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Marcel D Waldinger MD, PhD

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EXPERT OPINION

Pharmacotherapy for premature ejaculation

Marcel D Waldinger
Drexel University College of Medicine, Department of Pharmacology and Physiology, Philadelphia, USA

Introduction: Four premature ejaculation (PE) subtypes are distinguished on the basis of the duration of the intravaginal ejaculation latency time (IELT), its course in life, and frequency of complaints. Since the 1930s oral drug treatment and local anesthetics have been used to treat PE. Apart from dapoxetine, all currently available drugs to treat PE (SSRIs, clomipramine, and local anesthetics) are off-label. Not only men with lifelong and acquired PE, but also men with normal IELT values may want to postpone their ejaculation time.
Areas covered: The guideline of the International Society for Sexual Medicine for the treatment of PE has provided evidence-based recommendations for the pharmacotherapy of lifelong and acquired PE. Selective serotonin reuptake inhibitors (SSRIs) delay ejaculation by interfering with the serotonin (5-HT) neurotransmission system in the central nervous system. Attention is given not only to the well-known but also to the recently published, very rare side effects of SSRIs.
Expert opinion: Men with normal IELT values who want to postpone ejaculation do not need "drugs for the treatment of PE" but "ejaculation delaying drugs." Pharmacological research of these ejaculation-delaying drugs ought to be investigated in men with normal IELT values, such as in men with subjective PE, variable PE, and in male volunteers.

Keywords: clomipramine, dapoxetine, local anesthetics, post selective serotonin reuptake inhibitors sexual dysfunction, premature ejaculation, selective serotonin reuptake inhibitors, serotonin

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1. Introduction

Since the first publications of premature ejaculation (PE) at the beginning of the last century, pharmacotherapy of PE has been advocated as its first choice of treatment.[1,2] For example, Präjaculin, developed by Bernard Schapiro in the early 1930s, has been the first oral drug that was produced for the treatment of PE.[1] The use of topical local anesthetics, containing benzocaine or lidocaine, was another pharmacological way to treat PE in the years before and after World War II.[2] Despite the existence of these drugs and a psychosomatic view on the origin of PE, the prevailing view throughout the years has been that PE is a pure psychological disorder that had to be treated by psychotherapy.[3] Notably, similar to the fact that there is no evidence that psychotherapy "cures" PE, there is no evidence that drug treatment cures PE. Drug treatment only delays ejaculation as long as the drug is taken by the patient. On the other hand, psychotherapy or counselling may have beneficial effects on how to cope with PE.[4]

1.1 Definition of premature ejaculation

Recently, the International Society for Sexual Medicine has defined lifelong and acquired PE in a single definition.[5] According to this new definition, PE is characterized by: 1. An ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration (lifelong PE), or a clinically significant

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Article highlights.

- The distinction of four premature ejaculation (PE) subtypes is clinically relevant for PE treatment.
- Of all SSRIs, daily use of 20 mg paroxetine exerts the strongest ejaculation delay.
- Dapoxetine is the first drug that is registered by the EMA for on-demand treatment of PE.
- Topical treatment with local anesthetics has a low risk of side effects.
- In contrast to the other three PE subtypes, lifelong premature ejaculation is characterized by easily facilitated erections, premature ejaculation and immediate penile detumescence after ejaculation.
- "Ejaculation Delaying Drugs" should be distinguished from "Drugs for the Treatment of PE".
- Pharmacological research of "Ejaculation Delaying Drugs" ought to be investigated in men with normal IELTs and PE complaints (e.g., Variable and Subjective PE) as in men with no PE complaints (e.g., male volunteers).

This box summarizes key points contained in the article.

and bothersome reduction in latency time, often to about 3 min or less (acquired PE); 2. The inability to delay ejaculation on all or nearly all vaginal penetrations; and with 3. Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy. In the same period of time, the DSM 5.[6]uses a rather different definition of PE. According to the DSM 5, PE is "A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it. This must have been present for at least 6 months and must be experienced on almost all or all (approximately 75% – 100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts). In addition, it causes clinically significant distress in the individual and it is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition".[6] The DSM 5 adds that although the diagnosis PE may be applied to individuals engaged in non-vaginal sexual activities, specific duration criteria have not been established for these activities.

1.2 Classification of premature ejaculation

In 1943, Schapiro.[2]distinguished two types of premature ejaculation, type B and type A, which later have been renamed to lifelong and acquired premature ejaculation.[7] In lifelong PE, the individual suffers from early ejaculations since puberty at each coitus, with each female partner since puberty or adolescence. In contrast, in acquired PE the early ejaculations begin later in life after a period of normal ejaculatory performance. Recently, Waldinger and Schweitzer.[8,9]proposed an extension of the initial classification by Schapiro by adding the existence of two other subtypes, for example, subjective PE and variable PE, on the basis of the duration of the intravaginal ejaculation latency time (IELT), its course throughout life and the frequency of early ejaculations.[8,9] Moreover, this new classification was based on the results of two stopwatch mediated epidemiological IELT studies in five countries.[10,11] As predicted, it appeared that the prevalence of these four subtypes differs. In Turkey and a Chinese province, the prevalence of lifelong and acquired PE is 2 and 3%, and 4 and 5%, respectively.[12,13] The prevalence of subjective and variable PE is 5 and 7%, and 8 and 11%, respectively.[12,13] The total prevalence of 20 – 25% represents the number of men in the general population who are not satisfied with their ejaculation time. However, and importantly, not all of them have the same type of PE. The distinction of four PE subtypes is clinically relevant for PE treatment. For example, while the IELT in lifelong PE is consistently less than about 1 min.[14,15]– often even occurring within about 15 or 30 s.[14]– the IELT occurs within about 3 min in acquired PE.[5] In contrast, the IELT has a normal duration, for example, around 2 – 5 min or more, in subjective PE. Men with subjective PE complain of PE while having a normal IELT duration.[9] In variable PE, short IELTs occur rather sporadically, which may be considered as a natural variation of the IELT (Figure 1).[9] Whereas lifelong PE should be treated with medication, and the underlying somatic cause should be treated in acquired PE, counselling and psycho-education is more appropriate as treatment for subjective and variable PE, albeit these men may also benefit from local anesthetics.[9] The distinction of the four PE subtypes illustrates that there is not one particular pathophysiology of PE, but that there are different pathophysiologies and also treatments dependent on the type of PE.[9] A major advantage of the new classification system is that any male individual with a complaint of

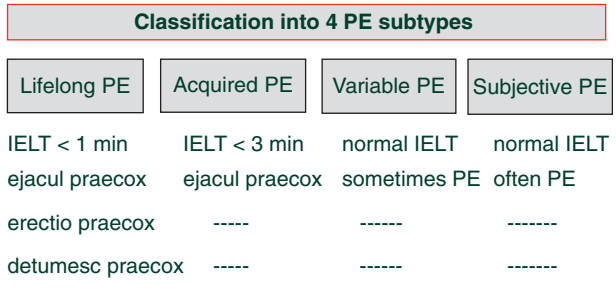

Figure 1. Classification of four premature ejaculation subtypes. The four PE subtypes are distinguished on the basis of the duration of the IELT, its course throughout life and the frequency of symptoms (See References.[8]and.[9].

premature ejaculation can be categorized in one of the four PE subtypes. In the last two decades, animal and human research works have focused their investigations on the neurobiological hypothesis of PE, that is, a disturbance of central serotonin neurotransmission and/or serotonin receptor functioning.[16] However, the four PE subtype classification, shows that the serotonin hypothesis probably only pertains to lifelong PE and partly to acquired PE. In other words, the serotonin hypothesis explains probably only a small percentage (2 – 5%) of complaints of PE in the general population. The pathophysiology of acquired PE is related to disturbances of peripheral neuronal functioning whereas the pathophysiology of subjective PE is speculated to be related to cognitive and/or unconscious mental processes.

2. Neurobiology and neuropsychopharmacology

The strong ejaculation delaying effects of daily SSRI treatment has stimulated *in vivo* animal psychopharmacological research which has been the major source of a better understanding of the involvement of central 5-HT neurotransmission and 5-HT receptors in relation to the ejaculatory process.[17-20] However, although the serotonergic system and other neurotransmitter systems, like the dopaminergic and oxytocinergic systems, are involved in SSRI-induced delay of ejaculation, the neurobiology of PE itself remains to be elucidated. For a better understanding of the strong ejaculation-delaying effects of daily SSRI treatment and the mild ejaculation-delaying effects of on-demand classical SSRI treatment, some basic knowledge of central serotonergic metabolism is pivotal.

2.1 Serotonin neurotransmission and serotonergic receptors

Serotonergic (5-hydroxytryptamine; 5-HT) neurons regulate their own activity by three mechanisms.[21] Under normal physiological conditions, endogenous somatodendritic release of 5-HT activates (presynaptic) 5-HT_{1A} autoreceptors that are present on the cell bodies and dendrites of serotonergic neurons in the raphe nuclei of the brainstem. Activation of these 5-HT_{1A} autoreceptors decreases firing of the 5-HT neuron and consequently lowers the 5-HT release from the presynaptic neuron into the synaptic cleft (mechanism 1). After release of 5-HT in the synapse, presynaptic 5-HT_{1B} autoreceptors become activated that in turn also inhibits the 5-HT release from the presynaptic neuron into the synaptic cleft (mechanism 2). As a result a tendency for increased 5-HT content in the synapse has become diminished. This feedback mechanism of the neuron probably prevents overstimulation of (post) synaptic 5-HT receptors. Another auto-mechanism to prevent overstimulation of postsynaptic 5-HT receptors is the immediate removal of 5-HT in the synapse back into the presynaptic neuron by 5-HT transporters (5-HTT), which are not only present at the pre-synaptic endings but also at the serotonergic cell bodies and dendrites (mechanism 3).

2.1.1 *Acute and chronic administration of SSRIs*

2.1.1.1 *Acute administration*

All 5-HT transporters are blocked after acute SSRI administration leading to higher 5-HT levels in the synaptic cleft and in the extracellular space around the cell bodies of 5-HT-containing nerves. The increased extracellular 5-HT levels activate 5-HT_{1A} autoreceptors and consequently lead to lower 5-HT release into the synaptic cleft within minutes. The diminished release of 5-HT in the synaptic cleft compensates (completely or partially) the initially increased 5-HT concentrations as the result of the SSRI-induced blockade of the 5-HT re-uptake by transporters from the synaptic cleft into the presynaptic neuron. Higher 5-HT concentrations in the synapse will increase the activation of presynaptic 5-HT_{1B} autoreceptors that by itself will attenuate 5-HT release. The net effect of acute SSRI administration, under physiological conditions, is only a mild or no increase of 5-HT neurotransmission and mild or no stimulation of all post-synaptic 5-HT receptors.[22]

2.1.1.2 *Chronic administration*

Chronic administration of selective serotonin reuptake inhibitors (SSRIs) leads to a number of adaptations. The ongoing blockade of 5-HTTs results in a persistent increase of 5-HT levels in the synaptic cleft and around somatodendritic cell bodies. This leads to desensitization of 5-HT_{1A} autoreceptors over the course of 2 weeks, possibly also desensitization of 5-HT_{1B} autoreceptors, and consequently to less inhibition on 5-HT release into the synaptic cleft. The net effect of chronic SSRI administration is thus a stronger enhancement of 5-HT neurotransmission with a consequently stronger activation of post-synaptic 5-HT receptors compared with acute SSRI administration.

2.1.2 *Serotonergic, dopaminergic and oxytocinergic system*

Various neurotransmitters, like serotonin, dopamine, and oxytocine are involved in the ejaculatory process.[23] It might well be that these three neurotransmitter systems are also involved in the pathophysiology of PE at least when PE is defined in terms of a persistently very short (i.e., less than 1 minute) ejaculation time concurrent with a persistent inability to delay ejaculation. Only in these men it is assumed that a neurobiological dysfunction underlies the very short IELT.

2.1.3 *Ejaculatio praecox, erectio praecox and detumescentia praecox*

Recently, Waldinger.[24]noted that for many decades one has – understandably – focused rather solely on the short ejaculation time (ejaculatio praecox) of men with lifelong PE, whereas Schapiro already noted that these men may also

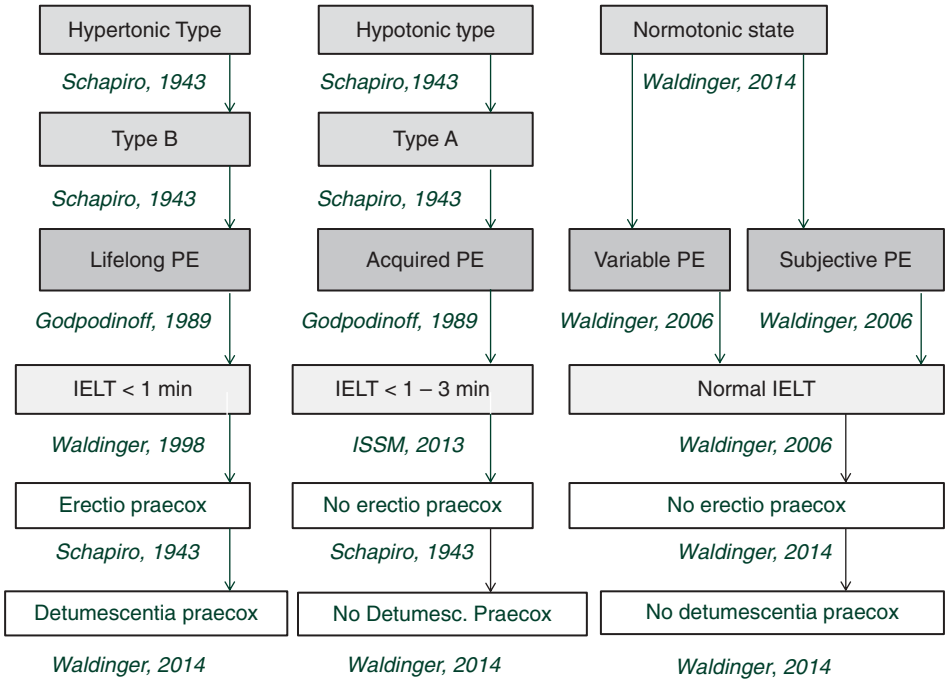

Figure 2. Historical overview of classification of four PE subtypes and symptomatology of lifelong premature ejaculation (See References.[2]and.[24].

experience a facilitated erection (erectio praecox). Waldinger introduced the term detumescentia praecox to denote the rather immediate penile detumescence that these men experience after each ejaculation.[24] In addition, he used the term hypertonic state to denote that as soon as these men get involved in an erotic situation their cerebro-genital system develops an elevated state of facilitated erection, facilitated ejaculation and a facilitated penile detumescence (Figure 2). As this hypertonic state cannot be explained by involvement of only the central serotonergic system, Waldinger adapted his serotonergic hypothesis on PE. Accordingly, he postulated that the hypertonic state is probably related to a central and peripheral interaction of a number of neurotransmitters (serotonin, dopamine, oxytocin, noradrenaline), hormonal factors (testosterone and prolactin), and genetic polymorphisms of the aforementioned systems.

2.1.4 *Hormonal factors*

In line with this new hypothesis are the data of endocrinological research that particularly in recent years have shown that hormonal factors are associated with the IELT. For example, testosterone acts on several areas within the central and peripheral nervous system, most of them related to the ejaculatory reflex.[25-27] In addition, it was found that prolactin levels are positively correlated with the ejaculation time, for example, prolactine levels are low in men with PE and high in men with delayed ejaculation.[26,27] Moreover, low TSH levels have been found in men with acquired PE. [26,27]but not in men with lifelong PE.[28] Interestingly, it was shown that medical treatment of hypothyroidism resulted in a reduction of the ejaculation time.[29]

3. Treatment of the four PE subtypes

Because of the very short IELT durations, lifelong PE should be treated with drugs that strongly delay ejaculation. It is a matter of debate whether additional counselling is always needed for these men. A lot of these men can be effectively treated by SSRIs without additional counselling, but it is advisable to inform all these men on the type of PE that affects them and the efficacy and side effects of the various drugs. Therefore, clinicians should take time to talk with these men, to inform them about the current knowledge of lifelong PE and to regularly check their well-being, particularly when using SSRIs on a daily basis.

Acquired PE needs to be treated with either drugs to treat underlying medical pathology, or psychotherapy to treat underlying psychological pathology, or both with or without additional other drug treatment options like SSRIs or topical anesthetics.[4]

Men with Subjective PE should be treated with counselling, psycho-education, psychotherapy or couple-therapy with or without combination of local anesthetics. Whether these men, particularly when they have a normal ejaculation time, should be treated with SSRIs remains a matter of debate. These men should be informed that in the case of a

normal or even long IELT duration psychological, cultural or relationship factors are likely to contribute to their complaint.

Men with Variable PE usually cope well with their coincidental early ejaculations, but in the case of seeking treatment, it is advised to inform them that the occurrence of sporadic early ejaculation is part of normal ejaculatory performance. Presumably, psychoeducation will probably be sufficient for these men to regain confidence. Due to the incidental nature of early ejaculations, one should not treat these men with SSRIs.

3.1 Drug treatment of premature ejaculation

There are six major treatments of premature ejaculation: i) daily use of SSRIs, ii) on-demand use of dapoxetine, iii) on-demand use of clomipramine, iv) on-demand use of topical local anesthetics, v) on-demand use of tramadol, and vi) on-demand use of phophodiesterase type-5 inhibitors.[4]

With the exception of dapoxetine, all these treatments are off-label. Although daily SSRI treatment very effectively delays ejaculation, none of the companies producing the SSRIs (paroxetine, fluoxetine, sertraline, citalopram and es-citalopram) has been interested to get a FDA or European Medicine Agency (EMA) registration for the treatment of PE, as it was argued that it would acknowledge an unwanted sexual side effect of their antidepressant drug. In 2005, the EMA has registered dapoxetine 30 mg and 60 mg, a fast-acting SSRI, for the on-demand treatment of PE.[30]

3.1.1 *Daily treatment with SSRIs*

The intravaginal ejaculation latency time (IELT) is defined as the time between the start of vaginal penetration and intravaginal ejaculation.[31] In scientific studies, it is measured with a stopwatch. A substantial number of randomized, double-blind, placebo-controlled studies have shown the efficacy of daily SSRIs treatment in mentally healthy men with complaints of PE.[32] With exception of fluvoxamine the SSRIs exert a clinically relevant ejaculation delay.[32] This effect is expressed as the fold-increase (FI) of the geometric mean IELT (Fold-increase = IELT value at the end of SSRI treatment/IELT value at baseline).[33]

A meta-analysis of daily SSRI treatment studies.[32] revealed a rather low placebo-effect, for example, a geometric mean 1.4-fold IELT increase (95% CI: 1.2 – 1.7). The meta-analysis also demonstrated a rank order of efficacy: i) paroxetine 8.8 FI (95% CI: 5.9 – 13.2); ii) clomipramine 4.6 FI (3.0 – 7.4); iii) sertraline 4.1 FI (2.6 – 7.0) and iv) fluoxetine 3.9 FI (3.0 – 5.4). Thus, in general, daily SSRI treatment studies generate a 2.6 to 13.2 geometric mean IELT-fold increase, dependent on the type of SSRI.[32] Moreover, of all SSRIs, daily use of 20 mg paroxetine exerts the strongest ejaculation delay in the investigated males. The meta-analysis also demonstrated that compared to stopwatch studies measuring the IELT, open and single-blind studies lead to exaggerated IELT values and that retrospective assessment of the IELT by a questionnaire or subjective report lead to far more variability of the IELTs.[32]

The outcome data of the SSRI treatment studies published between 2003 and 2015 hardly distort the findings of the meta-analysis of 2004 and therefore its conclusions are still valid today.

3.1.1.1 *Dosages of daily SSRI treatment*

Daily treatment can be performed with paroxetine 20 mg, clomipramine 10 – 40 mg, sertraline 50 – 100 mg, fluoxetine 20 mg, citalopram 20 mg, and escitalopram 20 mg.[4] (Table 1). Ejaculation delay usually starts a few days after intake. However, a clinically relevant effect only gradually occurs within 1 – 3 weeks. Most often the delay continues to exist for years, as long as the SSRI is used, but sometimes it may disappear after 6 – 12 months. The cause of this tachyphylaxis has not yet been clarified.[34]

Daily SSRI treatment is effective in delaying ejaculation, but it does not delay ejaculation in every patient and in the same extent. Ejaculation delay occurs in 70 – 80% of men. In about 20% of men with lifelong PE, SSRIs do not have relevant ejaculation-delaying effect. In such cases one may switch to another SSRI, but other SSRIs may not have an ejaculation-delaying effect either.

3.1.1.2 *Advantages and disadvantages of daily SSRI treatment*

A clear advantage of daily SSRI treatment is that there is a delayed ejaculation at every spontaneous sexual event. Daily intake does not interfere with the spontaneity of sexual activity. However, a disadvantage is the risk of specific side effects on the short and long term, the risk of a discontinuation syndrome.[35,36] rare side effects such as bleeding.[37] and priapism.[38,39] effects on spermatozoa and very rare

Table 1. Daily and On-demand treatment of premature ejaculation.

Treatment strategy	Medication
Daily intake	Paroxetine 20 mg Sertraline 50 – 100 mg Citalopram 20 mg Fluoxetine 20 mg Escitalopram 20 mg
On-demand intake	Dapoxetine 30 – 60 mg 1 – 3 h a.c. Clomipramine 10 – 40 mg 6 – 10 h a.c Local anesthetics 20 – 30 min a.c.

Most common drugs and their usual dosages.
a.c.: Ante coitus.

side effects such as Restless Genital Syndrome (ReGS) in the male.[40] and Post SSRI Sexual Dysfunction (PSSD).[41,42]

3.1.2 SSRI-induced side effects

3.1.2.1 Side effects on the short term

On the short-term fatigue, yawning, mild nausea, loose stools, or perspiration may occur. These side effects are usually mild, start in the first 1 – 2 weeks of treatment, and most often gradually disappear within 2 – 3 weeks.[34] Although a head-to-head comparative study has not yet been performed, drug treatment studies seem to indicate that in contrast to the side-effects in depressed patients, diminished libido and erectile dysfunction occur less frequently and also to a lesser extent in healthy non-depressed men with life-long PE.

3.1.2.2 Side effects on the long term

On the long term, weight gain and sexual side effects may occur. These sexual side effects are reversible, but in extremely rare cases they are irreversible.

3.1.2.3 SSRI discontinuation syndrome

Patients should be advised not to stop taking the SSRI acutely in order to prevent the occurrence of an SSRI discontinuation syndrome, which is characterized by symptoms like tremor, shock-like sensations when turning the head, nausea, and dizziness.[35,36] One should inform the patient at the beginning that discontinuation of the treatment should be carried out very gradually within about 2 and sometimes even 3 months.

3.1.2.4 Interaction with other drugs of substances

It is recommended that patients should diminish their use of alcohol particularly in the first weeks of SSRI treatment, as SSRIs may facilitate a "typsi" state. Young men should be informed not to use XTC while taking an SSRI. Its interaction may cause the potentially lifethreatening serotonergic syndrome. Older men should be informed not to take tramadol as its interaction with an SSRI may also lead to a serotonergic syndrome. One should not prescribe SSRIs to men <18 years and to men known with depressive disorder particularly when associated with suicidal thoughts. In those cases, referral to a psychiatrist is indicated.

3.1.2.5 Restless genital syndrome in the male

In rare cases, decreasing the dosage of an SSRI or discontinuation of an SSRI may give rise to the Restless Genital Syndrome (ReGS).[40] In males, ReGS is presumably caused by a sensoric neuropathy of the dorsal nerve of the penis, which is an endbranch of the pudendal nerve.[40] ReGS in the male is characterized by persistent, unwanted, disturbing penile sensations of ejaculatory urgency, usually at the basis and top of the penis, in the absence of erection, sexual desire, and/or sexual arousal. However, often these men also report some sort of penile sexual arousal.

3.1.2.6 Negative effects of SSRIs on spermatozoa

Particularly in young patients, one should inform the patients that hardly anything is known about the effect of SSRIs on spermatozoa, as research on this topic has hardly been performed. However, a few small studies have shown potential harmful effects of SSRIs on spermatozoa.[43,44] It is recommended that in the case of a wish for pregnancy, the male should not start SSRI treatment or when he is already using an SSRI for PE to gradually diminish the dosage of the SSRI and stop taking the drug for 3 – 4 months.[34] As it takes quite some time for spermatozoa to be renewed, it is advised to make love with a condom for 3 – 4 months after discontinuation of the drug, after which pregnancy is allowed. Notably, this advice is not based on any hard evidence, but only to prevent possible problems in the future when it may perhaps appear that SSRIs used by the male affect fertility or even may lead to congenital disorders.

3.1.2.7 Post-SSRI sexual dysfunction (PSSD)

Usually SSRI-induced sexual side effects are reversible, for example, their intensity diminishes with dose reduction and they disappear within a few days after SSRI discontinuation. However, in extremely rare cases, the sexual side effects are irreversible, for example, after SSRI discontinuation they do not disappear.[41] Recently, two types of post-SSRI sexual dysfunction (PSSD) have been distinguished.[42] Characteristic of both types is the occurrence of penile anesthesia or numbness of the penis, which may be the first symptom of PSSD. Therefore, patients using SSRIs should be informed to stop taking the SSRI as soon as the patient experiences genital anesthesia. PSSD may start within a few days to a few weeks after the start of SSRI treatment with complaints of sudden complete loss of libido, arousal, erection and ejaculation with genital anesthesia, or it may become manifest after SSRI discontinuation as an aggravation of already existing moderate sexual side effects.[42] Sofar the pathophysiology and treatment of PSSD remain unclear.

3.1.3 On-demand treatment with oral drugs and topical anesthetics

On-demand treatment with oral drugs may also give rise to side effects or interactions with other drugs. Patients should be informed about the risk of a serotonergic syndrome in case serotonergic drugs (dapoxetine/tramadol) are taken together with other serotonergic drugs.

3.1.3.1 Advantages and disadvantages of on-demand drug treatment

A clear advantage of on-demand oral drug treatment is that there is no risk of getting the side effects of long-term drug treatment. Another advantage is that one can use the drug

only when it is required for a better sexual performance. However, a disadvantage is that on-demand oral drug treatment may negatively interfere with the spontaneity of sexual activity, particularly when one is inclined to have sex at the spur of the moment.

3.1.3.2 On-demand treatment with dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI. It inhibits serotonin reuptake in the synapse similar to all other SSRIs. However, this mechanism of action occurs faster after intake. Dapoxetine is the first drug that is registered by the EMA for on-demand treatment of PE [30,45-48]. Dapoxetine (either 30 mg or 60 mg) should be taken 1–3 h prior to intercourse. Its efficacy and side effects have been investigated in more than 6,000 patients. Although the extent of ejaculation delay is usually rather small, studies have shown a 3.6- to 4.5-fold increase, reporting also that dapoxetine may lead to satisfaction and more feelings of control in men with lifelong and acquired PE. In the studies performed dapoxetine showed a good safety profile and a reasonable prevalence of dose-dependent side effects. The most common side effects include nausea, dizziness, and headache. Importantly, no SSRI discontinuation syndrome following abrupt withdrawal has been reported.[49]

3.1.3.3 On-demand treatment with clomipramine

On-demand use of clomipramine 10 – 40 mg is known to delay ejaculation in men with PE. Its efficacy has been investigated in a few studies.[32] The most common side effects include dry mouth, blurred vision, constipation, and nausea. However, with on-demand treatment these side effects disappear within 1 – 2 days.

3.1.3.4 On-demand treatment with topical local anesthetics

The use of topical local anesthetics is well established and is effective in delaying ejaculation in men with lifelong and acquird PE.[4] By diminishing the glans penis sensitivity it is argued that the spinal and cerebral input of sexually arousable impulses is reduced. However, unequivocal hard evidence for this hypothesis is not yet available.

Two recent meta-analyses confirmed the efficacy and low side effect profile of topical anesthetics.[50,51] Too much application may cause penile hypesthesia, numbness or erectile difficulties. Transfer of the cream to the female partner may lead to vaginal numbness. To avoid such transfer, the use of a condom is recommended. Analysis of eight trials has shown the efficacy and safety of topical anesthetic treatment for lifelong PE.[50,51] Currently, there are four local anesthetics for the treatment of PE: EMLA cream, TEMPE spray, Stud-100 spray and Promescent spray. However, these local anesthetics are not (yet) available in all countries of the world.

3.1.3.5 EMLA cream

Eutectic Mixture of Local Anesthetics or EMLA cream is a local anesthetic cream containing 2.5% each of lidocaine and prilocaine. In order to reduce penile sensibility, EMLA cream should be applied approximately 20 min before sexual intercourse.[52] In order not to transfer the cream to the vagina, it is advised to also use a condom.

3.1.3.6 TEMPE spray

Topical Eutectic Mixture for Premature Ejaculation or TEMPE is a spray containing lidocaine and prilocaine in a metered-dose aerosol-transfer system specifically intended for the treatment of PE. The spray delivers 7.5 mg lidocaine and 2.5 mg prilocaine base per actuation, with three actuations being a standard dose. Patients have to apply the spray to the glans penis 10 – 15 min before intercourse. As the content of the spray rapidly penetrates the skin, the use of a condom is not really necessary. Three randomized, double-blind, and placebo-controlled studies have shown its efficacy to delay ejaculation.[53-55]

3.1.3.7 Stud 100 spray

Being introduced in 1970, Stud 100 is the oldest topical anesthetic spray which is still on the market as an over-the-counter product. Stud Spray contains 9.6% w/w lidocaine presented as a metered aerosol spray delivering a dose of 7.7 mg lidocaine base per spray. The recommended dosage is three or more metered sprays with a maximum dose of 8 sprays (62 mg lidocaine).

3.1.3.8 Promescent spray

Promescent is a lidocaine spray in a metered-dose delivery system. It is only available in the US as an over-the-counter product. Each spray contains 10 mg of lidocaine in 130 µl of product with three sprays being a standard dose and ten sprays as a maximal dose. The spray has to be applied at the glans penis 10 – 15 min before intercourse.

3.1.3.9 On-demand treatment with tramadol

Three meta-analyses, albeit on a low number of studies, have supported the ejaculation delaying effect of on-demand use of tramadol 25 and 50 mg compared to placebo.[56-58] However, because of the potential risk of opioid addiction, one has to be very cautious for its use as a treatment for PE.

3.1.3.10 On-demand treatment with phosphodiesterase type-5 inhibitors

Phosphodiesterase type-5 (PDE-5) inhibitors are registered for the treatment of erectile dysfunction. Their use for the treatment of PE is controversial. According to a recent meta-analysis.[59] the method and designs of studies are too insufficient hampering a generalized conclusion of their efficacy to delay ejaculation. However, in the case of acquired PE due to erectile difficulties, the erectile dysfunction should be treated with a PDE-5 inhibitor.[4]

4. Conclusion

The classification of PE into four PE subtypes is relevant for pharmacotherapy and counselling of men with complaints of PE. Various drugs are currently available for the treatment of PE. One may use a daily treatment or an on-demand treatment strategy. However, with the exception of dapoxetine, all available drugs are off-label. Drug treatment of PE requires that prior to prescription the patient is informed about all possible side effects of the various drugs including the rare side effects, and particularly on PSSD in the case of prescribing an SSRI.

5. Expert opinion

5.1 Ejaculation-delaying drugs versus drugs for treatment of premature ejaculation

The prevalence data of the four PE subtypes have shown that only a minority of men who are not satisfied with their ejaculation suffer from lifelong and acquired PE. The rest are men with subjective and variable PE. Comparison of the ejaculation-delaying properties of SSRIs and other drugs has become successful by using an often common methodology and design of studies, for example, baseline measurements of the IELT, inclusion of men with an IELT of less than 1 minute, stopwatch assessment of the IELT, calculation of the geometric mean IELT, and a randomized, placebo-controlled strategy. The very short IELT of men with lifelong and acquired PE necessitated the use of such a strict design as both oral and local anesthetic drugs have to show a high fold increase in order to clinically relevantly delay ejaculation in these men. As a result these drugs have been shown to be "drugs for the treatment of premature ejaculation." They disrupt the 5-HT equilibrium at the synapse of central serotonergic neurons. However, as men with subjective and variable PE experience normal IELT values, it is not required for a drug – meant for these men – to possess the same strong ability for producing a high fold increase of the baseling IELT, as is required for a drug for lifelong and acquired PE. Accepting this pharmacological view means that the methodology and design of studies of drugs for subjective and variable PE may differ from those of lifelong and acquired PE. One may use the term "ejaculation delaying drugs" to differentiate them from "drugs for the treatment of PE," as both subjective and variable PE with normal IELTs differ from the short IELT of lifelong and acquired PE IELTs.[60] It should be noted that ejaculation-delaying drugs should be investigated in men with normal IELTs, for example, not only in men with subjective or variable PE but also in male volunteers with normal IELTs. This item has not yet had the required attention of both clinicians and pharmaceutical companies, probably because only lifelong PE and acquired PE are officially recognized as PE disorders by the DSM 5.

Still, there is a need for ejaculation-delaying drugs for men with normal IELT values who wish to have a more pleasurable sexual performance. For example, in an epidemiological stopwatch study in five countries, a considerable number of men with normal IELT values who did not have seeked medical treatment for PE and had no complaints of PE wanted to delay their ejaculation by medication, when available.[11] These men may have subjective PE or variable PE or even no PE but a desire to just have more control over their ejaculation. Sofar, hardly any research has been performed in the latter men, as they do not seek medical treatment.

Declaration of interest

MD Waldinger is a member of the Advisory Boards of Emotional Brain B.V., Menarini Netherlands and Pounds Int. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Affiliation

Marcel D Waldinger[1,2] MD, PhD
[1]Drexler University College of Medicine, Department of Pharmacology and Physiology, Philadelphia, USA
[2]Practice for Psychiatry and Neurosexology, Amstelveen, The Netherlands
Tel: +31 20 640 44 66,
E-mail: md@waldinger.demon.nl