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Treatment of Premature Ejaculation

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Introduction

In the 1920s, Bernard Schapiro developed Präjaculin, which was the first oral drug for the treatment of lifelong PE [1]. Präjaculin was produced by the German company Promonta in Hamburg from 1932 until the mid-1960s [1]. Therefore it is important to know that oral drug treatment for PE has been available since the first publications of PE in medical literature, even more than a decade before the first review article on PE was published by Schapiro in 1943 [2] and long before behavioral treatments were advocated as the first choice of treatment [3]. However, case reports of potential new drugs to delay ejaculation, such as monoamine oxidase inhibitors (MAOIs), mellaril, and clomipramine, started only to appear in the 1970s and 1980s. It was only after the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the early 1990s that drug treatment of PE became revolutionized [4]. In those days, a lack of an operationalized definition of PE and the absence of an objective measure of the ejaculation time hampered a truly scientific approach to investigate the efficacy of drugs in delaying ejaculation.

Evidence-Based Approach to Treatment

Therefore, and in order to develop an evidence-based methodology and design of drug treatment research, Waldinger et al. [5] introduced in 1994 the intravaginal ejaculation latency time (IELT) as a standardized measure of the ejaculation time. The IELT was defined as the time between the start of intravaginal penetration and intravaginal ejaculation [5]. By definition the IELT of an ejaculation outside the vagina (ejaculatio ante portam) is zero. The most objective way to measure the IELT is the use of a stopwatch, handled by the female partner [6]. In order to compare the extent of ejaculation delay, it is required to measure the IELT with a stopwatch at each coitus in a baseline period for a few weeks when no medication is used and to measure it as well at each coitus in an active drug treatment period of a few weeks. By comparing the IELT values of both periods the extent of ejaculation delay is calculated. As the IELT values of one person may have outliers, the statistically best way to calculate this difference is to calculate the geometrical mean IELT of both the baseline period and the active treatment period [7]. After having calculated the geometric mean IELT of both periods, it is easy to finally calculate the fold-increase of the geometric mean IELT. The fold-increase (FI) of the geometric mean IELT = geometric mean IELT value at end of drug treatment/geometric mean IELT value at baseline [5].

A fold increase of 1 means that there is no ejaculation delay induced by a drug. Placebo-controlled studies have shown that a fold-increase of 1 to 2 is a placebo response [8]. Clinically relevant ejaculation delay usually occurs between a fold-increase of 4 to 5. But a fold-increase higher than 7 means a really relevant ejaculation delay [8].

Apart from this prospective stopwatch-mediated methodology to measure the IELT, the design of such drug treatment studies is only evidence-based when one performs a randomized, double-blinded, placebo-controlled research protocol [4]. And of course it is required that the participants of such a study are quite similar. For example, they should not drink alcohol before intercourse, they should not use other drugs that may affect ejaculation, and they should fulfill to a lot of other inclusion and other exclusion criteria.

Drug Treatment of PE

There are six major treatments of premature ejaculation; (1) daily use of SSRIs, (2) on-demand use of dapoxetine, (3) on-demand use of clomipramine, (4) on-demand use of topical local anesthetics, (5) on-demand use of tramadol, and (6) on-demand use of phophodiesterase type-5 inhibitors [8].

With the exception of dapoxetine, all these treatments are off-label [8]. Although daily SSRI treatment very effectively

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delays ejaculation, none of the companies producing the SSRIs (paroxetine, fluoxetine, sertraline, citalopram, and escitalopram) has been interested to get a Food and Drug Administration (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 [9]. In 2005 the EMA has registered dapoxetine 30 mg and 60 mg, a fast acting SSRI, for the on-demand treatment of PE [10].

Daily Treatment with SSRIs

In scientific studies—but not in daily practice—the IELT has to be 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 [8]. With exception of fluvoxamine the SSRIs exert a clinically relevant ejaculation delay [8].

A meta-analysis of daily SSRI treatment studies [8] revealed a rather low placebo-effect, e.g., a geometric mean 1.4-fold IELT increase (95% CI: 1.2–1.7). The meta-analysis also demonstrated a rank order of efficacy: (a) paroxetine 8.8 FI (95% CI: 5.9–13.2); (b) clomipramine 4.6 FI (3.0–7.4); (c) sertraline 4.1 FI (2.6–7.0), and (d) fluoxetine 3.9 FI (3.0–5.4). Thus, in general, daily SSRI treatment studies generate a 2.6–13.2 geometric mean IELT fold increase, dependent on the type of SSRI [8]. 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 [8].

The outcome data of the SSRI treatment studies published between 2003 and 2014 hardly distort the findings of the meta-analysis of 2004 and therefore its conclusions are still valid today [9, 11, 12].

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 [13]. 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 [9, 12].

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 [12].

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 [14, 15], very rare side effects such as bleeding [16] and priapism [17, 18], effects on spermatozoa [19, 20] and very rare side effects such as restless genital syndrome (ReGS) in the male [21], and the extremely rare post SSRI sexual dysfunction (PSSD) [22, 23].

SSRI-Induced Side Effects

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 [9, 12]. 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 lifelong PE [9, 12].

Side Effects on the Long Term

On the long term weight gain may occur, and sexual side effects. These sexual side effects are reversible, but in extremely rare cases they are irreversible [9].

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 [15]. 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.

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 [9]. Young men should be informed not to use XTC while taking an SSRI [9]. Its inter-

action may cause the potentially life-threatening 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.

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 [9]. However, a few small studies have shown potential harmful effects of SSRIs on spermatozoa [19, 20]. It is recommended that in 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 [9, 12]. As it takes quite some time for spermatozoa to be renewed, it is advised to make love with a condom for 3 to 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.

Restless Genital Syndrome (ReGS) 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) [21]. In males, ReGS is presumably caused by a sensoric neuropathy of the dorsal nerve of the penis, which is an end branch of the pudendal nerve [21]. 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.

Post SSRI Sexual Dysfunction (PSSD)

Usually SSRI-induced sexual side effects are reversible, e.g., 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, e.g., after SSRI discontinuation they do not disappear [22, 23]. Recently, Waldinger distinguished two types of PSSD [23]. 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 [23]. 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 [23]. So far the pathophysiology and treatment of PSSD remains unclear.

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 [9, 12].

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 [9].

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 [10, 24–28]. 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 6000 patients. Although the extent of ejaculation delay is usually rather small, studies have shown a 3.6–4.5-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 [28].

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 [8]. Effective ejaculation delay occurs 6 hours after drug intake and also lasts about 6 h, e.g. until about 12 h after drug intake. 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.

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 acquired PE [29–34]. 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 [29, 30]. 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 [29, 30]. But despite these trials, a substantial number of men with lifelong PE and with IELTs of 5–30 s complain that local anesthetic sprays have not been effective in delaying ejaculation. These men may need stronger ejaculation delaying drugs such as daily or on-demand SSRIs or clomipramine. Particularly for men with subjective PE, the use of topical local anesthetics might be a good drug to delay ejaculation [9].

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.

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 [31]. In order not to transfer the cream to the vagina it is advised to also use a condom.

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 [32–34].

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).

Promescent Spray

Promescent is a lidocaine spray in a metered-dose delivery system. It is available in the USA and in Europe as an over the counter product. Each spray contains 10 mg of lidocaine in 130 microliters 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.

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 [35–37]. However, because of the potential risk of opioid addiction, one has to be very cautious for its use as treatment for PE.

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 [38] the method and designs of studies are too insufficient hampering a generalized conclusion of their efficacy to delay ejaculation. However, in case of acquired PE due to erectile difficulties, the erectile dysfunction should be treated with a PDE-5 inhibitor [9].

Ejaculation Delaying Drugs Versus Drugs for Treatment of Premature Ejaculation

The prevalence data of the four PE subtypes has 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, e.g., baseline measurements of the IELT, inclusion of men with an IELT of less than 1 min, stopwatch assessment of the IELT, calculation of the geometric mean IELT, and a randomized, placebo-controlled strategy [8]. The very short IELT of men with lifelong and acquired PE necessitated the use of 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 [9]. 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, Waldinger [9] recently argued that as men with subjective and variable PE experience normal IELT values, it should not be required for a drug—meant for these men—to possess the same strong pharmacological ability for producing a very high fold-increase of the baseline IELT, as is required for a drug for lifelong and acquired PE. Accepting this pharmacological view means that the methodology and design of studies for drugs for subjective and variable PE may differ from those of lifelong and acquired PE. This may also become illustrated when one starts to 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 significantly differ from the short IELT of lifelong and acquired PE IELTs [8]. Moreover, and importantly, Waldinger [9] argued that ejaculation delaying drugs should be investigated in men with normal IELT values, for example 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 sought medical treatment for PE and had no complaints of PE wanted to delay their ejaculation by medication, when available [39]. These men may have subjective PE or variable PE or even no PE but a desire to just have more control over their ejaculation. So far, hardly any research has been performed in the latter men, as they do not seek medical treatment.

Psychosocial Treatment

In 1956, James Semans described a behavioral intervention, the so-called stop-start technique, to control premature ejaculation [40]. By this technique sexual stimulation of the penis is paused at impeding ejaculation.

In 1970, Masters and Johnson offered a slight variation of Semans technique, which they called the squeeze technique [41]: withdrawal and squeeze of the frenulum of the penis, resulting in a partial loss of erection and total loss of the urge to ejaculate.

In both techniques the man is first sexually stimulated, and then just before ejaculation either the stimulation is halted (Semans) or the penis is squeezed below the frenulum (Masters and Johnson). Both techniques are usually applied in a graduated fashion, starting with masturbation and proceeding through manual stimulation by a partner to active thrusting during intercourse. For many years this was the most common approach to treat PE. Other therapeutic techniques, such as sensate focus exercises, communication training, education, reducing distracting cognitions, and reducing performance demands, have also been used. However, the explanations for the mechanisms by which these techniques are believed to delay ejaculation are vague. Moreover, evidence based studies of the level of the many drug treatment studies have hardly been performed on the behavioral techniques used to treat PE and have not shown a similar objective outcome of ejaculation delay. Nevertheless, psycho-education and counseling are essential for every patient who seeks medical treatment.

Conclusion

The classification of PE into four PE subtypes is relevant for pharmacotherapy, psycho-education and counseling of men with complaints of PE. Various drugs are currently available for the treatment of PE, but all of them, except dapoxetine, are off-label. Of all drugs, daily use of paroxetine 20 mg exerts the strongest ejaculation delay. However, daily use of SSRIs has various side effects, and particularly the irreversible but extremely rare side effect of PSSD should make one cautious with their off-label use to treat lifelong or acquired PE. On the other hand, one may use on-demand oral drugs. Of those, clomipramine 20–30 mg taken 6 h prior to sexual activity seems to be quite effective in delaying ejaculation. For subjective PE that is characterized by normal IELT values, topical local anesthetics seem to become the first choice of treatment. And obviously, any drug treatment of PE requires that prior to prescription the patient is informed about all possible side effects of the various drugs including the very rare side effects.

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