Current Sexual Health Reports (2019) 11:411–420
https://doi.org/10.1007/s11930-019-00232-9

UROLOGY, GYNECOLOGY, AND ENDOCRINOLOGY (J SIMON AND M LURIA, SECTION EDITORS)

Premature Ejaculation: 2020 Update

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Published online: 7 November 2019

Abstract

Purpose of Review Premature ejaculation (PE) is one of the most common forms of male sexual disorder. There are still different opinions and point of view regarding its definition, classification, prevalence, pathophysiology and treatment alternatives. For these reasons, we aim to recap the recently accumulated data on definition, classification, pathophysiology and treatment alternatives of PE. The literature pertaining to PE has been reviewed by the authors. All the related articles were critically analyzed and examined. Levels of evidence (Les) and grades of recommendation (Grs) are provided based on a thorough analysis of the literature and consensus.

Recent Findings After the initial evidence-based definition developed for lifelong PE, the International Society for Sexual Medicine (ISSM) advertised another unified definition for lifelong and acquired PE and confirmed the time criterion for the diagnosis of PE. The ISSM has also acknowledged the presence of the two more PE subtypes (variable and subjective PE) underlining the fact that more research is required to develop an evidence-based definition of these sexual problems. Although the pathophysiology of these four PE syndromes has not been completely elucidated yet, pharmacotherapy must be considered the treatment of choice for lifelong PE patients whereas treating the underlying pathology must be the initial goal for patients with acquired PE. To treat PE, we can use daily or on-demand use of SSRIs, on-demand use of topical anaesthetics, on-demand tramadol or phosphodiesterase type-5 inhibitors. Psychotherapy can be offered to patients who describe variable and subjective PE.

Summary Despite the recent progress reached in the field of PE, there are on-going debates regarding the definition, classification, pathophysiology and treatment of this common problem. Future clinical trials must be performed to understand the actual aetiology of the four PE syndromes and develop more effective and safe treatment alternatives.

Keywords Premature ejaculation · Definition · Classification · Genetics · Drug treatment · Epidemiology

Introduction

Premature ejaculation (PE) is one of the most common male sexual complaints [1, 2] (two level 3 studies). As the first report on this sexual problem was published over 100 years ago [3], there are still different points of view and opinions regarding its definition, classification, prevalence, pathophysiology and treatment alternatives [4]. These different views are mainly arising from the historical psychological theories, which are formulated before the area of evidence-based medical research. Moreover, different perspectives on the interpretation of the validity and reliability of the methods, designs and data of the new studies resulted in disagreements between researchers. A Dutch group has introduced intravaginal ejaculatory latency time (IELT) as the objective measurement for PE studies [4–8], whereas endocrinological (testosterone and prolactin) data have mainly been derived from an Italian group [9, 10•, 11, 12], and twin studies have been performed only by a Finnish group [13–16]. Although these recent data have resulted in the development of evidence-based PE definitions and guidelines [17–20], there is a continuous discussion on what ought to be considered PE and what biological, endocrinological, somatic and genetic factors play role in its aetiology.

This article is part of the Topical Collection on *Urology, Gynecology, and Endocrinology*

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In order to resolve the discussions around PE, the International Society for Sexual Medicine (ISSM) formulated new definitions for lifelong PE and acquired PE, based on studies that were more or less evidence-based or as much evidence based as has been possible at the time [17, 18] (two level 1 studies). The ISSM also developed guidelines for the management of patients who complain about lifelong and acquired PE [19, 20] (two level 1 studies). Furthermore, the American Psychiatric Association (APA) reviewed their PE definition in the recently published Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5) [21] and agreed on the 1-min time criterion for the diagnosis of PE and categorized PE severity relying on the duration of ejaculation.

In this review article, we will summarize the recently accumulated data on the definition, classification, pathophysiology and treatment alternatives of PE.

Definition of Premature Ejaculation

Table 1 lists definition of premature ejaculation according to different international societies. Unlike previous definitions of PE [22, 23], the ISSM included an operationalized time criterion in the definition of lifelong and acquired PE for the first time.

The DSM-5 differentiates a lifelong form, when the illness has been present since the beginning of sexual activity, and an acquired form, when the disturbance began after a period of relatively normal sexual function. In addition, the DSM-5 distinguishes "a generalized form when the disturbance is not limited to certain types of stimulation, situations, or partners, versus a situational form, when PE only occurs with certain types of stimulation, situations, or partners" [21].

The greatest advantage of the ISSM and DSM-5 definitions of PE is the inclusion of a quantified cut-off point of the ejaculation time for the diagnosis of PE. This is a historical change in the view of the APA as all previous DSM editions on PE have avoided to specify the ejaculation time duration and used nebulous descriptions as "shortly after" instead [24, 25]. However, a drawback of the DSM-5 definition is that it only defines lifelong PE and is rather improper for acquired PE. For clinical practice, DSM-5 does not include a separate definition for men who complain of early ejaculations but actually have a normal IELT, as is the case in variable and subjective [26].

Another well-known definition of PE has been developed by the World Health Organization (WHO) in the International Classification of Diseases and Related Health Problems 10th edition (ICD-10) [27].

Regardless of societies and definitions, when a patient presents with concerns regarding PE, treatment is warranted. In addition to the previously defined PE types (i.e. lifelong and acquired PE), Waldinger et al. [26] proposed two more PE syndromes, namely variable and subjective PE. However, more clinical data is required to develop evidence-based definitions of these PE syndromes.

Operationalization of the Criteria

All the PE definitions cover the three main essence of the disorder: (i) short ejaculatory latency, (ii) concomitant distress or a lack of sexual satisfaction and (iii) lack of self-efficacy regarding the condition [17]. Each of the three criteria above has been operationalized in the definition, although not always with consistency [28].

Table 1 Definition of premature ejaculation according to different international societies

ISSM	Ejaculation which always or nearly always happen previous to or within about 1 min of vaginal penetration (lifelong PE), or, a clinically significant and troublesome reduction in latency time, often to about 3 min or less (acquired premature ejaculation), and the inability to retard ejaculation on all or nearly all vaginal penetrations, and negative personal results, such as distress, bother, frustration and/or the avoidance of sexual intimacy [18]
DSM-5	A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 min following vaginal penetration and before the individual wishes it [21]. 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 defined by a nonsexual mental disorder or as a consequence of severe relationship distress or another medical condition.
ICD-10	Inability to delay ejaculation sufficiently to enjoy lovemaking, manifest as either of the following. Occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 s of the beginning of intercourse); ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity". However, it is not clear how this time criterion (15 s) has been established.

ISSM, International Society of Sexual Medicine; *DSM-5*, Diagnostic and Statistical Manual of Mental Disorders; *ICD-10*, International Classification of Diseases and Related Health Problems 10th edition

Ejaculation Time

The first criterion—short ejaculatory latency time—is typically operationalized by the IELT, defined as the time that occurs between vaginal intromission and the moment of intravaginal ejaculation [29]. Although masturbation ejaculation latency time (MELT) and oral ejaculation latency time (OELT) have been defined as objective measures for investigating ejaculatory performance [30], research related to them has not been performed in heterosexual men. Therefore, the IELT duration in heterosexual males has been considered the ideal measurement for the assessment of the ejaculation time [31]

The normal values of stopwatch-measured IELT have been demonstrated by two epidemiological studies, which have been conducted on the general male population in five countries [6, 7] (two level 3 studies). The IELT distribution of these two separate stopwatch studies showed a considerable similarity. In the first study, the median IELT was 5.4 min (range 0.55 to 44.1 min) [6] whereas it was 6.0 min (range 0.1 to 52.1 min) in the second study [7]. By using values beneath 0.5 and 2.5 percentiles as statistical standards of abnormality, both studies showed that IELT values less than 60 s are indeed abnormal in a cohort of the Western general male population [6, 7]. It is important to stress that a stopwatch study of the IELT in a cohort of men with lifelong PE showed that 85 % of these men ejaculate within 1 min and 34 % within 20 s [5] (one level 3 study). Another 14% of these men ejaculate between 1 and 2 min. Lately, it was demonstrated that the IELT distribution of both men with lifelong PE as of men in the general male population could be described by two different mathematical formulas [32] (one level 3 study). This ending may open a new approach in the research of the IELT.

Although stopwatch-measured IELT seems to be an excellent tool for drug researches, recent guidelines do not recommend its routine use in the daily clinical practice [19]. Moreover, there may be many men who seek for medical help although their stopwatch-measured IELT values are greater than 1 min. Therefore, the 1-min IELT criterion should be managed with flexibility in the clinical setting.

Classification of Premature Ejaculation

The classification of PE has been initially introduced in 1943 by Schapiro who discriminated two types of PE [33]. He named the first type "the sexually hypertonic or hypererotic type" or "type B" [33] (one level 4 study). According to Schapiro, this type, which was later called lifelong PE [34] (one level 4 study), was characterized by the presence of an "erectio praecox" or facilitated erection. The other type ("the hypotonic type" or "type A") was later named as acquired PE [33, 34] and was not characterized by an erectio praecox. Instead, type A was more associated with erectile problems [33]. Over the years, more efforts have been made to identify various types of PE, including several that have been incorporated in PE definitions (e.g. global vs situational, the effect of a substance) but none of these definitions were based on evidence.

An epidemiological stopwatch study demonstrates that men with normal IELT values may also prefer medications to delay their ejaculation [7] (one level 3 study). Considering these findings, Waldinger et al. [26] proposed to expand the two-type classification of PE into four PE subtypes by adding "subjective PE" and "variable PE" (one level 4 study). Men with subjective PE complain of early ejaculations in spite of having normal or even long ejaculatory latencies of 3 to 20 min. On the other hand, patients with variable PE suffer from early ejaculations only occasionally [26]. By this new classification, any man with the complaint of PE can be categorized into one of the four 4 PE subtypes. Serefoglu et al. [35, 36] and Gao et al. [37, 38] demonstrated a low prevalence of lifelong and acquired PE and a high prevalence of variable and subjective PE in the general male population whereas the majority of patients who seek treatment for their early ejaculation complaints described lifelong or acquired PE (four level 3 studies) (Table 2).

In 2014, Waldinger has also described the term "detumescentia praecox" to explain the rapid penile detumescence occurring shortly after ejaculation in lifelong PE patients [37]. In line with the terminology of Schapiro, he hypothesized that lifelong PE is characterized not only by an early ejaculation but also by an acute hypertonic state that occurs as soon as these men become engaged in an erotic contest [37]. This hypertonic state is characterized by a facilitated erection (erectio praecox), a facilitated ejaculation (ejaculatio praecox) and a facilitated penile detumescence (detumescentia praecox) [37].

Pathophysiology of Premature Ejaculation

According to the neurobiological-genetic theory hypothesized by Waldinger et al. in 1998 [39] and revised in 2014 [37], lifelong PE is a variation in the serotonergic central nervous system

Table 2 Classification of premature ejaculation

Type A	The hypotonic type [33]
Type B	The sexually hypertonic or hypererotic type or lifelong PE [33].
Subjective PE	Patient who complains of early ejaculations in spite of having normal or even long ejaculatory latencies of 3 to 20 min [26]
Variable PE	Patients who suffers from early ejaculations only occasionally [26]

mechanisms that regulate the ejaculation reflex through the lumbar spinothalamic (LSt) cells in the spinal cord [40] (one level 2 study). Notably, the mechanisms involved in the pathophysiology of lifelong PE may also be explained by the hypertonic state of the sexual behaviour [37] (one level 4 study). Erectio praecox, ejaculation praecox and detumescentia praecox observed among these patients reveal that dopaminergic, oxytocinergic, endocrinologic and genetic factors may also play a role in the lifelong PE aetiology [37, 41]. In contrast to lifelong PE, acquired PE can be caused by somatic disorders, such as prostatic disorders [42, 43] (two level 3 studies), thyroid pathologies [44, 45] (two level 3 studies) and erectile dysfunction [46, 47] (two level 3 studies). However, the exact mechanisms involved in PE remain elusive.

In order to understand the factors, which may be responsible in PE pathophysiology, several authors have conducted basic science studies and most of our knowledge related to the neurobiology of ejaculation is coming from in vivo animal rat studies that are sexually experienced and display normal sexual behaviour [48]. An animal model for ejaculation dysfunctions has been developed based on a natural biological variation of ejaculation in male rats [49–53]. In tests of more than 2000 male rats, Olivier et al. [53] found an inverted U-shaped distribution with relatively few animals with low or high numbers of ejaculations and high number of animals with 2–3 ejaculations per test. It was therefore suggested that animals with low ejaculations (sluggish rats) might model human delayed ejaculation, whereas the high ejaculators (rapid ejaculators) might model PE in men [49].

Authors performed three experiments comparing various specific serotonin reuptake inhibitors (SSRIs) for their ability to suppress sexual behaviour in male rats. In the first experiment, sexually experienced rats were tested 60 min after oral administration of clomipramine, fluvoxamine, fluoxetine (all in a range of 0, 3, 10 and 30 mg/kg p.o.), sertraline or paroxetine (both in a range of 0, 1, 3 and 10 mg/kg p.o.). Clomipramine, paroxetine and fluvoxamine did not significantly inhibit male sexual behaviour, although some trends were observed. Sertraline inhibited sexual behaviour at 3 and 10 mg/kg p.o.; the effects being stronger at 3 mg/kg p.o. Fluoxetine (3 mg/kg p.o.) facilitated sexual behaviour, while at 30 mg/kg p.o., a modest increase in the postejaculatory interval was noted. In the second experiment, sexual behaviour of sexually naive male rats was slightly inhibited by paroxetine 10 mg/kg p.o., but sertraline (range 1–10 mg/kg p.o.), fluvoxamine and fluoxetine (both in a range of 3–30 mg/kg p.o.) were ineffective. In the last experiment, the effects of paroxetine (0–10 mg/kg p.o.), fluvoxamine and fluoxetine (both 0–30 mg/kg p.o.) were studied during an exhaustion design in sexually experienced male rats. As rats get more 'sluggish' when they have had multiple ejaculations, we hoped to see stronger inhibitory effects in the last cycle prior to exhaustion. None of the drugs dose-dependently inhibited the pattern of sexual behaviour during the first sexual cycle (Table 3).

The differences in mounting behaviour of these rats may suggest differences in penile sensitivity, which has been demonstrated among men with PE [54]. Intromission frequencies and mount latencies, which are often demonstrated as a putative index of sexual motivation, are similar between "sluggish", "normal" and "rapid" ejaculators. These different sexual phenotypes can be considered endophenotypes, because they emerge in every population of rats and are very stable over time. The sluggish and rapid ejaculators are, therefore, well-usable animal models for delayed ejaculation and PE, respectively.

These observations support the neurobiological and genetic theory on lifelong PE as the IELT values of these men are consistent and throughout life within about 1 min [39]. It has been supposed that the persistent IELT of seconds is based on genetic and epi-genetic factors and dysfunctional neurobiological processes in the central and peripheral nervous system, but until now this has not been established with human data [39] (one level 4 study). To date, there are no strong data showing that lifelong PE is a classical Mendelian inheritable disorder affecting all male members of a family [55]. However, a hereditary component of PE was for the first time highlighted by Schapiro in 1943 [33] (1 level 4 study). He postulated that "heredity may play a part in the aetiology" of what is now called lifelong PE [33]. Waldinger et al. [56] have also recorded indications of a familial, but not genetic

Table 3 List of drugs regimens and related side effects

Drug	Side effects
Dapoxetine 30 mg or 60 mg	Fatigue, yawning, mild nausea, loose stools or perspiration, weight gain in the first 1–2 weeks of treatment.
	Long-term side effects include discontinuation syndrome, bleeding, priapism and infertility, and very rare disorders such as restless genital syndrome (ReGS) and post SSRI sexual dysfunction (PSSD)
Clomipramine 25 mg	Blurred vision, dry mouth, nausea and constipation
Topical anaesthetics	Penile hypaesthesia, numbness or erectile difficulties
Tramadol 25 mg or 50 mg	Opioid addiction
Phosphodiesterase type-5 inhibitors	Headache, flushing, runny nose, stomach pain, back pain (Cialis) and indigestion

hereditary, occurrence of lifelong PE in first-degree male relatives of some lifelong PE patients (1 level 3 study).

Based on animal data, Waldinger et al. [39] suggested that lifelong PE may be linked to genetic factors related to the diminished central 5-HT neurotransmission. He hypothesized that hyperfunction of 5-HT_{1A} receptors and/or hypofunction of 5-HT_{2C} receptors may be responsible for this ejaculation disorder [55].

The influence of 5-HTTLPR polymorphism (allele frequencies and genotypes of short (S) and long (L) variants of 5-HTTLPR) on IELT duration among lifelong PE patients has been initially demonstrated by Janssen et al. [57] (1 level 3 study). In this study, patients with LL genotype ejaculated within 13.2 s, whereas men with SL and SS genotype ejaculated within 25.3 and 26.0 s, respectively ($p < 0.05$) [57]. Moreover, men with LL genotype ejaculated 100% faster than men with SS genotype and 90% faster than men with SL genotype [57]. The authors could not identify any significant differences between these men and the control group which consisted of 92 men [57]. In a similar study, Janssen et al. [58] evaluated the impact of the C(1019)G polymorphism of the 5-HT_{1A} receptor gene on the IELT. Men with CC genotype ejaculated within 14.5 s, whereas men with CG and GG genotype ejaculated within 27.7 s and 36.0 s, respectively [58] (1 level 3 study). The authors demonstrated that men with CC genotype ejaculated 250% earlier than men with GG genotype [58]. Finally, the same authors assessed the association between the Cys23Ser polymorphism of the 5-HT2c receptor and the IELT [59]. The mean IELT duration among wildtypes (CysCys) was 22.6 s, whereas it was 40.4 s among the mutants (Ser/Ser) [59]. Therefore, men with CysCys genotype ejaculated 79% faster than the monozygote mutant (Ser/Ser) men [59] (1 level 3 study). Unfortunately, these findings have not been confirmed by other research groups by using the same study design of Janssen et al. [57–59]. However, few clinicians assessed the relationship between genetic polymorphisms and PE patient-reported outcome measures [16, 60] (2 level 3 studies). Conversely, some other studies demonstrated that lifelong PE patients have a greater SS genotype frequency compared with a control group [61–63] (three level 3 studies), without proper study design [64] (one level 2 study). Notably, an association of the 5-HT_{1A} receptor gene polymorphism has also been demonstrated in a Finish cohort of twins [15] (one level 3 study).

Considering the data gathered from aforementioned studies, the duration of IELT may be associated with polymorphism of certain genes (3 level 3 studies). Therefore, future genetic trials are required in order to elucidate the impact of certain genes on the 5-HT neurotransmission and ejaculation [65–67]

Treatment of Premature Ejaculation

By the recently accumulated data, the treatment of lifelong PE has shifted from psychotherapy to pharmacotherapy [68]. It is a theme of debate if concomitant counselling is always required for lifelong PE patients [41, 55]. Although daily practice shows that most men with lifelong PE can be effectively treated by local anaesthetic creams/gels or daily/on-demand SSRIs without additional counselling, it is recommended to address the psychosexual problems of these men and their partners [19, 20].

Acquired PE can be treated with medications for the treatment of underlying medical problem (e.g. chronic prostatitis, thyroid problems, erectile dysfunction) and/or psychotherapy for underlying psychological pathology [19, 20]. If there are not any underlying causes, SSRIs or topical anaesthetics can be administered [19, 20].

Men who describe variable PE usually do not seek treatment for their occasional early ejaculations. Those men can be educated about the occurrence of sporadic early ejaculation, which is a part of the normal sexual behaviour [41, 55]. Psychosexual counselling may assist variable PE patients for regaining their confidence.

Psychotherapy, behavioural sex therapy or couple therapy with or without local anaesthetics must be considered for men with subjective PE [41, 55]. Whether these men with normal IELT values had to be treated with SSRIs remains an issue of medical ethics and debate [41, 55]. Further research is needed to understand the dynamics associated with subjective PE.

Pharmacotherapy for Premature Ejaculation

There are six major pharmacological treatment options for PE; (i) daily long acting SSRIs, (ii) on-demand short-acting SSRIs (dapoxetine), (iii) on-demand/daily clomipramine, (iv) on-demand topical local anaesthetics, (v) on-demand tramadol and (vi) on-demand phosphodiesterase type-5 inhibitors [19, 20].

Daily Treatment with SSRIs All of the SSRIs recommended for the treatment of PE are used off-label (except dapoxetine). Even though daily SSRI treatments are associated with the most significant delay in IELT duration, none of the currently available SSRIs (fluoxetine, paroxetine, sertraline, citalopram and escitalopram) has applied for a Food and Drug Administration (FDA) or European Medicine Agency (EMA) approval for PE treatment [69]. The EMA has approved a fast-acting SSRI dapoxetine, for the on-demand treatment of PE in 2005 [70••]. A meta-analysis of daily SSRI treatment studies [71] revealed the rank order of SSRI efficacy in terms of fold increase (FI) of the geometric mean IELT [72] as follows: (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). Therefore, daily paroxetine is found to result in the most significant delay in ejaculation.

The delay in ejaculation usually becomes apparent couple days after the initiation of daily SSRI intake but maximal

effect can be observed after 1–3 weeks. Many times, the efficacy of these treatments continues as long as the SSRIs are used; however, it may fade after 6–12 months in some cases. The mechanisms of this tachyphylaxis phenomenon have not been elucidated yet [69].

Having a normal IELT during every sexual intercourse is an advantage of the daily SSRI treatment. However, side effects such as fatigue, yawning, mild nausea, loose stools or perspiration may be noticed in the first 1–2 weeks of treatment, and most often gradually decline within 2–3 weeks [69]. Weight gain may also occur, as well as sexual problems such as decreased libido and erectile dysfunction [19, 20]. Other long-term side effects include discontinuation syndrome [73, 74], bleeding [75], priapism [76, 77] and infertility [78–81], and very rare disorders such as restless genital syndrome (ReGS) [82] and post SSRI sexual dysfunction (PSSD) [83, 84]. Patients who are on daily SSRI treatment must decrease their alcohol consumption, as SSRIs may facilitate a "typsi" state [85, 86]. Older men must also be warned not to take tramadol while they are using SSRIs daily because using these medications concomitantly may cause serotonergic syndrome [87]. SSRIs should not be prescribed to boys younger than 18 years and to patients with major depression [88]. In those cases, referral to a psychiatrist is indicated.

On-demand Treatment with Dapoxetine Dapoxetine hydrochloride is a short-acting SSRI [89]. Similar to all other SSRIs, it inhibits serotonin reuptake in the neuronal synapses [90]. Dapoxetine is the first drug which has been approved by the EMA for the treatment of PE [91–95] (three level 1 studies). Dapoxetine should be taken 1–2 h before the planned sexual intercourse. Many clinical trials have shown a 3.6 to 4.5-fold increase in IELT under on-demand dapoxetine treatment which associated with improved satisfaction and ejaculatory control in lifelong and acquired PE patients [91–95]. The safety of dapoxetine has also been demonstrated in those studies, with several mild side effects such as dizziness, nausea and headache [91–96].

On-demand Treatment with Clomipramine On-demand use of clomipramine may also be associated with a delay in ejaculation among PE patients [97–99] (three level 3 studies). Adverse events of this treatment include blurred vision, dry mouth, nausea and constipation [97–99].

On-demand Treatment with Topical Local Anaesthetics Topical local anaesthetics (lidocaine and/or prilocaine containing creams, gels, or sprays) are well-established PE treatments and they are moderately effective in delaying IELT [20, 100–106] (two level 1 studies). When applied prior to the planned sexual intercourse, they decrease the sensitivity of penis and delay the spinal and cerebral input of sexually arousal impulses [107]. The efficacy and safety of topical anaesthetics have been demonstrated in several studies [105, 106] (two level 1 evidence). Side effects of this treatment include penile hypaesthesia, numbness or erectile difficulties. If these local anaesthetics are not cleaned prior to the sexual intercourse, they may be transferred to the female partner and result in vaginal numbness. Condoms may be also be used to avoid this problem [105, 106].

On-demand Treatment with Tramadol Several studies demonstrated that on-demand 25 and 50 mg tramadol is associated with a significant delay in ejaculation [108–110] (three level 1 studies). However, this treatment modality is not recommended because of the potential risk of opioid addiction [20].

On-demand Treatment with Phosphodiesterase Type-5 Inhibitors PDE-5 inhibitors are considered the first-line treatment for erectile dysfunction; however, recent studies also support their use in patients with PE [111] (one level 2 study). Although their efficacy in delaying IELT is not significant, these medications may restore the self-esteem of PE patients and they may be helpful in regaining erections for the second/third sexual intercourse [112, 113]. Some studies demonstrated the efficacy and safety of PDE-5 inhibitor plus dapoxetine containing combination tablets in patients with PE [114, 115••]. However, combining SSRIs with PDE-5 inhibitors may be associated with increased side effects [116]. Considering that acquired PE patients may experience this problem due to erectile difficulties [117], PDE-5 inhibitors must be the treatment of choice among patients acquired PE patients who also report erectile dysfunction [20] (one level 3 study).

Conclusion

Although the history of PE shows that the classification of PE into lifelong and acquired PE has been proposed almost 40 years ago, there are on-going debates about this classification and more research is needed to understand the essence of variable and subjective PE. Better understanding the characteristics of the four PE subtypes will be useful in developing effective therapies for these patients. 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; thus, patients must be informed about the potential side effects of each therapy.

Compliance with Ethical Standards

Conflict of Interest Dr. Serefoglu reports role as consultant for Virility Lts., Israel, outside of the submitted work. Dr. Russo declares no conflict of interest.

Research Involving Human Participants and/or Animals This article does not contain any studies with human or animal subjects performed by the author.

Abbreviations PE, premature ejaculation; Les, levels of evidence; Grs, grades of recommendation; ISSM, International Society for Sexual Medicine; IELT, intravaginal ejaculatory latency time; APA, American Psychiatric Association; DSM-5, Diagnostic and Statistical Manual for Mental Disorders, 5th edition; ICD-10, International Classification of Diseases and Related Health Problems 10th edition; MELT, masturbation ejaculation latency time; LSt, lumbar spinothalamic

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Laumann EO, Pail A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281:537–44.
2. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E, et al. Sexual problems among women and men aged 40-80 years: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res. 2005;17:39–57.
3. Gross S. Practical treatise on impotence and sterility. Edinburgh: Pentland; 1887.
4. Waldinger MD. History of premature ejaculation. In: Premature ejaculation. Jannini EA, McMahon CG, Waldinger MD (Editors). From Etiology to Diagnosis and Treatment. Springer-Verlag Italia 2013a: pp. 5-24
5. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. An empirical operationalization study of DSM-IV diagnostic criteria for premature ejaculation. Int J Psychiatry Clin Pract. 1998a;2: 287–93.
6. Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A multi-national population survey of intravaginal ejaculation latency time. J Sex Med. 2005;2:492–7.
7. Waldinger MD, McIntosh J, Schweitzer DH. A five-nation survey to assess the distribution of the intravaginal ejaculatory latency time among the general male population. J Sex Med. 2009;6: 2888–95.
8. Waldinger MD. Towards evidence-based drug treatment research on premature ejaculation: a critical evaluation of methodology. J Impotence Research. 2003;15:309–13.
9. Corona G, Jannini EA, Lotti F, Boddi V, De Vital G, Forti G, et al. Premature and delayed ejaculation: two ends of a single continuum influenced by hormonal milieu. Int J Androl. 2011;34:41–8.
10. • Corona G, Jannini EA, Vignozzi L, Rastrelli G, Maggi M. The hormonal control of ejaculation. Nat Rev Urol. 2012;9(9):508–19 **This paper is important since it analyses hormonal control of ejaculation. Evidence shows that oxytocin is actively involved in regulating orgasm and ejaculation via peripheral, central and spinal mechanisms. Associations between delayed and premature ejaculation with hypothyroidism and hyperthyroidism, respectively, have also been extensively documented. Some models suggest that glucocorticoids are involved in the regulation of the ejaculatory reflex, but corresponding data from human studies are scant. Oestrogens regulate epididymal motility, whereas testosterone can affect the central and peripheral aspects of the ejaculatory process.**
11. Sansone A, Romanelli F, Jannini EA, Lenzi A. Hormonal correlations of premature ejaculation. Endocrine. 2015;49:333–8.
12. Corona G, Mannucci E, Jannini EA, Lotti F, Ricca V, Monami M, et al. Hypoprolactinemia: a new clinical syndrome in patients with sexual dysfunction. J Sex Med. 2009;6:1457–66.
13. Jern P, Santtila P, Witting K, Alanko K, Harlaar N, Johansson A, et al. Premature and delayed ejaculation: genetic and environmental effects in a population-based sample of Finnish twins. J Sex Med. 2007;4(6):1739–49.
14. Jern P, Santilla P, Johansson A, Varjonen M, Witting K, Algars M, et al. Indicators of premature ejaculation and their associations with sexual distress in a population-based sample of young twins and their siblings. J Sex Med. 2008;5:2191–201.
15. Jern P, Westberg L, Johansson A, Gunst A, Eriksson E, Sandnabba K, et al. A study of possible associations between single nucleotide polymorphisms in the serotonin receptor 1A, 1B, and 2C genes and self-reported ejaculation latency time. J Sex Med. 2012;9:866–72.
16. Jern P, Eriksson E, Westberg L. A reassessment of the possible effects of the serotonin transporter gene linked polymorphism 5-HTTLPR on premature ejaculation. Arch Sex Behav. 2013;42(1): 45–9.
17. McMahon CG, Althof S, Waldinger MD, Porst H, Dean J, Sharlip I, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med. 2008;5:1590–606.
18. Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, et al. An evidence- based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. J Sex Med. 2014;11: 1423–41.
19. Althof SE, Abdo CHN, Dean J, Hackett G, McCabe M, McMahon CG, et al. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. J Sex Med. 2010;7:2947–69.
20. Althof SE, McMahon CG, Waldinger MD, Serefoglu EC, Shindel AW, Adaikan PG, et al. An Update of the International Society of Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). J Sex Med. 2014;11:1392–422.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed) (DSM-5). Washington: American Psychiatric Association; 2013. p. 443–6.
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Third edition) (DSM-III). Washington: American Psychiatric Association; 1980.
23. Masters WH, Johnson VE. Human Sexual Inadequacy. Boston: Little Brown; 1970.
24. Waldinger MD, Schweitzer DH. Changing paradigms from an historical DSM-III and DSM-IV view towards an evidence based definition of premature ejaculation. Part I: Validity of DSM-IV-TR. J Sex Med. 2006;3:682–92.
25. Waldinger MD, Schweitzer DH. Changing paradigms from an historical DSM-III and DSM-IV view towards an evidence based definition of premature ejaculation. Part II: Proposals for DSM-V and ICD-11. J Sex Med. 2006;3:693–705.
26. Waldinger MD. Premature ejaculation: different pathophysiologies and etiologies determine its treatment. J Sex & Marital Ther. 2008;34:1–13.
27. International Classification of Diseases and Related Health Problems (10th ed) Geneva: World Health Organization; 1994. https://icd.who.int/browse10/Content/statichtml/ICD10Volume2_en_2008.pdf

28. Rowland DL, Cooper SE, Schneider M. Defining premature ejaculation for experimental and clinical investigations. Arch Sex Behav. 2001;30:235–53.
29. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. Am J Psychiatry. 1994;151:1377–9.
30. Waldinger MD. Four measures of investigating ejaculatory performance. J Sex Med. 2007;4:20.
31. Waldinger MD, Zwinderman AH, Schweitzer DH, et al. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. Int J Impot Res. 2004;16:369–81.
32. Janssen PKC, Waldinger MD. The mathematical formula of the intravaginal ejaculation latency time (IELT) distribution of lifelong premature ejaculation differs from the IELT distribution formula of men in the general male population. Investig Clin Urol. 2016;57:119–28.
33. Schapiro B. Premature ejaculation, a review of 1130 cases. J Urol. 1943;50:374–9.
34. Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. J Sex and Marital Ther. 1989;15:130–3422.
35. Serefoglu EC, Yaman O, Cayan S, Asci R, Orhan I, Usta MF, et al. Prevalence of the complaint of ejaculating prematurely and the four premature ejaculation syndromes: results from the Turkish Society of Andrology Sexual Health Survey. J Sex Med. 2011;8:540–8.
36. Serefoglu EC, Cimen HI, Atmaca AF, Balbay MD. The distribution of patients who seek treatment for the complaint of ejaculating prematurely according to the four premature ejaculation syndromes. J Sex Med. 2010;7:810–5.
37. Gao J, Zhang X, Su P, Liu J, Xia L, Yang J, et al. Prevalence and factors associated with the complaint of premature ejaculation and the fourpremature ejaculation syndromes: a large observational study in China. J Sex Med. 2013;10(7):1874–81.
38. Zhang X, Gao J, Liu J, Xia L, Yang J, Hao Z, et al. Distribution and factors associated with four premature ejaculation syndromes in outpatients complaining of ejaculating prematurely. J Sex Med. 2013;10:1603–11.
39. Waldinger MD, Berendsen HHG, Blok BFM, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. Behav Brain Res. 1998;92:111–8.
40. Truitt WA, Coolen LM. Identification of a potential ejaculation generator in the spinal cord. Science. 2002;297:1566–9.
41. Waldinger MD. The pathophysiology of lifelong premature ejaculation. Transl Androl Urol. 2016 (in press);5(4):424–33.
42. Liang CZ, et al. Prevalence of premature ejaculation and its correlation with chronic prostatitis in Chinese men. Urology. 2010;76:962–6.
43. Mo MQ, et al. Sexual dysfunctions and psychological disorders associated with type IIIa chronic prostatitis: A clinical survey in China. Int Urol Nephrol. 2014;46:2255–61.
44. Cihan A, Demir O, Demir T, Asian G, Comlekci A, Esen A. The relationship between premature ejaculation and hyperthyroidism. J Urol. 2009;18:1273–80.
45. Carani C, Isidori AM, Granata A. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab. 2005;90:6472–9.
46. El-Sakka AI. Efficacy of sildenafil citrate in treatment of erectile dysfunction: impact of associated premature ejaculation and low desire. Urology. 2006;68:642–7.
47. El-Sakka AI. Severity of erectile dysfunction at presentation: effect of premature ejaculation and low desire. Urology. 2008;71:94–8.
48. Olivier B, Chan JS, Pattij T, de Jong TR, Oosting RS, Veening JG, et al. Psychopharmacology of male rat sexual behavior: modeling human sexual dysfunctions? Int J Impot Res. 2006;18(Suppl 1):S14–23.
49. Pattij T, de Jong TR, Uiterdijk A, Waldinger MD, Veening JG, Cools AR, et al. Individual differences in male rat ejaculatory behaviour: searching for models to study ejaculation disorders. Eur J Neurosci. 2005;22(3):724–34.
50. Mos J, Mollet I, Tolboom JT, Waldinger MD, Olivier B. A comparison of the effects of different serotonin reuptake blockers on sexual behaviour of the male rat. Eur Neuropsychopharmacol. 1999;9(1-2):123–35.
51. Chan JS, Waldinger MD, Olivier B, Oosting RS. Drug-induced sexual dysfunction in rats. Curr Protoc Neurosci 2010; Chapter 9: Unit 934
52. Chan JS, Olivier B, de Jong TR, Snoeren EM, Kooijman E, van Hasselt FN, et al. Translational research into sexual disorders: pharmacology and genomics. Eur J Pharmacol. 2008;585(2-3):426–35.
53. Olivier B. Serotonin: a never-ending story. Eur J Pharmacol. 2015;753:2–18.
54. Rowland DL. A psychophysiological approach to assessing premature ejaculation. Int J Impot Res. 1998;10(Suppl 2):S44–8 discussion S9-51.
55. Waldinger MD. Pharmacotherapy for premature ejaculation. Expert Opin Pharmacother. 2015;16:2615–24.
56. Waldinger MD, Rietschel M, Nothen MM, Hengeveld MW, Olivier B. Familial occurrence of primary premature ejaculation. Psychiatr Genet. 1998;8:37–40.
57. Janssen PK, Bakker SC, Réthelyi J, Zwinderman AH, Touw DJ, Olivier B, et al. Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. J Sex Med. 2009;6:276–84.
58. Janssen PKC, van Schaik R, Zwinderman AH, Olivier B, Waldinger MD. Of the 5-HT_{1A} receptor gene only the C(1019)G promoter polymorphism influences the Intravaginal Ejaculation Latency Time in Dutch Caucasian Men with lifelong premature ejaculation. Pharmacol Biochem Behav. 2013), in press;121:184–8.
59. Janssen PKC, van Schaik R, Olivier B, Waldinger MD. Of the largest coding region for the 5-HT_{2C} receptor gene only the Cys23Ser polymorphism influences the Intravaginal Ejaculation Latency Time in Dutch Caucasian men with lifelong premature ejaculation (2013, submitted)
60. Zuccarello D, Ghezzi M, Pengo M, Forzan M, Frigo AC, Ferlin A, et al. No difference in 5-HTTLPR and Stin2 Polymorphisms frequency between premature ejaculation patients and controls. J Sex Med. 2012;9:1659–68.
61. Safarinejad MR. Polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran. J Urol. 2009;181:2656–61.
62. Ozbek E, Tasci AI, Tugcu V, Ilbey YO, Simsek A, Ozcan L, et al. Possible association of the 5-HTTLPR serotonin transporter promoter gene polymorphism with premature ejaculation in a Turkish population. Asian J Androl. 2009;11:351–5.
63. Luo SW, Wang F, Xie ZY, Huang XK, Lu YP. Study on the correlation of the 5-HTTLPR polymorphism with premature ejaculation in Han Chinese population. Beijing Da Xue Xue Bao. 2011;43:514–8.
64. Janssen PKC, Olivier B, Zwinderman AH, Waldinger MD. Measurement errors in polymerase chain reaction are a confounding factor for a correct interpretation of 5-HTTLPR polymorphism effects on lifelong premature ejaculation: a critical analysis of a previously published meta-analysis of six studies. PLoS One. 2014;9(3):e88031.
65. Ahlenius S, Larsson K, Svensson L, Hjorth S, Carlsson A, Lindberg P, et al. Effects of a new type of 5-HT receptor agonist

on male rat sexual behavior. Pharmacol Biochem Behav. 1981;15: 785–92.
66. Berendsen HH, Broekkamp CL. Drug-induced penile erections in rats: indications of serotonin1B receptor mediation. Eur J Pharmacol. 1987;135:279–87.
67. Foreman MM, Love RL, Hall JL. Effects of LY237733, a selective 5-HT2 receptor antagonist, on copulatory behavior of male rats. Soc Neurosci Abstr. 1988;14:374.
68. Waldinger MD, Schweitzer DH, Olivier B. On-demand SSRI treatment of premature ejaculation: pharmacodynamic limitations for relevant ejaculation delay and consequent solutions. J Sex Med. 2005;2:120–31.
69. Waldinger MD. Premature ejaculation: definition and drug treatment. Drugs. 2007;67:547–68.
70.•• Pryor JL, Althof SE, Steidle C, Dapoxetine Study Group, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet. 2006;368(9539):929–37 **This paper analyses the efficacy and tolerability of on-demand dapoxetine in patients with severe premature ejaculation.**
71. Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. Int J Impot Res. 2004;16:369–81.
72. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Geometric mean IELT and premature ejaculation: appropriate statistics to avoid overestimation of treatment efficacy. J Sex Med. 2008;5:492–9.
73. Ditto KE. SSRI discontinuation syndrome; awareness as an approach to prevention. Postgrad Med. 2003;114:79–84.
74. Black K, Shea C, Dursun S, Kutcher S. Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci. 2003;25:255–61.
75. Weinrieb RM, Auriacombe M, Lynch KG, Lewis JD. Selective serotonin re-uptake inhibitors and the risk of bleeding. Expert Opin Drug Saf. 2005;4:337–44.
76. Ahmad S. Paroxetine-induced priapism. Arch Intern Med. 1995;155:645.
77. Rand EH. Priapism in a patient taking sertraline. J Clin Psychiatry. 1998;59:538.
78. Koyuncu H, et al. Escitalopram treatment for premature ejaculation has a negative effect on semen parameters. Int J Impot Res. 2011;23:257–61.
79. Koyuncu HC, Ozdemir AT, Hellstrom WJ. Deleterious effects of selective serotonin reuptake inhibitor treatment on semen parameters in patients with lifelong premature ejaculation. Int J Impot Res. 2012;24:171–3.
80. Tarikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. Urology. 2007;69:185 e5–7.
81. Tanrikut C, Feldman AS, Altemus M, Paduch DA, Schlegel PN. Adverse effect of paroxetine on sperm. Fertil Steril. 2010;94: 1021–6.
82. Waldinger MD, Venema PL, van Gils AP, de Lint GJ, Schweitzer DH. Stronger evidence for small fiber sensory neuropathy in restless genital syndrome: two case reports in males. J Sex Med. 2011;8(1):325–30.
83. Csoka AB, Bahrick AS, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Sex Med. 2008;5:227–33.
84. Waldinger MD, van Coevorden RS, Schweitzer DH, Georgiadis J. Penile anesthesia in Post SSRI Sexual Dysfunction (PSSD) responds to low-power laser irradiation: a case study and hypothesis about the role of transient receptor potential (TRP) ion channels. Eur J Pharmacol. 2015;753:263–8.
85. Menkes DB, Herxheimer A. Interaction between antidepressants and alcohol: signal amplification by multiple case reports. Int J Risk Saf Med. 2014;26:163–70.
86. Alusik S, Kalatova D, Paluch Z. Serotonin syndrome. Neuro Endocrinol Lett. 2014;35:265–73.
87. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician. 2015;18:395–400.
88. Gordon M, Melvin G. Selective serotonin re-uptake inhibitors–a review of the side effects in adolescents. Aust Fam Physician. 2013;42:620–3.
89. Modi NB, Dresser MJ, Simon M, et al. Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. J Clin Pharmacol. 2006;46: 301–9.
90. Dresser MJ, Kang D, Staehr P, et al. Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: impact of age and effects of a high-fat meal. J Clin Pharmacol. 2006;46: 1023–9.
91. Pryor JL, Althof SE, Steidle C, Rosen RC, Hellstrom WJ, Shabsigh R, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet. 2006;368(9539): 929–37.
92. Buvat J, Tesfaye F, Rothman M, et al. Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. Eur Urol. 2009;55:957–67.
93. McMahon C, Kim SW, Park NC, et al. Dapoxetine 3003 Study Investigators. Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. J Sex Med. 2010;7(1 Pt 1):256–68.
94. Kaufman JM, Rosen RC, Mudumbi RV, et al. Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. BJU Int. 2009;103:651–8.
95. McMahon CG, Althof SE, Kaufman JM, et al. Efficacy and safety of dapoxetine for the treatment of premature ejaculation: integrated analysis of results from five phase 3 trials. J Sex Med. 2011;8: 524–39.
96. Mirone V, Arcaniolo D, Rivas D, et al. PAUSE study team. Results from a prospective observational study of men with premature ejaculation treated with dapoxetine or alternative care: the PAUSE study. Eur Urol. 2014;65:733–9.
97. Strassberg DS, de Gouveia Brazao CA, Rowland DL, Tan P, Slob AK. Clomipramine in the treatment of rapid (premature) ejaculation. J Sex Marital Ther. 1999;25:89–101.
98. Rowland DL, De Gouveia Brazao CA, Koos SA. Effective daily treatment with clomipramine in men with premature ejaculation when 25 mg (as required) is ineffective. BJU Int. 2001;87:357–60.
99. Waldinger MD, Zwinderman AH, Olivier B. On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. Eur Urol. 2004;46:510–5.
100. Dinsmore WW, Hackett G, Goldmeier D, et al. Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. BJU Int. 2007;99:369–75.
101. Dinsmore WW, Wyllie MG. PSD502 improves ejaculatory latency, control and sexualsatisfactionwhenappliedtopically5minbeforeintercourse in men with premature ejaculation: results of a phase III, multicentre, double-blind, placebo-controlled study. BJU Int. 2009;103:940–9.
102. Carson C, Wyllie M. Improved ejaculatory latency, control and sexual satisfaction when PSD502 is applied topically in men with premature ejaculation: results of a phase III, double-blind, placebo-controlled study. J Sex Med. 2010;7:3179–89.

103. Berkovitch M, Keresteci AG, Koren G. Efficacy of prilocaine-lidocaine cream in the treatment of premature ejaculation. J Urol. 1995;154:1360–1.
104. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. BJU Int. 2004;93:1018–21.
105. Xia JD, Han YF, Zhou LH, Chen Y, Dai YT. Efficacy and safety of local anaesthetics for premature ejaculation: a systematic review and meta-analysis. Asian J Androl. 2013;15(4):497–502.
106. Pu C, Yang L, Liu L, et al. Topical anesthetic agents for premature ejaculation: a systematic review and meta-analysis. Urology. 2013;81:799–804.
107. Wieder JA, Brackett NL, Lynne CM, Green JT, Aballa TC. Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. Urology. 2000;55:915–7.
108. Wu T, Yue X, Duan X, Luo D, et al. Efficacy and safety of tramadol for premature ejaculation: a systematic review and meta-analysis. Urology. 2012;80:618–24.
109. Yang L, Qian S, Liu H, Liu L, Pu C, Han P, et al. Role of tramadol in premature ejaculation: a systematic review and meta-analysis. Urol Int. 2013;91(2):197–205.
110. Martyn-St James M, Cooper K, Kaltenthaler E, Dickinson K, Cantrell A, Wylie K, et al. Tramadol for premature ejaculation: a systematic review and meta-analysis. BMC Urol. 2015;15(1):6.
111. Asimakopoulos AD, Miano R, FinazziAgrò E, et al. Does current scientific and clinical evidence support the use of phosphodiesterase type 5 inhibitors for the treatment of premature ejaculation? A systematic review and meta-analysis. J Sex Med. 2012;9:2404–16.
112. Saitz TR, Serefoglu EC. Advances in understanding and treating premature ejaculation. Nat Rev Urol. 2015;12(11):629–40.
113. Krishnappa P, Fernandez-Pascual E, Carballido J, Martinez-Salamanca JI. Sildenafil/Viagra in the treatment of premature ejaculation. Int J Impot Res. 2019;31(2):65–70.
114. Tuken M, Culha MG, Serefoglu EC. Efficacy and safety of dapoxetine/sildenafil combination tablets in the treatment of men with premature ejaculation and concomitant erectile dysfunction-DAP-SPEED Study. Int J Impot Res. 2019;31(2):92–6.
115.•• Qin Z, Wang Y, Zhu J, et al. Safety and efficacy characteristics of oral drugs in patients with premature ejaculation: a Bayesian network meta-analysis of randomized controlled trials. Int J Impot Res. 2019. https://doi.org/10.1038/s41443-019-0146-7 **This paper is very important since previous studies have investigated the safety and efficacy characteristics of oral drugs in patients with premature ejaculation (PE), the available results remained inconsistent. Hence, this article was conducted to comprehensively compare the effectiveness of oral drugs and several relevant complications in patients with PE.**
116. Sridharan K, Sivaramakrishnan G, Sequeira RP, Al-Khaja KA. Pharmacological interventions for premature ejaculation: a mixed-treatment comparison network meta-analysis of randomized clinical trials. Int J Impot Res. 2018;30(5):215–23.
117. McMahon CG, Jannini EA, Serefoglu EC, Hellstrom WJ. The pathophysiology of acquired premature ejaculation. Transl Androl Urol. 2016;5(4):434–49.