

Pharmacotherapy for Premature Ejaculation

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Abstract: Aim. To provide an overview of current knowledge on pharmacotherapy of premature ejaculation (PE).

Materials and Methods. A comprehensive review of the literature was conducted using MEDLINE and analysis of cross-references. The key points of methodology and pharmacology of various articles have been analysed and critically reviewed.

Results. PE may have significant negative impact on quality of life. Various recommendations for drug treatment of PE have been found in the available literature, varying from anesthetic ointments to various antidepressants and phosphodiesterase inhibitors. Due to disturbing side effects, various drugs are not suitable for general use. On the other hand, topical anesthetics, clomipramine and some SSRIs have repeatedly been found safe and effective to delay ejaculation.

Conclusions. Remarkable progress has been made in the treatment of PE. Further research into the neural, psychological and molecular mechanisms involved in PE will lead to the development of even safer, more effective and more convenient therapies for men with PE.

Key Words: Premature ejaculation, treatment, diagnosis.

INTRODUCTION

The three major forms of male sexual dysfunction are ejaculatory dysfunction, erectile dysfunction (ED), and decreased libido. PE is the most prevalent male sexual dysfunction. Erectile dysfunction and decreased libido are less common [1]. The World Health Organization (WHO) includes the right to sexual health among its fundamental rights for the individual. There should be "a freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive freedom". PE has been associated with erosion in sexual self-confidence [2] and low sexual satisfaction in men and their female partners [3]. Before the last decade, the major approach to treating PE was behavioral and psychotherapy, relying on such techniques as the 'pause' and 'squeeze' methods [4,5]. However, the application of the principles of evidence-based medicine shows that there is little evidence to support the psychological approach and behavioral treatment [6]. This paper reviews pharmacological agents in treatment of PE. It describes some of the issues for drug development in this indication, reviewing many of the clinical studies that have already been completed.

DEFINITION OF PREMATURE EJACULATION

There are a number of definitions, none of which is wholly satisfactory. Most men with PE readily recognize their problem and there is no lack of self-assessment. Most men who report PE usually ejaculate prior to or within 1–2 min after vaginal intromission. A small proportion of men ejaculate prior to intromission. A universally accepted definition of PE has yet to be established. Masters and

Johnson proposed one of the earliest definitions that focused on the inability to delay ejaculation long enough for the woman to achieve orgasm 50% of the time, assuming that PE is the sole cause of the female anorgasmia [4]. Kaplan first suggested that PE is primarily a problem of voluntary control over timing of ejaculation [5]. It is obvious that their definition is inadequate because it implies that any partners of a woman who has difficulty in reaching orgasm in half the attempts have PE. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition Text Revision) (DSM-IV-TR) [7] defines PE as "persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it".

Until recently, any scientific basis for the DSM-IV definition was lacking. For instance, the meaning of 'persistent', 'recurrent', 'minimal' and 'shortly after' is vague and certainly needs further qualification. Waldinger *et al.* [8] attempted to operationalise the DSM-IV criteria for PE. They studied 110 men suffering from life long PE and demonstrated that about 10% of the men ejaculated at 1–2 min but most (90%) ejaculated within 1 min of intromission, and 80% were actually ejaculating within 30 seconds, whereas 60% ejaculated within 15 seconds. They also empirically defined life long PE as an ejaculation of <1 min in >90% of episodes of sexual intercourse, independent of age and duration of relationship. Intravaginal ejaculation latency time (IELT) was measured by methods of verbal estimation, list based, imagined (with clock and without) or by using a stopwatch during intercourse. Most men and partners considered the stopwatch as an accurate measurement of their IELT.

The WHO second International Consultation on Sexual Dysfunction proposed a multivariate definition for PE: "Premature ejaculation is persistent or recurrent ejaculation

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with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control which causes the sufferer and/or his partner bother or distress.”

While the above definitions identify multiple criteria for a PE diagnosis, IELT has been the most commonly used endpoint in recent PE studies. In general, an IELT of less than 2 minutes—probably most accurately determined using stopwatch methodology [9]—is thought to provide appropriate definition for PE [10,11].

PE may be classified into various subtypes based on the developmental history and response characteristics. Primary PE is defined as PE that has always been present and secondary PE as the development of PE after a period of perceived normal ejaculatory functioning.

EPIDEMIOLOGY

There is limited information concerning the extent of PE in the general population. In a random survey of 1511 men in the USA, about one third considered that they had ejaculated prematurely over the past year [1]. However, the proportion that perceived their condition as problematic was not stated. Data from the National Health and Social Life Survey have revealed a prevalence of 21% in men ages 18 to 59 in the United States [12]. In general, however, the prevalence of PE is reported as being between 22–38% of adult male population [1,13].

In 1943 Schapiro noted that men with PE seemed to have family members with similar complaints [14]. Waldinger [15] reported that odds of family occurrence is much higher than the suggested population prevalence rate of 4% to 39% and suggested that premature ejaculation is also genetically determined. In addition the psychiatric literature on the prevalence of such disorders is suggestive of family or genetic origins [16].

PATHOPHYSIOLOGY

The ejaculatory response is triggered by genital and cortical stimulation. The glans penis has tactile receptors that are connected *via* the dorsal penile and pudendal nerve to the sacral spinal cord. The sympathetic nerves involved in emission originate from the intermediolateral columns of the spinal cord (T₁₀–L₂) and travel *via* the sympathetic chain and hypogastric nerve to the pelvic plexus and from there *via* the cavernous nerve to the vas deferens. Sympathetic impulses produce smooth muscle contractions of the epididymis and vas deferens that move sperm to the posterior urethra. Seminal vesicles and prostatic glands contract expelling and mixing their fluids with sperm. Eventually this mixture in turn intermixes with fluid from the bulbourethral glands making semen. Semen causes pressure in the wall of the ampullae urethra that culminates to afferent impulses, which reach the spinal cord (S_{2–4}) through the pudendal and pelvic nerves. Expulsion is mediated by motor neurons in the nucleus of Onuf that *via* the pudendal nerve provide coordinated contractions of the bulbo-cavernosus and ischio-cavernosus muscles of the pelvic floor.

Idiopathic primary premature ejaculators may have lower penile sensory thresholds [17] and/or greater cortical penile

representation [18] than their normal counterparts. Animal and sexual psychopharmacological human studies [19] attributed a serotonergic genesis [20–22] and possible genetic etiology [23] to the neurobiological view of PE.

The inhibitory effect of serotonin on libido, ejaculation and orgasms is well documented and has been attributed to a serotonin-induced decrease in dopamine (a neurotransmitter enhancing sexual function) level in the central nervous system. [24,25] Therefore, tricyclic antidepressants (clomipramine) and selective serotonin reuptake inhibitors (SSRIs); (paroxetine, fluoxetine, sertraline) have merged as safe and effective new treatments for patients with PE. In addition, selective noradrenaline reuptake inhibitors nortriptyline and protriptyline have been found to be associated with delayed ejaculation [26]. Among the different subtypes of 5-hydroxytryptamine (5-HT) receptors, the most important ones on ejaculation are 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{2C} receptors [27]. Because the rapid onset of postponement of ejaculation by some of the SSRIs has a similar time course as their synaptic effect on 5-HT, it is suggested that the effect on ejaculation is mediated by acute enhancement of 5-HT neurotransmission or by differential activation of different 5-HT receptor populations, notably 5-HT_{1A} and 5-HT_{2C} receptors [28,29]. Activation of the 5-HT_{1B/1D} receptors also inhibit 5-HT release and male rat ejaculatory behavior [30]. The total absence of ejaculation delay in men who took nefazodone was attributed to its 5-HT_{2C} and 5-HT_{2A} receptor-blocking properties [31].

Organic (e.g. PE secondary to neurological disease, diabetes, pelvic injury, vascular disease, prostatic hypertrophy, chronic prostatitis, hypogonadotropic hypogonadism, pelvic surgery, radical prostatectomy) psychological, behavioral, and biogenic causes have been implicated [32–34]. Both anxiety and depression have been associated with PE [5] although this may be a consequence of the condition rather than a cause. Others have failed to find such an association [35]. As with other sexual disorders, PE is probably caused by a combination of biological-psychological, psychophysiological, and sociobiological; except in unusual cases when a pure cause can be demonstrated [32,36,37]. For example, Grenier *et al.* [38] reported that: "It is more likely that PE is the result of a number of factors that interact than the result of a single factor". Also in another study, Athanasiadis [39] emphasized that: "The hypothesis about a possible interaction between factors might propose a more satisfactory explanation for PE than a one-dimensional approach".

A number of genetic theories have also been proposed to explain PE. It is possible that some racial groups are more susceptible than others to PE [40], particularly men from the Indian subcontinent who may present with the Dhat syndrome [41]. Some or all of the following features characterizes this syndrome: concern about spontaneous seminal loss, affective illnesses, psychosomatic complaints and PE.

DIAGNOSIS

American Urological Association (AUA) guideline on the pharmacologic management of PE recommended, "The

diagnosis of PE is based on sexual history alone. A detailed sexual history should be obtained from all patients with ejaculatory complaints” [42]. In most cases an apparent organic cause is not evident at diagnosis [43,44]. Limited attempts to provide a consensus and more objective criteria for the diagnosis of PE have not succeeded. The diagnosis based on DSM-IV relies on subjective self-reported symptoms. Parameters that are necessary and/or sufficient to make a diagnosis of PE according to the DSM-IV are unclear. Organic causes such as those previously mentioned should be ruled out. In general, an IELT of less than 2 minutes—probably most accurately determined using stopwatch methodology—is thought to provide adequate sensitivity for diagnosis.

TREATMENT

General Considerations

Medical treatment in PE needs careful interpretation with respect to design and methodology of studies [45,6]. Subjective estimation and questionnaire assessments of ejaculation latency may lead to higher variability in clinical outcome measures [45], therefore, for the most accurate determination of ejaculation latency the best method is the use of stopwatch. Treatment of PE should primarily attempt to alleviate concern about the condition as well as to increase sexual satisfaction in the patient and partner. The risks and benefits of all treatment options should be discussed with the patient prior to any intervention. Patient and partner satisfaction is the primary target outcome for the treatment of PE. Men with PE secondary to erectile dysfunction, other sexual dysfunction or organic causes should receive appropriate etiology specific treatment. Simple measures such as education to discuss sexual norms, and facilitation of sexual negotiation between the couple may be useful.

Some medications cause sexual dysfunction as a side effect (Table 1). Use of some sympathomimetics [47] such as ephedrine sulfate, pseudoephedrine hydrochloride, and phenylpropanolamine hydrochloride and withdrawal from some other drugs, such as trifluoperazine hydrochloride [48], and opiates [49-51] can cause PE. Simply discontinuing an agent that is thought to cause PE in order to eliminate it from the body may be considered if the general health and physician permit it.

Psychosexual Behavioral Therapy

Historically the cause of PE has been considered to be psychological. The psychoanalytic idea of unconscious conflicts being the cause of PE has never been investigated in a manner that allowed generalization, as only case reports on psychoanalytic therapy have been published. This is also true for behavioral therapy. These have included psychoanalytical approaches although it is the behavioral and cognitive approaches that have proven most effective. These include the stop-squeeze method [52] developed in 1956 and later adopted by Masters and Johnson in their sex therapy clinic as well as other approaches that have become the gold standard for treatment of PE [53]. Stop-start and squeeze techniques or the sensate-focus phase are used in therapeutic programs for the treatment of PE. The techniques are performed as effective treatments that delay PE by reducing

or removing stimulation, [4,54] but longitudinal follow-up results of treatment for PE are even rarer than controlled outcome investigations, and long-term success rates are disappointing [36]. In addition, the application of the principles of evidence-based medicine shows that there is little evidence to support the psychological approach and behavioral treatment [6].

Drug Therapy

The primary therapeutic approach to PE is pharmacotherapy. Pharmacological treatment of men with PE may include a variety of approaches. No pharmacological agents are licensed for use for PE. However many centrally and peripherally acting drugs have been proposed to treat primary PE. These include

- 1- Selective serotonin reuptake inhibitors (SSRIs)
- 2- Tricyclic antidepressants
- 3- Monoamine oxidase inhibitors
- 4- Topical anesthesia
- 5- Neuroleptics
- 6- Sympatholytics
- 7- Phosphodiesterase inhibitors

In the next paragraphs an overview will be presented of the various drug treatment studies for premature ejaculation that have been published since 1943. Apart from the phosphodiesterase inhibitor studies, all of these drug treatment studies have previously been categorized in a systematic review and meta-analysis study, published by Waldinger *et al.* in 2004 [9].

Selective Serotonin Reuptake Inhibitors (SSRIs)

Probable mechanism of these drugs is the enhancement of net serotonergic transmission by blocking the presynaptic 5-hydroxytryptamine (serotonin, 5-HT) uptake site [20,55]. Pre-clinical researches clearly indicate the role of serotonin in ejaculatory processes. Among the different subtypes of 5-HT receptors, the most important ones on ejaculation are HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{2C} receptors. Administration SSRIs, results in active blockade of presynaptic membrane 5-HT transporters, and the resultant higher synaptic cleft levels of 5-HT activate post-synaptic 5-HT_{2C} and 5-HT_{1A} receptors and delay ejaculation. 5-HT_{1A} receptor activation by the selective 5-HT_{1A} receptor agonist 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylaminotetralin) or flesinoxan inhibits the release of 5-HT in the synaptic cleft, shortens the ejaculation latency time and reduces the number of intermissions preceding ejaculation in animals. 5-HT_{2C} receptor agonists D-LSD (D-lysergic acid diethylamide) and quipazine cause ejaculation delay [56]. In summary, SSRIs activate the 5-HT_{2C} receptor and therefore switch the threshold to a higher level, leading to a delay in ejaculation.

There are 2 drug treatment strategies to treat PE with SSRIs: 1) daily treatment 2) as-needed treatment. Waldinger *et al.* reported that, on-demand SSRI treatment has less ejaculation-delaying effects than daily SSRI treatment [57]. Acute administration of various SSRIs, such as,

Table 1. Sexual Side Effects of Common Prescription Medications

Type of drug	Generic name	Sexual side effects
<i>Antihypertensive medications</i>		
Diuretics	Spironolactone Thiazides, Furosemide	Decreased libido, breast swelling, impotence Impotence None
Centrally acting agents	Methyldopa Clonidine Reserpine	Decreased libido, impotence Impotence Decreased libido, impotence, depression
α -Adrenergic blockers	Prazosin Terazosin	“Dry” (retrograde) ejaculation “Dry” (retrograde) ejaculation
β -Adrenergic blockers	Propranolol Metoprolol	Impotence, decreased libido Impotence, decreased libido
Combined α - and β -adrenergic blockers	Labetalol	Inhibited ejaculation
Nonadrenergic vasodilator	Hydralazine	None
Sympathetic nerve blocker	Guanethidine	Impotence, “dry” (retrograde) ejaculation
Angiotensin-converting enzyme inhibitors	Captopril Enalapril Lisinopril	None None Impotence in a small percentage (1%) of cases
<i>Psychiatric medications</i>		
Antidepressants		
Tricyclics	Amitriptyline Amoxapine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline	Inhibited ejaculation, impotence Decreased libido, impotence Inhibited ejaculation Inhibited ejaculation, impotence Inhibited ejaculation, impotence Inhibited ejaculation Inhibited ejaculation Inhibited ejaculation, impotence
Atypical agent	Trazodone	Priapism
Monoamine oxidase inhibitors	Isocarboxazid Phenelzine Tranlycypromine	Inhibited ejaculation Inhibited ejaculation, decreased libido Inhibited ejaculation
Antipsychotic medications		
Phenothiazine group	Thioridazine Chlorpromazine Mesoridazine Fluphenazine	Inhibited ejaculation, priapism, decreased libido Inhibited ejaculation Inhibited ejaculation, decreased libido Inhibited ejaculation, decreased libido

(Table 1. Contd....)

Type of drug	Generic name	Sexual side effects
Serotonin reuptake inhibitors	Fluoxetine Perphenazine Trifluoperazine	Anorgasmy (8%) Inhibited ejaculation Inhibited ejaculation
Thioxanthene group	Chlorprothixene Thiothixene	Inhibited ejaculation Inhibited ejaculation, impotence
Butyrophenone	Haloperidol	Inhibited ejaculation
Antimania medication	Lithium carbonate	Possible impotence
<i>Antiulcer medications</i>		
	Cimetidine Ranitidine Famotidine	Decreased libido, impotence, gynecomastia None None
<i>Antifungal agent</i>		
	Ketoconazol	Impotence

citalopram, clomipramine, paroxetine, sertraline, fluoxetine and fluvoxamine did not have any delaying effects on ejaculation in male rats [58]. After acute paroxetine (a SSRI) administration there is an initial increased serotonin release, rapidly followed by a decreased serotonergic neurotransmission associated with minimal post-synaptic 5-HT_{2C} receptor stimulation. After chronic paroxetine administration, however, ejaculation delay is not only due to an important increased amount of serotonergic (5-HT) neurotransmission but also to desensitization of presynaptic 5-HT_{1A} autoreceptors and post-synaptic 5-HT_{2C} receptors. The net effect of chronic SSRI administration is thus a stronger enhancement of 5-HT neurotransmission with a consequently stronger activation of postsynaptic 5-HT receptors compared with acute SSRI administration [20,55]. Also human studies demonstrated that, acute SSRI administration has only weak IELT delaying effect [59]. Some prefer that these agents be taken "as needed" rather than as chronic drug treatment, because of the reduced risk, side effects and cost [60,61]. Our preference is daily administration of these agents.

All SSRIs have potential side effects. These drugs are well absorbed from the gastrointestinal tract and are metabolized by the liver and excreted by the liver and kidneys. Therefore, the dose should be adjusted downward in men with hepatic or renal impairment. The adverse event profiles of the SSRIs reported in the treatment of PE are similar to those reported in patients being treated for depression. The type and rate of occurrence of side effects appear to be acceptable to most patients and typically include gastrointestinal upset, dry mouth, drowsiness, dizziness, headache and reduced libido.

All the SSRIs are absolutely contraindicated in combination with the monoamine oxidase inhibitors (MAOIs). The SSRI should also not be prescribed to men with prior or

active seizure disorders, anxiety disorders, or recent myocardial infarctions [39].

Except for fluoxetine it is advised not to stop the SSRIs acutely, but to do so gradually over 3–4 weeks, to avoid withdrawal symptoms [6].

Since the late 1980s, five SSRIs have been licensed for the treatment of depression: citalopram, paroxetine, sertraline, fluoxetine, and fluvoxamine.

Citalopram

Ranking SSRIs regarding their selectivity reveals citalopram, sertraline, paroxetine, fluvoxamine, and fluoxetine, in decreasing order [62]. If selectivity for the serotonergic system over other systems would be the determining factor for the inhibitor process on ejaculation, it would be expected that citalopram would cause considerable delay in ejaculation. Work on citalopram has been inconsistent. For example, in a randomized, double-blind study 31 men with PE were randomly assigned to receive paroxetine (20 mg/day) and citalopram (20 mg/day) for 5 weeks. Paroxetine exerted a strong delay (8.9-fold increase, whereas citalopram mildly delayed ejaculation (1.8-fold) [62]. However, a later study showed clear benefit [63]. Thirty men were randomly assigned to two groups on a double-blind basis. Fifteen patients received citalopram (group 1) for 8 weeks while the remainders receive no therapy (group 2). Patients in group 1 initially received 20 mg/day citalopram for 1 week; this was titrated up to 60 mg/day according to the patient's tolerability and clinical response (Final dose of citalopram, 30.7mg). IELT increased from 38.5 seconds at baseline to 362 seconds after 8 weeks of treatment. Atmaca *et al.* reported that citalopram treatment considerably increases IELT [64]. Williamson *et al.* [65] and de Jong *et al.* [66] had found that acute administration of citalopram in male rats had no

4–6 hours prior to intercourse induced a six [85], and four fold-increase [61,71,93] of the ejaculation time, respectively. The side-effects of clomipramine may consist of nausea, dry mouth and fatigue. Sometimes clomipramine and the SSRIs may give rise to reversible feelings of diminished libido or moderately decreased rigidity of the penis [6]. Generally for treatment of PE, clomipramine is administered 25mg/day.

Monoamine Oxidase Inhibitors

Case reports of the delaying effects of nonselective, irreversible monoamine oxidase inhibitors, for example isocarboxazid [94] and phenelzine, [95] were published. However, the use of these various drugs is not recommended for treatment of PE due to their disturbing and sometimes quite serious side effects [9]. It must be remembered that, all the SSRIs are absolutely contraindicated in combination with the monoamine oxidase Inhibitors.

Topical Anesthesia

Some investigators have evaluated patients with PE by penile biothesiometry and have demonstrated that patients with primary PE have penile hypersensitivity and can be treated by desensitizing preparations [96]. Patients with PE have changes in the autonomic reflex pathways related to ejaculation [97], including a lower vibratory threshold for ejaculation, shorter bulbocavernous reflex latency time, and higher bulbocavernous evoked potentials [96]. Therefore local anesthetic creams have been used to reduce sensory stimulation from the body and glans penis during foreplay and intercourse and thereby prolong ejaculatory latency. The use of topical anesthetic ointments is probably the oldest treatment for delaying ejaculation. The disadvantage of topical desensitizing creams is the unpleasant effect of penile numbness. Also, some men report that their partners complain of vaginal or clitoral anesthesia, especially if the man does not use a condom. In addition, possible transvaginal absorption can result in vaginal numbness and resultant female anorgasmia unless a condom is used. Condoms are always advised when using these preparations to avoid transferring the cream to the partner. The condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Topical anesthetics are contraindicated in patients who are either allergic themselves or have partners who are allergic to any component of the product.

EMLA Cream

Lidocaine 2.5% and prilocaine 2.5% cream is a eutectic mixture of local anesthetics (EMLA), which can penetrate intact skin and provide reliable local analgesia. The local topical anesthetic combination of prilocaine and lidocaine is among the most effective formulations. When EMLA Cream is applied for 15 min, both the sensory and the pain thresholds increase further and dermal analgesia persists for 1–2 h after removal of the cream [98]. Prolonged application of topical anesthetic (30 to 45 minutes) has been reported to result in loss of erection due to numbness of the penis in a significant percentage of men [99]. EMLA Cream has been found to be efficient for local anesthesia in PE [100]. This agent has also been successfully used off-label for treating PE [99]. Application of EMLA Cream for 20 min has been

determined as the optimum period in the treatment of premature ejaculation [99].

SS-Cream

Another pharmacologic treatment option is the topical SS-cream. This made from the extracts of nine natural products. It has not yet been approved by the FDA and is not available in USA. The pharmacological constituents and active chemical have not been described [101]. In the Far East good results were reported with SS-cream, a regionally manufactured cream consisting of various herbs [101-103], used 1–2 h before intercourse. Xin *et al.* reported a decrease in the amplitude of somatosensory potentials with the use of SS-cream, applied to the glans penis of patients with PE [102]. Once available in USA, physicians may wish to suggest it to their patients.

Neuroleptics

In the 1960s case reports described the ejaculation delaying effects of some neuroleptics. Thioridazine [104,105] and chlorprothixene [106] delayed ejaculation by blocking central dopamine receptors. However, the use of neuroleptics is not recommended, because they have disturbing and sometimes quite serious side effects.

Sympatholytics

Adrenergic, dopaminergic and serotonergic systems are all involved in the regulation of male sexual function [107–109]. Sympatholytic agents such as phenoxybenzamine, yohimbine and doxazosin have been shown to inhibit the response of rat seminal vesicle to electrical field stimulation [110]. Human ejaculation is peripherally activated by α_1 -noradrenergic nerve stimulation [55]. An α -adrenergic blocker may induce dysfunctional ejaculation by decreasing contractions of the seminal vesicles, ampulla and ductus deference [111]. Some authors tried to influence the peripheral sympathetic nervous system by administering sympatholytic drugs, such as the α_1 and α_2 -adrenergic blocker, phenoxybenzamine [112,113] or the selective α_1 -adrenergic blockers alfuzosin and terazosin [114]. Clinically, phenoxybenzamine [112] has been used to treat PE.

In a double-blind, cross-over trial alfuzosin and terazosin were effective in 50% of 91 premature ejaculators resistant to psychological therapy as judged by an ejaculation latency proving satisfactory for patient and partner [115]. Tamsulosin, an α_{1A} -adrenoreceptor antagonist used for the treatment of benign prostatic hypertrophy causes abnormal ejaculation in 4.5–14% men as an adverse event and in a dose related fashion [116]. There are not sufficient evidences to support a recommendation for sympatholytic use in treatment of PE.

Phosphodiesterase Inhibitors

Hull *et al.* observed that nitric oxide (NO) may inhibit seminal emission in male rats, probably by decreasing sympathetic nervous system activity [117]. Kriegsfeld *et al.* noted that mice lacking endothelial NO synthase (eNOS) showed a higher incidence of premature ejaculation [118]. In addition, Heuer *et al.* observed *in vitro* that the NO-cGMP cascade in part regulates human seminal vesicle contractility [119]. Furthermore, it has been suggested that nitric oxide

activity in the medial preoptic area tonically inhibits ejaculation by decreasing sympathetic tone [120]. These are rationales for using NO donating drugs as pharmacotherapy for PE. Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5, which has been approved as a first line oral therapy for erectile dysfunction [121,122]. It thus enhances the relaxant effect of nitric oxide released in response to sexual stimulation by increasing cGMP concentrations in the corporal smooth muscle [123]. In a study sildenafil administered as needed as a single treatment for PE, increased IELT more than paroxetine (15 versus 4 minutes) [93]. In that study sildenafil proved to be superior to all other treatment methods in terms of IELT control and overall satisfaction ($p < 0.0001$). In contrast, clomipramine, sertraline and paroxetine appear to be comparable in terms of safety and efficacy.

A number of studies suggest that adding a PD₅ inhibitor such as sildenafil to an SSRI such as paroxetine is better for PE than either drug alone [124,125]. Abdel-Hamid *et al.* attributed the excellent success associated with sildenafil use to three possible mechanisms. The first is reduction in performance anxiety, the second is that sildenafil may maintain erection and increase the erection time, and ejaculation latency time was reported to be dependent on erection time, and the third is a possible central effect. The recommended dose of sildenafil for treatment of PE is 50 mg 3-5 hours before planned intercourse.

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