindicated for concomitant nitrate use).

PT-141 (Palatin Technologies, Cranbury, NJ, U.S.A.) is a melanocortin agonist currently in phase III development that has demonstrated efficacy and safety in ED patients and in subsets of patients who have not responded to Viagra® (Molinoff *et al*., 2003; Diamond *et al*., 2004; Rosen *et al*., 2004b).

Female sexual dysfunction

Female Sexual Dysfunction (FSD) has received much attention recently both as an area of potential clinical development

and as a focus of unmet medical need. Unlike ED in men, where approved treatments are available, to date no agents have been approved to treat FSD of various subtypes. There is also an absence of universally recognized clinical guidelines in this area. FSD has a high worldwide prevalence. In the U.S.A. alone, approximately 40 million women have been estimated to suffer from the condition (Berman *et al*., 1999). One survey of 1749 women and 1410 men, aged between 18 and 59 years, showed that sexual dysfunction was more prevalent in women than men (43 *versus* 31%, respectively (Laumann *et al*., 1999a). A more recent estimate of 987 women in the U.S.A. suggests that 24.4% are seriously affected by the condition (Bancroft *et al*., 2003).

Recent findings from Brazil (Abdo *et al*., 2004), which surveyed 1219 women, showed that 49% had some form of sexual dysfunction; 26.7% had decreased sexual desire; 23.1% had painful intercourse; and 21% had orgasmic disorder. The prevalence increased with age, lower educational status, and presence of cardiovascular illness and depression. Similar prevalence rates have been reported in Europe, including an estimate of 48% in Sweden (Fugl-Meyer & Fugl-Meyer, 2002).

FSD has many causes, which may be physiological, psychological, or interpersonal in origin. Decreased sexual desire may be related to a dopamine imbalance, decreased sexual arousal may be associated with deficiencies in nitric oxide and acetylcholine, and orgasmic disorders may be linked with serotonin and norepinephrine changes. Age-related changes can also have an effect on FSD. Physiological changes can also have an effect on FSD. Physiological changes during menopause can result in decreased tactile stimulation, shortening and thinning of the vagina, deceased mucous secretions, atrophy of reproductive organs and the bladder. It is not therefore surprising that a decline in sexual arousal and desire, and dyspareunia (painful intercourse), are linked to the menopause. Hormonal changes occurring during menarche, menstrual cycling, pregnancy, lactation, the post-partum period, and the menopause can also have a negative impact on sexual function. Medical conditions, particularly those that affect the neurological, vascular, and endocrine systems, can result in FSD. Prescription drugs (e.g. antidepressants), alcohol, tobacco, illicit drugs, and stress can also contribute to FSD.

At present, FSD consists of four recognized disorders with the following symptoms (APA, 1994; Basson *et al*., 2000):

- hypoactive sexual desire disorder (HSDD – decreased arousal and sexual aversion);
- female sexual arousal disorder (FSAD – decreased arousal and/or arousal problems);
- orgasmic disorder (difficulty or inability to achieve orgasm).
- sexual pain disorder (complex disorders including dyspareunia, vaginismus, and noncoital sexual pain).

These four categories may be further subdivided based on their origin: organic, psychogenic, mixed or unknown, and whether they are intrinsic or acquired *via* specific or general extrinsic causes. A patient can have more than one of these problems, and can actually move between the four recognized FSD disorders, making diagnosis and treatment a challenge.

The two subtypes of FSD that have been the focus of therapeutic development activities are FSAD and HSDD.

Hypoactive desire disorder

The role of androgen deficiency has been discussed for some time in relation to sexual pathology (Judd & Yen, 1973; Judd, 1976; Guay, 2001; Guay *et al*., 2001). Most recent development activities have centered on the value of testosterone replacement in women diagnosed with HSDD. The publication in 2000 of a phase II study highlighted the potential role of a transdermal testosterone patch system in treating HSDD (Shifren *et al*., 2000), which led to subsequent development of the Intrinsa™ Transdermal Testosterone System (Proctor & Gamble). The original work by Shifren *et al*. evaluated the effect of transdermal testosterone in 57 women who were surgically menopausal (i.e. had been oophorectomized and hysterectomized) and who were suffering from impaired sexual function. On a number of PROs focusing on sexual domains, reports of improvement were noted accompanied with an increase in serum testosterone. The treatment also appeared to be tolerated well, with acceptable AEs in the form of androgenic side effects. This study has recently been replicated in a larger setting (Braunstein *et al*., 2005). In December 2004, a FDA advisory panel outcome was not in favour of approving the transdermal testosterone patch based on concerns pertaining to the lack of availability of long-term exposure safety data regarding steroid hormones, coupled with concerns about interpretation of end points, which on face value appeared to offer little numerical improvement over placebo in end points assessing sexual function domains. The findings of a difference in one sexual satisfactory event between active and placebo at completion of 24 weeks of treatment using the sexual activity log reported in the recent transdermal testosterone system study (Braunstein *et al*., 2005) has highlighted the need to place into context the relevance of the clinically meaningful changes that patients suffering from HSDD are reporting when a number of PROs are assessed in totality. This is the primary challenge that researchers and developers are facing in the development of compounds in sexual medicine – that is, to provide adequate and robust information to regulators in terms of benefit to risk ratio, with assessments using validated instruments that are condition specific. Other testosterone preparations are currently also being developed (Libigel™–Biosante and Tostrelle® by Cellegy).

FSAD

The mechanistic basis for development focus in FSAD has centered on the presence of two main pathways that lead to primary clitoral vascular engorgement (the lack of which is thought to be the main pathological focus in FSAD). The two pathways involve cAMP and cGMP phosphodiesterase isoenzymes 3, 4, and 5. Cyclic GMP is one of the secondary messengers modulating intracellular calcium levels in vascular smooth muscle cells and ultimately smooth muscle tone (Park *et al*., 1998). The balance between cGMP synthesis by guanylyl cyclase, induced by nitric oxide, and its hydrolysis regulated by phosphodiesterase (PDE) 5 determines the intracellular concentration of cGMP (Andersson & Wagner, 1995; Beavo, 1995; Burnett, 1997) This pathway has been the focus of development of PDE5is in FSAD.

Cyclic AMP-PDE has been shown to be more abundant in clitoral stromal tissue and nerve fibers (Ueckert *et al*., 2003). The adenylate cyclase-dependent conversion of adenosine

triphosphate (ATP) to cAMP is a pathway that is influenced by prostaglandin E_1 (PGE_1), the other main entity being evaluated in FSAD.

In terms of the cGMP pathway, the role of PDE5is has been evaluated in FSAD. Lann *et al*. (2002) demonstrated in a small healthy volunteer crossover study the effect of sildenafil citrate (Viagra®) 50 mg and placebo on vaginal vasocongestion. Vaginal and clitoral engorgement were noted, but not a subjective improvement in arousal (Laan *et al*., 2002).

Following the aforementioned study, a larger study was completed evaluating sildenafil citrate in a flexible dose-randomized double-blind, placebo-controlled 12-week trial in 202 postmenopausal women diagnosed with FSAD (Berman *et al*., 2003). The primary end points were questions 2 (increased genital sensation during intercourse or stimulation) and 4 (increased satisfaction with intercourse and/or foreplay) from the Female Intervention Efficacy Index (FIEI). Secondary end points were the remaining questions from this index, the Sexual Function Questionnaire and sexual activity event log questions. The results showed significant improvements in FIEI questions 2 ($P=0.017$) and 4 ($P=0.015$) with sildenafil compared with placebo. For women with FSAD without concomitant hypoactive sexual desire disorder (HSDD), sildenafil citrate was associated with significantly greater improvement in five of six FIEI items compared with placebo ($P<0.02$). No significant improvements were shown for women diagnosed with concomitant HSDD. Most AEs were mild to moderate, with headache, flushing, rhinitis, nausea, and visual symptoms reported most frequently.

The most recent developments in FSAD have centered on alprostadil (Alista™-Vivus Inc.) – a prostaglandin E1 agonist. While data are limited, recent results have been presented at the AUA in 2005 in postmenopausal women diagnosed with FSAD (Costabile *et al*., 2005). Following a 4-week nontreatment run-in period, 51 premenopausal women with a diagnosis of FSAD, as confirmed by medical history, questionnaire assessments, and subject interview, were randomly assigned to treatment with alprostadil 400 mcg and placebo in a double-blind, crossover-design study. Each treatment period lasted for 2 months, and treatments were administered in random order. Efficacy measures were based on the proportion of successful and satisfactory sexual encounters, and the number of successful and satisfactory encounters per unit time, as recorded in subject diaries. Additional end points included changes in other diary questions assessing arousal, and Female Sexual Function Index (FSFI) questionnaire responses. The results showed that 64% of alprostadil doses resulted in satisfactory sexual events when compared to placebo ($P<0.05$), in the group of women who received at least one dose each of placebo and active drug. The use of alprostadil also resulted in significant improvement in orgasm, as measured by the increase in the number of events that resulted in orgasm ($P<0.05$) and by the increase in the orgasm domain score of the FSFI questionnaire ($P<0.05$). Application site burning, the most common AE, was reported by 36% of subjects following placebo and 43% following alprostadil administration. The majority of these reports were described as 'mild' and transient with few discontinuations. Currently Alista™ is in phase III development. A topical cream variant of alprostadil (Femprox® – NexMed Inc.) is also undergoing evaluation in FSAD patients.

Conclusions

New emerging clinical therapies for both male and FSD that are on the horizon appear to be effective and well tolerated for potential patients suffering with disorders that, while not being life-threatening, can pose serious burden on individuals and their relationships. However, the current regulatory environment demands a greater focus on the safety profiles of emerging therapies providing appropriate challenges to researchers and developers of such therapies. Consequently, there is a greater impetus to understand, mechanisms that contribute to sexual dysfunction both at the patient level and at the molecular/cellular level. As further evidence-based data are accumulated and published pertaining to new entities in both MSD and FSD, it is hoped that compelling scientific and clinical arguments as to the suitable benefit-to-risk ratio for such compounds is more widely and appropriately debated within regulatory, scientific, clinical, and societal settings, so that appropriate therapies for patients suffering from these unmet medical needs can be provided.

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