

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	Spirolactone 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

significant effects on copulatory parameters, including ejaculation time and number of ejaculations. The recommended dose of citalopram is 20mg/day.

Paroxetine

Paroxetine has proved to be effective, well tolerated oral treatment for PE in patients without any organic causes [59,67,68]. The drug is absorbed well *via* gastrointestinal tract and is metabolized by the liver. A steady-state concentration is reached in the serum within 7–14 days, and 64% is excreted by the kidneys and 36% by the liver [67]. A meta-analysis of all drug treatment studies, conducted by Waldinger *et al.* [9] showed that paroxetine exerts the greatest ejaculation delay. The rank order of efficacy (fold increase of IELT) is (1) paroxetine (8.8; 95% CI: 5.9–13.2); (2) clomipramine (4.6; 3.0–7.4); (3) sertraline (4.1; 2.6–7.0); and (4) fluoxetine (3.9; 3.0–5.3) [11].

Waldinger *et al.* reported the first trial of an SSRI for PE in 1994 [59]. This randomized, double-blind, placebo-controlled study found that paroxetine significantly improved PE. Giammusso *et al.*, Ludovico *et al.* and McMahon have also reported significant improvement in ejaculatory control with paroxetine [67,69,70]. Daily administration of paroxetine however, was more efficacious than as needed [71]. On-demand 20 mg paroxetine had no clinical relevant ejaculation delay in men with life long PE with an IELT of less than 1 minute [71]. In a double-blind stopwatch study in men with life long PE, it was found that on-demand treatment with 20 mg paroxetine exerted a fold-increase IELT of only 1.41 (95% CI: 1.22–1.63) at a drug coitus interval time of approximately 5 hours [71]. The daily dose of 20 mg paroxetine is an adequate treatment for PE.

Sertraline

Recently, sertraline turned out to be a potentially very useful drug. Mendels *et al.* described the first use of sertraline in PE in 1995 showing that sertraline increased IELT in men with PE [72]. In a cross-over, single-blind, placebo-controlled trial, sertraline 50 mg once daily for 4 weeks significantly increase IELT (mean 0.3 increased to 3.2 min) in 37 men with PE [73]. In another double-blind, placebo-controlled, cross-over trial, Kim and Seo [74] compared the efficacy of placebo, fluoxetine 40 mg once daily, sertraline 100 mg once daily and clomipramine 50 mg once daily over 4 weeks for the treatment of PE. The mean pre-treatment IELT was less than 1 min and over 4 weeks this was significantly increased to 2.27, 2.3, 4.27 and 5.75 min, respectively.

In one study, two thirds of the patients on continuous sertraline for 7 months maintained their improvement after drug withdrawal [75]. The majority of evidence shows effectiveness with 50 mg daily dosing.

Fluoxetine

The fluoxetine hydrochloride is an antidepressant with strong action as selective serotonin re-uptake inhibitor. In addition of its SSRI property, it increases IELT seemingly by its action of elevating the penile sensory threshold value without changing the variables of cortical somatosensory evoked potential and sacral evoked response tests [76].

Fluoxetine inhibits ejaculation in male rats presumably by influencing serotonergic receptors in the nucleus paragigantocellularis. In an animal study the ejaculation delay induced by fluoxetine was reversed by the administration of oxytocin [77]. This finding suggests that fluoxetine induced delayed ejaculation is also related to inhibited oxytocin release.

In various double-blind, placebo controlled studies 20 mg fluoxetine, have been shown to be effective for treatment of PE [78,79]. Manasia *et al.* [80] compared the efficacy and safety of 90 mg fluoxetine weekly with 20 mg fluoxetine daily. There was no statistical difference between the different doses. However, the cure rate was greater with 90 mg fluoxetine weekly. They concluded that this new dose of fluoxetine for the treatment of PE has the advantage of administration of 1 capsule per week. Their study also showed that 90 mg fluoxetine weekly increased significantly IELT. The recommended dose of fluoxetine is 20 mg/day.

Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor and is widely used in the treatment of depression and other psychiatric disorders [81]. Waldinger *et al.* [82] compared the efficacy of fluoxetine, fluvoxamine, paroxetine, and sertraline in 60 men with PE. At baseline, the mean IELT was approximately 20 seconds. After 6 weeks of treatment, fluoxetine, paroxetine, and sertraline all increased the mean IELT above this placebo level significantly while fluvoxamine did not. In another study, 100 mg. fluvoxamine daily resulted only mild to moderate delay in IELT [19]. The mild delay of fluvoxamine was replicated in a placebo controlled male rat study using a chronic administration treatment model [83]. Fluvoxamine is therefore not recommended for the treatment of PE.

Tricyclic Antidepressants

Clomipramine

Clomipramine is a tricyclic antidepressant that inhibits the reuptake of norepinephrine as well as serotonin and was the first to be investigated in men who suffered from PE [84,85]. Clomipramine activate 5-HT_{2C} receptor and, therefore, change the set point to a higher level, leading to a delay in ejaculation [15]. Clomipramine has also been shown to be effective in the treatment of PE by its action to elevate the penile sensory threshold without changing the variables of cortical somatosensory evoked potential and sacral evoked response tests [86]. Besides serotonin reuptake inhibition, clomipramine also inhibits the reuptake of noradrenaline. Selective noradrenaline reuptake inhibitors nortriptyline and protriptyline have been found to be associated with delayed ejaculation [87]. Eaton published the first open study of clomipramine in men with PE in 1972 [88]. Later case reports and double-blind studies, repeatedly demonstrated the effectiveness of clomipramine at low daily doses for delaying ejaculation [84,89-91]. Clomipramine, sertraline and paroxetine appear to be comparable in terms of safety and efficacy [9]. Clomipramine has improved IELT and other measures of PE when prescribed at doses of 25 and 50 mg/day or 25 mg 4 to 24 hours prior to intercourse [92]. Three on-demand studies with 25 mg of clomipramine taken

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.

REFERENCES

- [1] Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; 281: 537-544.
- [2] Symonds T, Roblin D, Hart K, Althof S. How does premature ejaculation impact a man's life? *J Sex Marital Ther* 2003; 29: 361-70.
- [3] Byers ES, Grenier G. Premature or rapid ejaculation: Heterosexual couples' perceptions of men's ejaculatory behavior. *Arch Sex Behav* 2003; 32: 261-70.
- [4] Masters WH, Johnson VE. *Human Sexual Inadequacy*. Boston: Little, Brown, 1970; 92-142
- [5] Kaplan, H. S. *The New Sex Therapy: Active Treatment of Sexual Dysfunctions*. New York: Brunner/Mazel, 1974.
- [6] Waldinger MD. Life long premature ejaculation: From authority based to evidence based medicine. *Br J Urol Int Update Series* 2004; 93: 201-7.
- [7] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 4th edn. Text Revision*. Washington DC: American Psychiatric Association; 2000.
- [8] Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. An empirical operationalisation study of DSM IV diagnostic criteria for premature ejaculation. *Int J Psych Clin Pract* 1998; 2: 287-293.
- [9] Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: A systematic review and meta-analysis. *Int J Impot Res* 2004; 16: 369-81.
- [10] Rowland DL, Cooper SE, Schneider M. Defining premature ejaculation for experimental and clinical investigations. *Arch Sex Behav* 2001; 30: 235-53.
- [11] Perelman MA, McMahon CG, Barada JH. Evaluation and treatment of the ejaculatory disorders. In: Lue T, editor. *Atlas of male sexual dysfunction*. Philadelphia, PA: Current Medicine, Inc: 2004; 127-57.
- [12] Fisher E. Common sexual problems in general practice. *Aust Fam Phys* 1986; 15: 43-47.
- [13] Spector IP, Carey MP. Incidence and prevalence of sexual dysfunctions. A critical review of the empirical literature. *Arch Sex Behaviour* 1990; 19:4: 389-408.
- [14] Schapiro B. Premature ejaculation: a review of 1130 cases. *J Urol* 1943; 50: 374-9.
- [15] Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol* 2002; 168: 2359-2367.
- [16] Stoudemire A. (Ed.). *Clinical psychiatry for medical students* (2nd ed.). Philadelphia: J. B. Lippincott 1994.
- [17] Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. *J Sex Marital Ther* 1989; 15: 130-134.
- [18] Colpi GM, Fanciullacci F, Beretta G, Negri L, Zanolla A. Evoked sacral potentials in subjects with true premature ejaculation. *Andrologia*. 1986; 18: 583-586.
- [19] Waldinger MD, Hengeveld MW. Neuroseksuologie en seksuele psychofarmacologie. *Tijdschr Psychiatr* 2000; 8: 585-9.
- [20] Olivier B, van Oorschoot R, Waldinger MD. Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behaviour. *Int Clin Psychopharmacol* 1998; 13(Suppl. 6): S9-14.
- [21] Waldinger MD, Olivier B. Selective serotonin reuptake inhibitors (SSRIs) and sexual side effects: differences in delaying ejaculation. In: *Fluvoxamine: Established and Emerging Roles in Psychiatric Disorders. Advances in Preclinical and Clinical Psychiatry*. Edited by E. Sacchetti and P. Spano. Milan: Excerpta Medica, 2000; vol. 1: 117-130.
- [22] Waldinger MD, Olivier B. Hersenonderzoek en farmacologie: serotonine, seks en agressie. In: *Het Brein Belicht: Opstellen over Niet-Aangeboren Hersenletsel*. Edited by M. H. J. Wolters-Schweitzer and C. L. Beuger. Utrecht: Uitgeverij Lemma, 2001; 55-63.
- [23] Waldinger MD, Rietschel M, Nothen MM, Hengeveld MW, Olivier B. Familial occurrence of primary premature ejaculation. *Psychiatr Genet* 1998; 8: 37-40.
- [24] Remy L. The effect of selective 5HT reuptake inhibitors on 5-methoxy-N, N-dimethyltryptamine induced ejaculation in the rat. *Br J Pharmacol* 1986; 87: 639-48.
- [25] Baldesarani RJ, Mars E. Fluoxetine and side effects. *Arch General Psychiatry* 1990; 47: 191-2.
- [26] Pollack MH, Reiter S, Hammerness P. Genitourinary and sexual adverse effects of psychotropic medication. *Int J Psychiat Med* 1992; 22: 305-27
- [27] Ahlenius S, Larsson K, Svensson L, *et al.* Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. *Pharmacol Biochem Be* 1981; 15: 785-92.
- [28] Szele FG, Murphy DL, Garrick NA. Effects of fenfluramine, m-chlorophenylpiperazine and other serotonin-related agonists and antagonists on penile erections in non-human primates. *Life Sci* 1988; 43:1297-303.
- [29] Molewijk HE, van der Heyden JAM, Olivier B. Lower lip retraction is selective mediated by activation of the 5-HT1A receptor. *Eur J Neurosci* 1989; 214(suppl. 2), 121.
- [30] Hillegaart V, Ahlenius S. Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT1A and 5-HT1B receptor agonists. *Brit J Pharmacol* 1998; 125: 1733-43.
- [31] Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomized, placebo-controlled, fixed-dose study with paroxetine, sertraline, and nefazodone. *J Clin Psychopharm* 2001; 21: 293-7.
- [32] Rowland DL, Slob AK. Premature ejaculation: psychophysiological considerations in theory, research and treatment. *Ann Rev Sex Res* 1997; 8: 224-253.
- [33] Goldmeier D, Keane FEA. The aetiology and treatment of premature ejaculation. *Sexual Dysfunction* 1998; 1: 59-69.
- [34] Garippa P. Multiple severe sexual dysfunctions resolved in brief sex therapy. *J Sex Marital Ther*. 1991; 17: 220-223.
- [35] Strassberg DS, Mahoney JM, Schaugaard M, Hale VE. The role of anxiety in premature ejaculation. A psychophysiological model. *Arch Sex Behav* 1990; 19: 251-257.
- [36] Metz ME, Pryor JL. Premature ejaculation: A psychophysiological approach for assessment and management. *J Sex Marital Ther* 2000; 26: 293-320.
- [37] Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological, and physical problems in men and women: A cross-sectional population survey. *J Epidemiol Commun H* 1999; 53: 144-148.
- [38] Grenier G, Byers ES. Rapid ejaculation: A review of conceptual, etiological, and treatment issues. *Arch Sex Behav* 1995; 24: 447-472.
- [39] Athanasiadis L. Premature ejaculation: Is it a biogenic or a psychogenic disorder? *Sexual & Marital Therapy* 1998; 13: 241-255.

- [40] Rushton JP, Bogaert AF. Race versus social class differences in sexual behaviour: a follow up test of the r/K dimension. *J Res Personal* 1988; 22: 259-272.
- [41] Bhatia MS, Malik SC. Dhat syndrome – a useful diagnostic entity in Indian culture. *Brit J Psychiatry* 1991; 159: 691-695.
- [42] Montague DL, Jarow J, Broderick GA, *et al.* American Urological Association guideline on pharmacologic management of premature ejaculation. 2004; 172: 290–294.
- [43] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington DC: APA, 1994.
- [44] McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol* 1999; 161: 1826-30.
- [45] Waldinger MD. Towards evidence-based drug treatment research on premature ejaculation: A critical evaluation of methodology. *Int J Impot Res* 2003; 15: 309–13.
- [46] Sae Chul K, Kyung Keun S. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol* 1998; 159: 425-427.
- [47] Thomas AJ. Ejaculatory dysfunction. *Fertil Steril* 1983; 39: 445–
- [48] Keitner GI, Selub S. Spontaneous ejaculations and neuroleptics. *J Clin Psychopharm* 1983; 3: 34–36.
- [49] Blachly PH. Management of the opiate abstinence syndrome. *Am J Psychiatry* 1986; 122: 742–744.
- [50] Buffum J. Pharmacosexology. The effects of drugs on sexual function: A Review. *Journal of Psychoactive Drugs* 1982; 14: 5–44.
- [51] Buffum J. Prescription drugs and sexual function. *Psychiatr Med* 1992; 10: 181–198.
- [52] Semans J. Premature ejaculation. *Southern Med J* 1956; 49: 352–358.
- [53] Seftel AD, Althof SE. Premature ejaculation. In: Mulcahy JJ ed. *Diagnosis and management of male sexual dysfunction*. New York: Igaku-Shoin, 1997; 196–203.
- [54] Rowland DL, Cooper SE, Slob AK. The treatment of premature ejaculation: psychological and biological strategies. *Drugs Today*. 1998; 34: 879–899.
- [55] Waldinger MD, Berendsen HHG, Blok BFM, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressant-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res* 1998; 92: 111–118.
- [56] Ahlenius S, Larsson K, Svensson L. Further evidence for an inhibitory role of central 5-HT in male rat sexual behavior. *Psychopharmacology (Berl.)* 1980; 8(3): 17-20.
- [57] Waldinger MD, Zwinderman AH, Olivier B. On-Demand SSRI Treatment of Premature Ejaculation: Pharmacodynamic Limitations for Relevant Ejaculation Delay and Consequent Solutions. *J Sex Med* 2005; 2: 121–131.
- [58] Mos J, Mollet I, Tolboom JTB, Waldinger MD, Olivier B. A comparison of the effects of different serotonin reuptake blockers on sexual behaviour of the male rat. *Eur neuropsychopharmacol* 1999; 9: 123–35.
- [59] Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: A double-blind, randomised, placebo-controlled study. *Am J Psychiatry* 1994; 151: 1377–9.
- [60] Haensel SM, Rowland DL, Kallan KT. Clomipramine and sexual function in men with premature ejaculation and controls. *J Urol* 1996; 156: 1310-5
- [61] Strassberg DS, de Gouveia Brazao CA, Rowland DL, Tan P, Slob AK. Clomipramine in the treatment of rapid (premature) ejaculation. *J Sex Marital Ther* 1999; 25: 89–101.
- [62] Waldinger MD, Zwinderman AH, Olivier B. SSRIs and Ejaculation: A Double-Blind, Randomized, Fixed-Dose Study With Paroxetine and Citalopram. *J Clin Psychopharmacol* 2001; 21: 556-60.
- [63] Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Semercioz A. Serum leptin levels in patients with premature ejaculation before and after citalopram treatment. *BJU Int* 2003; 91: 252-4.
- [64] Atmaca M, Karadag F, Tezcan E. Serum Antioxidant Enzymes and Malondialdehyde Levels in Patients with Premature Ejaculation Before and After Pharmacotherapy. *J Sex Med* 2005; 2: 254–258.
- [65] Williamson IJR, Turner L, Woods K, Wayman CP, van der Graaf PH. The 5-HT_{1A} receptor antagonist robalzotan enhances SSRI-induced ejaculation delay in the rat. *Br J Pharmacol* 2003; 138(suppl.1): PO32.
- [66] de Jong TR, Pattij T, Veening JG, *et al.* Citalopram combined with a silent 5-HT_{1A} receptor antagonist strongly inhibits male rat sexual behavior and ejaculation-related Fos expression. *Neuroscience Poster. Second Dutch Endo-Neuro-Psychomeeting*. Doorwerth. The Netherlands, June 2003.
- [67] Ludovico GM, Corvasce A, Pagliarulo G, Cirillo-Marucco E, Marano A, Pagliarulo A. Paroxetine in the treatment of premature ejaculation. *Br J Urol* 1996; 77: 881-82.
- [68] Waldinger MD, Hengeveld MW, Zwinderman AH. Ejaculation-retarding properties of paroxetine in patients with primary premature ejaculation: a double-blind, randomized, dose-response study. *Br J Urol* 1997; 79: 592-5.
- [69] Giammusso B, Morgia G, Spampinato A, Motta M. Paroxetine in the treatment of premature ejaculation. *Arch Ital Urol Androl* 1997; 69: 11-3.
- [70] McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride. *Int J Impot Res* 1999; 11: 241–246.
- [71] Waldinger MD, Zwinderman AH, Olivier B. On-demand treatment of premature ejaculation with clomipramine and paroxetine: A randomized, double-blind fixed-dose study with stopwatch assessment. *Eur Urol* 2004; 46: 510–6.
- [72] Mendels J, Camera A, Sikes C. Sertraline treatment for premature ejaculation. *J Clin Psychopharmacol* 1995; 15: 341–6.
- [73] Roblin D. Premature ejaculation: diagnosis and pharmacotherapy. *Int J Pharm Med* 2000; 14: 313–318.
- [74] Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind placebo controlled study. *J Urol* 1998; 159: 425–427.
- [75] McMahon G. Treatment of premature ejaculation with sertraline: a single blind placebo controlled crossover study. *J Urol* 1998; 159: 1935-1938.
- [76] Yilmaz U, Tatlisin A, Turan H, Arman F, Ekmekcioglu O. The effects of fluoxetine on several neurophysiological variables in patients with premature ejaculation. *J Urol*. 1999; 161(1): 107-11.
- [77] Cantor JM, Binik YM, Pfaus JG. Chronic fluoxetine inhibits sexual behavior in the male rat: reversal with oxytocin. *Psychopharmacology* 1999; 144: 355-62.
- [78] Kara H, Aydin S, A_argin MY, Odabas Ö, Yilmaz Y. The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind placebo controlled study. *J Urol* 1996; 156: 1631-2.
- [79] Murray MJ, Hoerberman D. Fluoxetine and prolonged erection. *Am J Psychiatry* 1993; 150: 167-8.
- [80] Manasia P, Pomerol J, Ribe N, Gutierrez del Pozo R, Alcover Garcia J. Comparison of the efficacy and safety of 90 mg versus 20 mg fluoxetine in the treatment of premature ejaculation. *J Urol*. 2003; 170(1): 164-5.
- [81] Palmer KJ, Benfield P. Fluvoxamine: an overview of its pharmacological properties and review of its therapeutic potential in non-depressive disorders. *CNS Drugs*. 1994; 1: 57–87.
- [82] Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: A double-blind, randomized, placebocontrolled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol* 1998; 18: 274–81.
- [83] Waldinger MD, van De Plas A, Pattij T, *et al.* The selective serotonin re-uptake inhibitors fluvoxamine and paroxetine differ in sexual inhibitory effects after chronic treatment. *Psychopharmacology* 2002; 160: 283-9
- [84] Segraves RT, Saran A, Segraves K, Maguire E. Clomipramine vs placebo in the treatment of premature ejaculation: a pilot study. *J Sex Marital Ther* 1993; 19: 198–200.
- [85] Riley AC, Riley EJ. Pharmacotherapy for sexual dysfunction: current status. In AJ Riley, M Peet, and C Wilson, eds. *Sexual Pharmacology*. Oxford: Clarendon, 1993; 211–26.
- [86] Colpi GM, Fanciullacci F, Aydos K, Grugnetti C. Effectiveness mechanism of clomipramine by neurophysiological tests in subjects with true premature ejaculation. *Andrologia* 1990; 23: 45-7.
- [87] Kilic S, Ergin H, Baydinc YC. Venlafaxine extended release for the treatment of patients with premature ejaculation: a pilot, single-blind, placebo-controlled, fixed-dose crossover study on short-term administration of an antidepressant drug. *Int J Androl* 2005; 28(1): 47-52.

- [88] Eaton H. Clomipramine in the treatment of premature ejaculation. *J Int Med Res* 1973; 1: 432.
- [89] Goodman RE. An assessment of clomipramine (anafranil) in the treatment of premature ejaculation. *J Int Med Res, suppl* 1980; 8: 53-9.
- [90] Porto R. Essai en double aveugle de la clomipramine dans l'éjaculation prematuree. *Med Hygiene* 1981; 39: 1249-54.
- [91] Girgis SM, El-Haggen S, El-Hermouzy S. A doubleblind trial of clomipramine in premature ejaculation. *Andrologia* 1982; 14: 364-8.
- [92] Althof SE, Levine SB, Corty EW, Risen CB, Stern EB, Kurit DM. A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry* 1995; 56: 402-7.
- [93] Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. *Int J Impot Res* 2001; 13: 41-5.
- [94] Bennett D. Treatment of ejaculatio praecox with monoamine oxidase inhibitors (letter to the editor). *Lancet* 1961; 2: 1309.
- [95] Rapp MS. Two cases of ejaculatory impairment related to phenelzine. *Am J Psychiatry* 1976; 136: 1200-1.
- [96] Xin ZC, Chung WS, Choi YD, Seong DH, Choi YJ, Choi HK. Penile sensitivity in patients with primary premature ejaculation. *J Urol* 1996; 156: 979-981.
- [97] Vignoli G. Premature ejaculation: new electrophysiologic approach. *Urology* 1978; 11: 81-2
- [98] Arendt-Nielsen L, Bjerring P. Laser-induced pain for evaluation of local analgesia: a comparison of topical application (EMLA) and local injection (lidocaine). *Anesth Analg* 1985; 57: 997-1005.
- [99] Atikeler MK, Gecit I, Senol FA. Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia* 2002; 34: 356-69.
- [100] Berkovitch M, Keresteci AG, Koren G. Efficacy of prilocaine-lidocaine cream in the treatment of premature ejaculation. *J Urol* 1995; 154:1360-1361.
- [101] Choi HK, Xin ZC, Choi YD, Lee WH, Mah SY, Kim DK. Safety and efficacy study with various doses of SS-cream in patients with premature ejaculation in a double-blind, randomized, placebo controlled study. *Int Impot Res* 1999; 11: 261-264.
- [102] Xin ZC, Choi YD, Lee SH, Choi HK. Efficacy of a topical agent SS-cream in the treatment of premature ejaculation: preliminary clinical studies. *Yonsei Med J* 1997; 38: 91-5.
- [103] Choi HK, Jung GW, Moon KH, *et al.* Clinical study of SS-cream in patients with lifelong premature ejaculation. *Urology* 2000; 55: 257-61.
- [104] Singh, H. A case of inhibition of ejaculation as a side effect of Mellaril. *Am J Psychiatry* 1961; 117: 1041, 1961.
- [105] Freyhan FA. Loss of ejaculation during mellaril treatment. *Am J Psychiatry* 1961; 118: 171-2.
- [106] Ditman KS. Inhibition of ejaculation by chlorprothixene. *Am J Psychiatry* 1964; 120: 1004-5.
- [107] Bitran D, Hull EM. Pharmacological analysis of male rat sexual behavior. *Neurosci Biobehav Rev* 1987; 11: 365-89.
- [108] Kimura Y, Kisaki N, Sakurada S, Tadano T. On the brain monoaminergic systems relating to ejaculation. I. Brain dopamine and ejaculation. *Andrologia* 1976; 8: 313-20.
- [109] Kimura Y, Kisaki N, Sakurada S, Tadano T. On the brain monoaminergic systems relating to ejaculation. II. Brain serotonin and ejaculation. *Andrologia* 1977; 9: 50-4.
- [110] Swartz DA. Sertraline HCl for premature ejaculation. *J Urol* 1994; 151:345A, abstract 471.
- [111] Kedia K, Markland C. The effect of pharmacological agents on ejaculation. *J Urol.* 1975; 114(4): 569-73.
- [112] Shilon M, Paz GF, Hommonai ZT. The use of phenoxybenzamine treatment in premature ejaculation. *Fertil Steril* 1984; 42: 659-61.
- [113] Hommonai ZT, Shilon M, Paz GF. Phenoxybenzamine: an effective male contraceptive pill. *Contraception* 1984; 29: 479-81.
- [114] Cavallini G. Alpha-1 blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. *Eur Urol* 1995; 28: 126-30.
- [115] Hsieh JT, Liu SP, Hsieh CH, Chend JT. An *in vivo* evaluation of the sympatholytic agents on premature ejaculation. *BJU Int* 1999; 84: 503-506.
- [116] Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. *Ann Pharmacother* 2000; 34: 188-99.
- [117] Hull EM, Lumley LA, Matuszewich L, Dominguez J, Moses J, Lorrain DS. The roles of nitric oxide in sexual function of male rats. *Neuropharmacology* 1994; 33: 1499-504.
- [118] Kriegsfeld LJ, Demas GE, Huang PL, Burnett AL, Nelson RJ. Ejaculatory abnormalities in mice lacking the gene for endothelial nitric oxide synthase (eNOS^{-/-}). *Physiol Behav* 1999; 67: 561-6.
- [119] Heuer O, Uckert S, Machtens SA, *et al.* Effects of various nitric oxide donating agents on the contractility and cyclic nucleotide turnover of human seminal vesicles *in vitro*. *Urology* 2002; 59: 958-62.
- [120] Pfau JG. Neurobiology of sexual behavior. *Curr Opin Neurobiol* 1999; 9: 751 - 758.
- [121] Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* 1998; 338: 1397-404.
- [122] McMahon, C. G., Samali, R. and Johnson, H.: Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. *J Urol*, 164: 1192, 2000.
- [123] Padma-Nathan H, Shabsigh R. Sildenafil citrate (Viagra): a review. *AUA update series* 1999; 18: 274 - 280.
- [124] Abdel-Hamid A. Phosphodiesterase 5 inhibitors in rapid ejaculation: Potential use and possible mechanisms of action. *Drugs* 2004; 64: 13-26.
- [125] Salonia A, Maga T, Colombo R, *et al.* A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. *J Urol* 2002; 168: 2486-2489.