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Premature Ejaculation: State of the Art

Marcel D. Waldinger, MD, PhD[a,b,*]

[a]*Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, The Hague, The Netherlands*
[b]*Section of Psychopharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*

It has become customary to start an article on premature ejaculation (PE) with the following introduction: ''PE is the most prevalent male sexual *disorder* affecting some 20% to 30% of men.'' This sentence mirrors a general belief that PE always represents a male sexual ''disorder.'' However, if one distinguishes PE as a ''complaint'' versus PE as a ''disorder,'' it appears more appropriate to state ''PE is the most prevalent male sexual *complaint* affecting some 20% to 30% of men. The prevalence of PE as a sexual *disorder* has not yet been investigated in the general male population, but is assumed to be much lower.'' The omission of the distinction complaint versus disorder has been blurring the debate on definition, classification, epidemiology, and treatment of PE.

Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases definition of premature ejaculation

Currently, there are two official definitions of PE. In the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*), which is issued by the American Psychiatric Association, premature ejaculation is defined as a ''persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity'' [1]. According to this definition, PE can only be diagnosed when ''the disturbance causes marked distress or interpersonal difficulty'' [1]. According to the International Classification of Diseases (ICD-10), issued by the World Health Organization, PE is defined as ''the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible'' [2].

Interestingly, in contrast to the *DSM* definition, the ICD-10 uses a cutoff point for the ejaculation time of 15 seconds, but does not provide literature on which this quantification is based. In reverse, and in contrast to the ICD-10, according to the *DSM-IV-TR*, PE needs to cause marked distress and/or interpersonal difficulty before it can be classified as the sexual disorder PE.

However, the distress and/or interpersonal difficulty requirement for the diagnosis of PE is not based on evidence-based studies but on the subjective idea of the *DSM-IV* Task Force that any mental disorder in the *DSM* should cause distress and/or interpersonal difficulty [3].

It should be noted that both the *DSM* and ICD definition of PE are based on authority-based opinions and not on well-controlled clinical and epidemiologic studies [3]. Recently, it has been shown that the *DSM-IV-TR* definition of PE has a low positive predictive value when the required criterium ''short ejaculation latency time'' is not applied [3]. This low positive predictive value is therefore related to the absence in the *DSM* definition of a quantified cutoff point of the intravaginal ejaculation latency time (IELT), which is the time between vaginal intromission and intravaginal ejaculation.

* Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, Leyweg 275, 2545 CH The Hague, The Netherlands.
E-mail address: md@waldinger.demon.nl

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This means that erroneously men with long IELT values of, for example 10 to 20 minutes, may be diagnosed as having PE in case they perceive themselves as suffering from PE [4]. The existence of men who complain of PE, while at the same time having normal and even long durations of the IELT, became evident in the study of Patrick and colleagues [5], in which experienced clinicians diagnosed PE according to the *DSM-IV-TR* criteria of PE thereby ignoring the required criterium ''short ejaculation latency time''. Obviously, due to the low positive predictive value of the *DSM-IV-TR* definition, there is a high chance of false-positive diagnoses of PE, which hampers clinical practice and epidemiologic and drug treatment research [3].

Proposal for new definition of premature ejaculation

Recently, a new proposal for the pending *DSM-V* and ICD-11 definition of PE has been put forward [6,7]. According to this proposal, PE should be classified according to a ''syndromal'' approach, incorporating well-controlled clinical and epidemiologic stopwatch studies [6]. PE as a clinical entity or a syndrome has for the first time been described by Schapiro in 1943 [8]. He distinguished Types A and B that were later termed ''lifelong'' and ''acquired'' PE by Godpodinoff [9]. Both types have been mentioned but not further operationalized in the *DSM-IV-TR* definition of PE.

Recently, the existence of two other PE syndromes have been proposed: ''natural variable PE'' [3] and ''premature-like ejaculatory dysfunction'' [7]. In natural variable PE, men only occasionally suffer from early ejaculations. This should be regarded as part of the normal variability of ejaculatory performance and not a symptom of pathology. As such, natural variable PE is not a real syndrome [3]. In premature-like ejaculatory dysfunction men experience and/or utter complaints of PE, while having objectively normal and even long durations of the IELT of 5 to 20 minutes [6]. In the new proposal, the four PE syndromes are defined according to the following symptomatology.

Lifelong premature ejaculation

Lifelong PE is a syndrome characterized by the cluster of the following core symptoms:

1) ejaculation occurs too early at nearly every intercourse,
2) with (nearly) every woman,
3) from about the first sexual encounters onward,
4) in the majority of cases (80%) within 30 to 60 seconds, or between 1 and 2 minute (20%) and
5) remains rapid during life (70%) or can even aggravate during aging (30%)
6) the ability to control ejaculation (ie, to withhold ejaculation at the moment of imminent ejaculation) may be diminished or lacking, but is not obligatory for the diagnosis.

Some men already get an ejaculation during foreplay, before penetration, or soon as their penis touches the vagina (ejaculatio ante portas). It should be noted that there are no hard indications that lifelong premature ejaculation can be cured, either by drug treatment or psychotherapy. In other words, lifelong PE is a chronic ejaculatory dysfunction.

Acquired premature ejaculation

The complaints of acquired premature ejaculation differ in relation to the underlying somatic or psychologic problem.

1) early ejaculation occurs at some point in a man's life,
2) the man has usually had normal ejaculation experiences before the start of complaints
3) there is either a sudden or gradual onset
4) the dysfunction may be due to:
   - urologic dysfunctions, for example, erectile dysfunction or prostatitis [10].
   - thyroid dysfunction [11].
   - psychologic or relationship problems [12,13].
5) the ability to control ejaculation (ie, to withhold ejaculation at the moment of imminent ejaculation) may be diminished or lacking, but is not obligatory for the diagnosis.

In contrast to lifelong PE the acquired form of PE can be cured by treatment of the underlying cause.

Natural variable premature ejaculation

In natural variable PE men only coincidentally and situationally experience early ejaculations. This type of PE should not be regarded as a symptom or manifestation of true pathology but of normal variation in sexual performance [3]. The syndrome is characterized by the following symptoms

1) early ejaculations are inconsistently and occur irregularly

2) the ability to control ejaculation, that is, to withhold ejaculation at the moment of imminent ejaculation may be diminished or lacking, but is not obligatory for the diagnosis
3) experiences of diminished control of ejaculation go along with either a short or normal ejaculation time, that is, an ejaculation of less or more than 1.5 minutes.

Premature-like ejaculatory dysfunction

Men with premature-like ejaculatory dysfunction experience or complain of PE while the ejaculation time is in the normal range, that is, around 3 to 6 minutes, and may even be of very long duration, that is, between 5 and 25 minutes [7]. This type of PE should not be regarded as a symptom or manifestation of true medical pathology. Psychologic and/or relationship problems may underlie the complaints [7]. The syndrome is characterized by the following symptoms.

1) Subjective perception of consistent or inconsistent rapid ejaculation during intercourse.
2) Preoccupation with an imagined early ejaculation or lack of control of ejaculation.
3) The actual intravaginal ejaculation latency time is in the normal range or may even be of longer duration (ie, an ejaculation that occurs between 5 and 25 minutes).
4) Ability to control ejaculation (ie, to withhold ejaculation at the moment of imminent ejaculation) may be diminished or lacking, but is not obligatory for the diagnosis.
5) The preoccupation is not better accounted for by another mental disorder.

Continuum of neurobiology and psychology

The distinction of the four PE syndromes shows a continuum of PE along a line from mainly neurobiologically to mainly psychologically determined forms (Fig. 1). For example, from both human and animal research it may be derived that lifelong PE is presumably highly neurobiologically and perhaps also genetically determined. However, as yet, one cannot rule out that certain forms of lifelong PE are psychologically determined. As is the case in major depression, a biologic marker of lifelong PE has not yet been found. However, the positive response on daily selective serotonin reuptake inhibitor (SSRI) drug treatment indicates that both major depression and PE are neurobiologically, that is, serotonergically, mediated, and may have a neurobiologic etiology. Acquired PE may be medically (prostatitis, thyroid dysfunction) or psychologically (relationship problems) determined. The sporadic early ejaculations in natural variable PE have been postulated to represent the normal variation of ejaculatory performance in men, and are presumably not an expression of underlying pathology. The complaints of early ejaculations in men with premature-like ejaculatory dysfunction that occurs at normal and even long durations of the IELT, have been postulated to be due to mainly psychologic factors [7].

Prevalences

Epidemiologic research has repeatedly shown a prevalence of PE of 20% to 30% [14]. Erroneously, by not distinguishing PE as a complaint and as a syndrome, it has been concluded that

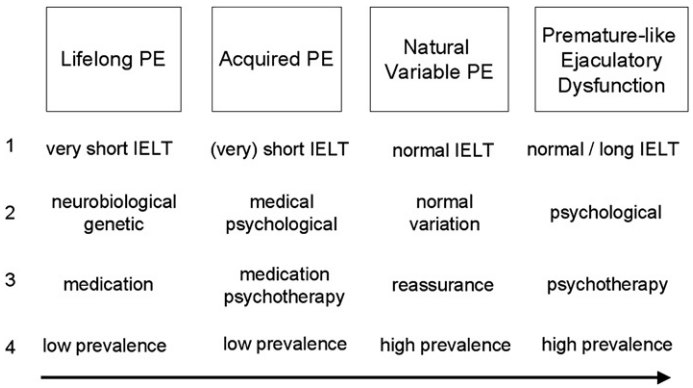

Fig. 1. Continuum of the four PE syndromes; Lifelong PE is more neurobiologically determined while Premature-like Ejaculatory Dysfunction is more psychologically determined. 1. Duration IELT, 2. Etiology, 3. Treatment, 4. Prevalence.

the ''disorder'' PE has a high prevalence. However, these studies have only shown that the ''complaint'' of PE in the general male population has a high prevalence of 20% to 30%. Studies into the prevalence of lifelong PE and acquired PE have never been conducted. However, it is of note that the prevalence of lifelong PE, defined in terms of lifelong consistent IELTs of <1 to 1.5 minutes along feelings of diminished control, has been suggested to be rather low (2%–5%). Further epidemiologic research to confirm this hypothesis is warranted. It is suggested that in case the prevalence of lifelong PE appears to be rather low, it should be argued that only a small percentage of men with ''complaints'' of PE suffer from PE that is mainly neurobiologically and genetically determined. This is of major importance for genetic studies on PE. New epidemiologic research may also contribute to confirm the hypothesis that the high percentage of ''complaints'' of PE (20%–30%) is due to the large number of males in the general population that either have natural variable PE or premature-like ejaculatory dysfunction.

Pathophysiology

The distinction of the four PE syndromes illustrates that there is not one particular pathophysiology of PE, but that there a different pathophysiologies dependent on the type of PE. For example, the serotonin hypothesis of PE, that is, a disturbance of serotonin neurotransmission and/or serotonin receptor functioning [15], pertains only 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 premature-like ejaculatory dysfunction is speculated to be related to cognitive and unconscious mental processes.

Diagnosis of premature ejaculation syndromes

Lifelong, acquired, natural variable PE, and premature-like ejaculatory dysfunction are recognizable by taking a brief medical and sexual history with special attention to the duration of the ejaculation time, the frequency of occurrences, and the course since the first sexual encounters. In daily clinical practice, diagnosis of the four PE syndromes is not difficult, and therefore, evaluation with questionnaires or the use of a stopwatch is not required [4]. However, for drug treatment trials and epidemiologic research, stopwatch assessment and questionnaires of satisfaction and quality of (sexual) life are a prerequisite.

Treatment

The distinction of the four PE syndromes has consequences for treatment. Lifelong PE should be treated with drugs that strongly delay ejaculation. It is a matter of debate whether additional counseling is always needed for these men. A lot of these men will manage without additional counseling. However, 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 psychologic pathology, or both with or without additional other drug treatment options like SSRIs or topical anesthetics.

Men with natural variable PE usually cope well with their coincidental early ejaculations, but in 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 a priori treat these men with ejaculation delaying drugs with potential side effects. Men with premature-like ejaculatory dysfunction should better not be treated with ejaculation delaying drugs but with counselling, psychoeducation, psychotherapy, or couple therapy. One should inform these men that the actual ejaculation time is in the normal range, but that psychologic or relationship factors are likely to contribute to their complaint.

Evidence-based drug treatment

Apart from randomized, double-blind controlled study designs, drug treatment studies of PE should include a baseline and a drug treatment period in which the IELT is measured prospectively at each coitus using a stopwatch handled by the female partner. The IELT is expressed in seconds or minutes, and in case an ejaculation

occurs outside the vagina (ejaculatio ante portas), the IELT is by definition equal to zero. As the IELT distribution is positively skewed, IELT values should be logarithmically transformed and results should be reported as geometric mean IELT or median IELT [4]. In addition, ejaculation delay should be expressed as percentage or fold increase from baseline with 95% confidence intervals (CIs) [4]. Adverse effects should be assessed with a validated questionnaire. Moreover, side effects of on-demand treatment should be assessed at the day of drug intake and the next day [4].

Daily selective serotonin reuptake inhibitor treatment

During the last decade, daily use of SSRIs, on-demand use of the tricyclic antidepressant clomipramine, and topical use of anesthetics has become most popular to treat PE [16]. Although none of these treatment options have been approved by the Food and Drug Administration, their use has been recognized and is supported by evidence-based studies [16]. The serotonergic antidepressants modify the course of PE by modulating the central serotonergic system, and the anesthetics suppress the sensitivity of the glans penis. A number of studies further reported efficacy of the on-demand use of phosphodiesterase type 5 (PDE-5) inhibitors, but their role in the treatment of PE without erectile dysfunction is disputable. Recently, two studies reported ejaculation-delaying effects of the on-demand use of tramadol. Actually, one can distinguish two major strategies to treat PE by medication: daily and on-demand treatment.

Daily treatment with clomipramine

In 1973, Eaton [17] published the first publication on the efficacy of clomipramine, the most serotonergic tricyclic antidepressant, to treat premature ejaculation. Particularly, in the 1970 to 1980s, but also in the 1990s, various studies demonstrated its efficacy in delaying ejaculation in daily rather low dosages of 10 to 30 mg [18].

Daily treatment with selective serotonin reuptake inhibitors

The introduction of the SSRIs in psychiatry, however, would lead to a revolutionary change in the understanding of and treatment of PE. After the first publication in 1994 [19] on the efficacy of daily treatment with paroxetine hemihydrate, various studies confirmed its strong ejaculation-delaying effects at dosages of 20 to 40 mg [16,20]. Moreover, it appeared that nearly all SSRIs, except fluvoxamine, exerted a clinically relevant ejaculation-delaying effect [16]. Currently, daily treatment with SSRIs or combined daily treatment with on-demand use of some SSRIs has become the first choice of treatment. In 2004, Waldinger and colleagues [16] published a systematic review and meta-analysis of all drug treatment studies that have been published between 1943 and 2003. Of all 79 studies, a meta-analysis was only feasible on 35 clomipramine and SSRI daily treatment studies that were conducted between 1973 and 2003 [16]. The outcome data of the few SSRI treatment studies published between 2003 and 2007 hardly distort the findings of the systematic review and meta-analysis, and therefore its conclusions are still valid today. The meta-analysis revealed a placebo effect of a geometric mean 1.4-fold IELT increase (95% CI: 1.2–1.7). Furthermore, it was demonstrated that the rank order of efficacy (geometric mean fold-increase of IELT) was (a) paroxetine (8.8; 95% CI: 5.9–13.2), (b) clomipramine (4.6; 3.0–7.4), (c) sertraline (4.1; 2.6–7.0), and (d) fluoxetine (3.9; 3.0–5.4). Thus, in general, daily SSRI treatment studies generate a 2.6-fold to 13.2-fold geometric mean IELT increase, dependent on the type of SSRI. Daily treatment can be performed with paroxetine 20 to 40 mg, clomipramine 10 to 50 mg, sertraline 50 to 100 mg, fluoxetine 20 to 40 mg, citalopram 20 to 40 mg, and 10 to 20 mg escitalopram [4]. Ejaculation delay usually starts a few days after drug intake, but becomes more manifest after 1 to 2 weeks. The delay continues to exist for years, but sometimes may diminish after 6 to 12 months. The cause of this tachyphylaxis of SSRIs has not yet been clarified [4].

Daily SSRI treatment is most often, but not always, effective in delaying ejaculation. The reason that SSRIs sometimes fail to delay ejaculation has not yet been clarified. Patients should be informed about the short-term and long-term side effects of SSRIs. 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 to 2 weeks of treatment, and most often gradually disappear within 2 to 3 weeks. 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 are less frequently and also to a lesser extent reported by healthy nondepressed men with lifelong PE.

Waldinger has hypothesized that this may be related to the involvement of an increased oxytocin release in men with lifelong PE [4,21]. Obviously, further controlled research to confirm and elucidate this phenomenon is needed.

A rather rare side effects of SSRIs is the risk of bleeding. Clinicians should caution patients about combining SSRIs with aspirin or nonsteroidal anti-inflammatory drugs, as this may further increase the risk of bleeding. A very rare side effect is priapism [22]. Although very rare, it is advised to inform all patients using SSRIs about the risk of priapism and its need for immediate medical treatment. One should not prescribe these drugs to young 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. On the long term, weight gain might occur with an associated risk for diabetes mellitus type II.

Patients should be advised not to stop taking the medication acutely 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 [23].

Generic versus brand-name selective serotonin reuptake inhibitors

A special note should be made to the use of generic SSRIs. The most relevant studies on SSRI treatment of PE have been conducted in the early and mid-1990s using the brand name SSRIs, simply because at that time generic SSRIs where not yet on the market. In contrast, today, generic SSRIs are frequently prescribed. In a review of the few publications comparing the bioequivalence and efficacy of brand name and generic psychoactive drugs, it was shown that there are differences between the generic drugs and the brand name drugs that had not been noted in the original bioequivalence studies [24]. This issue has consequences for drug treatment of PE [4].

Paroxetine hemihydrate

Daily treatment studies of PE with paroxetine, has been investigated with paroxetine hydrochloride hemihydrate and not with the generic drug paroxetine hemihydrate and/or paroxetine mesylate. The ejaculation delaying efficacy and relative mild side effect profile of paroxetine hemihydrate has been repeatedly demonstrated in well-controlled studies [16]. Based on these studies, there are no real objective contraindications to use the generic paroxetine hemihydrate to treat PE [4].

Paroxetine mesylate

Drug treatment studies on PE have not been performed with paroxetine *mesylate*. There are some indications that particularly the side-effect profile of the generic paroxetine mesylate is different from paroxetine hemihydrate [24,25]. Therefore, and due to the lack of placebo-controlled comparative studies investigating the efficacy and side effect profile of both paroxetine hemihydrate and paroxetine mesylate in the treatment of PE, it is advised to prescribe only paroxetine hydrochloride hemihydrate to men with lifelong PE and not paroxetine mesylate [4].

Daily treatment with α_1 adrenoceptor antagonists

Ejaculation is peripherally controlled by the sympathetic nervous system. Blocking the sympathetic system by α_1 adrenoceptor antagonists (α_1-blockers) may theoretically delay ejaculation. Terazosin and alfuzosin are two selective α_1-blockers whose ejaculation delaying effects have been investigated in men with PE. In a placebo-controlled study in 91 men with PE both terazosin 5 mg/d and alfuzosin 6 mg/d proved effective in approximately 50% of the cases [26]. In another placebo-controlled study in 90 men with PE and urinary tract symptoms without chronic prostatitis and benign prostatic hyperplasia, daily use of terazosin 5 to 10 mg showed a clinically significant improvement [27]. However, the methodology of both studies has been rather weak. Efficacy was measured by merely qualitative measures like satisfaction and subjective feelings of improvement. Prolongation of the IELT was not assessed by a stopwatch. Although α_1-blockers may affect ejaculatory performance, they do not always delay ejaculation [28]. Despite the aforementioned limitations in methodology and the rather low rate of clinically relevant ejaculation delaying effects, α_1-blockers, and particularly terazosin 5 to 10 mg, may be a good alternative to treat men with PE who also have urinary tract dysfunction. However, further well-designed studies are pivotal to evaluate the place of α_1-blockers in the armentarium of drugs in the treatment of PE.

On-demand drug treatment

Despite any study investigating patient preferences, it has recently become rather fashionable to state that on-demand treatment of PE would be more favorable than daily treatment. This is rather peculiar, as contrary to daily treatment, on-demand strategies may quite negatively interfere with the spontaneity of having sex, particularly as one usually decides to have sex at the spur of the moment. This is particularly so in young adults with children when the couple often take the opportunity to have sex at a sudden moment when the chance to be disturbed is very low. Also, the argument that daily treatment is not preferable because one has to wait 1 to 2 weeks before ejaculation delay occurs is not based on evidence. Most men with lifelong PE will report that after many years of having had PE, it is no problem to wait another 1 to 2 weeks before medication becomes effective. Moreover, a clear advantage of daily treatment is that ejaculation is delayed at every moment of the day that one wished to have intercourse. Recently, Waldinger and colleagues [29] conducted the first study investigating the preferences of men with lifelong PE for the currently existing PE treatment options. In this study in 88 men with lifelong PE, it was shown that 81% preferred *daily* drug treatment mainly because patients feared that on-demand treatment would negatively interfere with the spontaneity of having sex [29].

Nevertheless, on-demand drug treatment contributes to the armentarium of drug treatment of PE. In recent years, on-demand treatment studies have been conducted with topical anesthetics, clomipramine, SSRIs, dapoxetine, tramadol, and PDE-5 inhibitors. Due to differences in methodology and design, a meta-analysis comparing the efficacy of these drugs has not yet been feasible.

On-demand treatment with topical anesthetics

The use of topical local anesthetics such as lidocaine and/or prilocaine in the form of a cream, gel, or spray is the oldest drug treatment strategy and is still practiced today [30]. The topical anesthetics delay ejaculation by reducing the sensitivity of the glans penis. However, only a few studies have been conducted to show their efficacy. The application is rather simple, but still may lead to side effects like complete anesthesia of the penis, which may lead to erectile difficulties. Patients should be informed that its use may also lead to vaginal numbness. This may be prevented by the use of a condom.

On-demand treatment with clomipramine

On-demand use of 20 to 40 mg clomipramine can effectively delay ejaculation after 3 to 5 hours [31,32]. However, it might also give rise to nausea at the day of intercourse and the next day.

On-demand treatment with selective serotonin reuptake inhibitors

In the systematic review of 2003 only eight studies on on-demand treatment with SSRIs and clomipramine were reported [16]. These eight on-demand studies greatly differed in methodology. A meta-analysis on the published on-demand SSRI studies could not be performed as the studies were unbalanced for the antidepressants used, baseline IELT values, design (double-blind versus open) and assessment techniques (questionnaire versus stopwatch) [16]. Despite the absence of a meta-analysis on on-demand SSRI treatment studies, there are indications that on-demand use of SSRIs, like 20 mg paroxetine, do not strongly delay ejaculation after 3 to 5 hours of intake [33].

On-demand treatment with dapoxetine

Recently, a multicenter study with dapoxetine, an SSRI with a short half-life, has shown that despite minimal ejaculation delay, objectivated with stopwatch assessment, feelings of satisfaction and control were improved [34]. However, the study did not use the appropriate statistics to measure ejaculation delay and did not use the appropriate method to investigate the dapoxetine-induced side effects [35]. In 2005, the Food and Drug Administration did not approve dapoxetine for the treatment of PE.

On-demand treatment with tramadol

Recently, two studies in men with PE have shown the ejaculation delaying effects of on-demand use of 50 mg tramadol [36]. Tramadol is registered as a centrally acting analgesic agent combining μ-opioid receptor activation and reuptake inhibition of serotonin and noradrenaline. The most common adverse of tramadol were nausea (15.6%), vomiting (6.2%), and dizziness (6.2%), but they were reported to be mild. However, it should be noted that despite that tramadol has a weak μ-opioid agonistic effect, long-term follow-up studies are also needed to investigate the risk of opioid addiction.

On-demand treatment with phosphodiesterase type 5 inhibitors

In recent years, a number of authors have suggested that on-demand use of PDE-5 inhibitors is effective to treat PE. However, most of these studies lack a good methodology, which makes the results difficult to interpret. Recently, McMahon and colleagues [37] published a well-designed systematic review of all publications on the use of PDE-5 inhibitors against PE that have been published between 2001 until 2006. The review analyzed 14 studies, which reported the use of sildenafil, vardenafil, and tadalafil [37]. The majority of these studies did not fulfil the current criteria of evidence-based medicine. Of the 14 studies, only one fulfilled these criteria. It was concluded that there is no convincing evidence of any direct effect of PDE-5 inhibitors on the central or peripheral control of ejaculation, or for any role in the treatment of PE, except for men with PE and comorbid erectile dysfunction [37].

On-demand treatment with intracavernous vasoactive drug injection

A special comment should be made regarding intracavernous self-injection treatment. This strategy to treat premature ejaculation is advocated by a few institutions. However, it should be noted that there is not any evidence-based support for the efficacy of this strategy. Actually, there has only been one single study investigating this treatment method [38]. In this open study of eight men, patients injected vasoactive drugs into the corpus cavernosum. From the eight men, three stated that they were cured and stopped the treatment, whereas the other five men continued using the medication after 14 months. However, the methodology of this study was very weak. There were no baseline assessments of the IELT, and a prolongation of the IELT was not measured with a stopwatch. Moreover, success of treatment was defined by prolongation of erectile function after ejaculation and not by the measure of a delayed ejaculation. As long as there are no well-controlled studies showing the efficacy of injection treatment to delay ejaculation time, one should not treat PE with intracavernosal injection of vasoactive drugs.

Summary

The *DSM-IV-TR* definition has a high risk for false-positive diagnoses of PE. Recently, a new classification of four PE syndromes has been proposed for the pending *DSM-V*. According to this classification PE can no longer be defined in one overall descriptive definition, but should be defined according to the symptomatology of the underlying PE syndrome.

The high prevalence rate of 20% to 30% is more likely to reflect the percentage of men that has ''complaints'' of PE, rather than the percentage of men that suffer from the ''disorder'' lifelong PE and acquired PE. The percentage of men that are in need for drug treatment is probably much lower than the high percentage of men than have ''complaints'' of PE without suffering from PE syndromes. Similarly, it is likely that only a small percentage of PE is neurobiologically and/or genetically determined. It has been suggested that a much higher percentage of men only occasionally experience early ejaculations, representing the normal variation of ejaculatory performance. Similarly it has been suggested that presumably a high percentage of men complain of early ejaculation while having normal and even long durations of the IELT. Treatment of PE is dependent of its etiology. Drug treatment is particularly indicated for men with lifelong PE and acquired PE. This may be combined with counselling or behavioral therapy. Psychotherapy is particularly indicated for men with premature-like ejaculatory dysfunction or secondary PE due to psychologic problems. Psychoeducation should be provided to men with natural variable PE. Of the various drug treatment options, daily drug treatment with SSRIs, particularly paroxetine, on-demand use of clomipramine, and/or topical anesthetics has become most popular, and their efficacy has been based on evidence-based research.

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