

## Accepted Manuscript

Title: Current therapies for premature ejaculation

Author: Serap Gur Philip J. Kadowitz Suresh C. Sikka

PII: S1359-6446(16)30154-4

DOI: <http://dx.doi.org/doi:10.1016/j.drudis.2016.05.004>

Reference: DRUDIS 1810



To appear in:

Received date: 19-1-2016

Revised date: 1-4-2016

Accepted date: 4-5-2016

Please cite this article as: Gur, S., Kadowitz, P.J., Sikka, S.C., Current therapies for premature ejaculation, *Drug Discovery Today* (2016), <http://dx.doi.org/10.1016/j.drudis.2016.05.004>

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# Current therapies for premature ejaculation

Serap Gur<sup>1,2</sup>, Philip J. Kadowitz<sup>3</sup>, and Suresh C. Sikka<sup>2</sup>

<sup>1</sup>Department of Pharmacology, School of Pharmacy, Ankara University, Ankara, Turkey

<sup>2</sup>Department of Urology, Tulane University Health Sciences Center, New Orleans, LA, USA

<sup>3</sup>Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA, USA

*Corresponding author:* Gur, S. (serapgur@ankara.edu.t; serapgur@gmail.com)

*Teaser:* Despite scientific advances, many questions remain on the topic of premature ejaculation (PE). We review the benefits and limitations of current treatments for men with PE.

*Keywords:* premature ejaculation; dapoxetine; tramadol; SSRI; PDE5 inhibitors.

**Premature ejaculation (PE) subjectively affects 20–30% of men globally. Until recently, understanding of PE was hampered by the absence of, a widely accepted definition, paucity of evidence-based clinical studies, and the absence of an appropriate animal model. Here, we elaborate on the current definition of PE, its pathogenesis, currently available therapies, and future treatment prospects. Most treatments for PE are 'off-label' and include selective serotonin reuptake inhibitors (SSRIs), topical anesthetics, tramadol, and phosphodiesterase type 5 (PDE5) inhibitors. Such knowledge of the benefit and limitations of each treatment will help to direct future drug design and formulations.**

## Introduction

PE is a common male sexual disorder, subjectively affecting 20–30% of adult men worldwide [1,2]. The National Health and Social Life Survey reported the prevalence of PE in men aged 18–59 years in the USA to be 21% [3]. Historically, the etiology of PE includes a range of biological and psychological factors and should be considered as a psycho-neuro-uro-endocrine disorder affecting the couple [4]. Men with recurring PE suffer from significant distress, frustration, anxiety, interpersonal difficulties, and avoidance of sexual intimacy. Sexual dysfunction, infertility, lower urinary tract symptoms (LUTS), including prostatitis and/or chronic pelvic pain syndrome, are recognized risk factors for PE [5].

Pharmacotherapy is the current foundation of PE management. Classic antidepressants and topical anesthetics remain off-label treatments. Tramadol (opioid analgesic), and PDE5 inhibitors are second-line medications. Dapoxetine, a SSRI, is the only currently approved oral medicine in some countries [6]. In this review, we highlight the current definition, classification, prevalence, etiologic factors, and current as well as future treatment options for PE.

## Ejaculation

The normal male sexual copulation response involves four different major events: erection, emission, ejaculation, and orgasm. Ejaculation is mediated by a spinal reflex that is centrally regulated in a complex manner [7] and requires the coordination of numerous sensory receptors and afferent nerve pathways, as well as motor and sensory areas of the brain, and the spinal ejaculation generator (SEG) located at the T12–L1-2 level of the spinal cord. The central targets identified include serotonergic, dopaminergic, and oxytocinergic neurotransmitters, opioid receptors, and mechanisms involved in the control of the SEG [8]. Furthermore, the spinal control center integrates this outflow with inputs conveying biochemical and a mechanical message from the accessory sex organs, producing coordinated contractions of the epididymis, vas deferens, seminal vesicles, and prostate. The serotonergic system inhibits the ejaculatory reflex at the hypothalamic level [9], whereas the dopaminergic pathway stimulates ejaculation [10]. Additionally, androgens promote ejaculation [11]. Low serum testosterone levels have been inconsistently associated with PE [12] and low prolactin levels have been found in patients with PE [13]. A high prevalence of PE has been found in patients with hyperthyroidism, and delayed ejaculation has been associated with hypothyroidism [11]. Oxytocin and vasopressin are both involved in the regulation of contractility of the male genital tract in some animal species [14,15].

## Current definition and subtypes of PE

The treatment and epidemiology of PE are dependent on how PE is defined. The current definition from the International Society for Sexual Medicine (ISSM) pertains to both lifelong and acquired PE, and is classified as: (i) an ejaculation that always, or nearly always, occurs before, or within about 1 min of, vaginal penetration (lifelong PE), or a clinically significant and bothersome reduction in latency time, often to about 3 min or less (acquired PE); (ii) the inability to delay ejaculation on all, or nearly all, vaginal penetrations; and (iii) PE with negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [16]. This definition is currently reasonable for clinical practice, and recognizes a significant contrast between lifelong PE (more related to neurobiological dysfunction in nature) and acquired PE (more related to psychological, endocrine, neurological, and urological factors). The intravaginal ejaculation latency time (IELT) is defined as the time between vaginal penetration and intravaginal ejaculation, which, in most scientific studies, is measured with a stopwatch.

Waldinger and Schweitzer [17,18] proposed four PE subtypes: (i) lifelong PE; (ii) acquired PE; (iii) natural variable PE; and (iv) subjective PE [17] (Figure 1). The prevalence of these subtypes differs by the duration of the IELT and frequency of complaints. With lifelong PE, the individual experiences early ejaculations from puberty or adolescence. Lifelong PE consistently demonstrates IELT at less than 1 min, suggesting an underlying neurobiological disturbance [19]. Thus, lifelong PE should be treated with medication that significantly delay ejaculation, and clinicians should regularly check their patient's psychological profile.

In acquired PE, the early ejaculations begin later in life after a period of normal ejaculatory activity. Acquired PE involves medical, psychological, and social causes. Thus, treatment for acquired PE can involve psychotherapy and drug therapy [20].

In natural variable PE, short IELTs occur sporadically, which is considered a natural variation of ejaculation [21,22]. Psychological counseling is usually sufficient for these men to regain confidence. It is important to inform them that the occurrence of sporadic early ejaculation is part of the normal ejaculatory performance.

In subjective PE, men complain of PE while having a typical IELT duration (~2–5 min or more) [9]. These complaints are likely related to psychological and cultural factors. Men with subjective PE should be treated with counseling, psychoeducation, psychotherapy, or couples therapy, with or without the use of local anesthetics.

### Pharmacotherapy

Numerous therapeutic approaches for PE are available (Figure 2). Topical anesthetic creams, tramadol, selective SSRIs, and PDE5 inhibitors are widely used. There are very few well-controlled clinical trials demonstrating that the many oral agents discussed below are efficient and safe for the treatment of men with all types of PE. Psychological therapies and behavioral procedures have not been entirely neglected [23,24].

#### *SSRI treatment of PE*

Serotonergic (5-hydroxytryptamine; 5-HT) neurons regulate their activity by 5-HT receptor-mediated mechanisms [10]. Although many distinct 5-HT receptor subtypes have been identified, only the 5-HT1A, 5-HT1B, 5-HT2C, and 5-HT7 subtypes have been shown to be involved in the mechanism of ejaculation [25].

SSRI antidepressants (dapoxetine, paroxetine, fluoxetine, citalopram, escitalopram, and sertraline) have been shown to enhance ejaculatory control and delay ejaculation in men with PE (Figure 2). Delayed ejaculation is a known adverse effect of these antidepressants. A substantial number of randomized, double-blind, placebo-controlled studies have shown the efficacy of daily SSRI treatment in healthy men complaining of PE [26,27]. As yet, none of these SSRIs have been approved by the US Food and Drug Administration (FDA) for the treatment of PE.

In 2008, the SSRI dapoxetine hydrochloride (Priligy; Janssen Pharmaceutica NV, Beerse, Belgium) was the first drug initially approved for the on-demand treatment of PE in seven European countries (Austria, Finland, Germany, Italy, Portugal, Spain, and Sweden) [28]. Currently, dapoxetine has not been approved in the USA. Dapoxetine hydrochloride prevents the transport, rather than the reuptake, of serotonin. Unlike classical SSRIs, dapoxetine reaches maximum concentration in the body in about an hour and then is rapidly removed from the body. Dapoxetine at the minimum dose has been found to double the time to ejaculation, and larger doses can bring longer delays. An integrated analysis of five Phase III trials indicated that dapoxetine 30 and 60 mg significantly ameliorated PE and IELT by 3.5–4-fold increases compared with placebo (Table 2) [29–31]. Also, dapoxetine has a similar efficacy profile both in men with lifelong PE and men with acquired PE [23]. A recent meta-analysis by Castiglione et al. showed that dapoxetine therapy significantly improved IELT in patients with PE but with modest efficacy [32]. Also, combined dapoxetine and sexual behavioral therapy were more effective than dapoxetine alone in the management of lifelong PE (Table 2) [6]. In a recent prospective open-label study by McMahon [33], flexible dosing of dapoxetine (30 and 60 mg) appeared to be effective in the treatment of PE. In a prospective, 12-week, open-label, postmarketing observational, multinational study (PAUSE, which enrolled 7545 patients), dapoxetine demonstrated a favorable safety profile in the mood and related adverse events, neurocognitive system, urogenital system, sexual function, and the lack of any relevant cardiovascular adverse events compared with the alternate oral treatment group in the study population [34]. Dapoxetine is the only drug available for which efficacy could be confirmed in a meta-analysis of such a large, well-designed, clinical trial [32].

Daily SSRI treatment with paroxetine (20 mg), clomipramine (10–40 mg), sertraline (50–100 mg), fluoxetine (20 mg), citalopram (20 mg), and escitalopram (20 mg) [4] resulted in ejaculation delay that usually takes effect several days after drug administration (Figure 2). A clinically relevant effect only gradually occurs within 1–3 weeks as long as the SSRI is used and the ejaculatory delay continues to exist for many years. However, in some cases, the effect may disappear after 6–12 months.

There is a risk of both short- and long-term adverse effects, as well as the risk of a discontinuation syndrome [35]. Regarding the short-term adverse effects, fatigue, yawning, mild nausea, loose stools, or perspiration can occur. Prolonged use of this class of medication has been associated with minor, but bothersome adverse effects. In prolonged SSRI therapy, the most troubling adverse effects are sexual dysfunction [hypoactive sexual desire disorder, erectile dysfunction (ED), anorgasmia, anejaculation], weight gain, and sleep disturbance [35]. Although antidepressant drugs are effective in restoring ejaculatory control, these drugs can significantly worsen ED, and are strongly contraindicated for patients with both PE and ED. Gastrointestinal adverse effects are most frequently reported with fluvoxamine, whereas anxiety, agitation, and insomnia are most often reported with sertraline and

fluoxetine. Overall, citalopram appears to be the best-tolerated SSRI, followed by fluoxetine, sertraline, paroxetine, and fluvoxamine.

#### *Tramadol*

Tramadol is a promising and efficient alternative to the currently used oral pharmacological treatments for patients with PE [36] who fail to respond to SSRIs. Tramadol on-demand results in a significant improvement in mean IELT and partner sexual satisfaction scores compared with placebo. However, only a few studies have supported the ejaculation-delaying effect of the on-demand use of tramadol 25 and 50 mg compared with placebo [24]. In several clinical trials, tramadol significantly increased IELT score in a dose-dependent manner in men with varying degrees of PE, improved patient satisfaction, and was also well tolerated (Table 1) [37]. Kurkar et al. reported that tramadol hydrochloride exhibited a significantly better dose-related efficacy and adverse effects profile compared with placebo for PE treatment [38].

A tramadol-containing orally disintegrating tablet (ODT, Zertane™) also significantly increased median IELT compared with placebo; such increases were 1.6-fold for placebo, 2.4-fold with 62 mg tramadol ODT, and 2.5-fold with 89 mg tramadol ODT [39]. Men had significant improvement in all four measures of the PEP [QA1] with both doses of tramadol ODT compared with placebo, indicating that on-demand 62mg tramadol ODT is a safe and effective treatment option for managing mild to severe PE [39]. In the study by Essa and El-Shazly, a total of 300 patients presenting with lifelong PE were given either placebo or active ingredient tramadol hydrochloride at different therapeutic dosages for 24 weeks [40]. The mean IELT significantly increased in all groups compared with baseline, suggesting that on-demand tramadol hydrochloride at various doses is effective, safe, and tolerable, with adverse effects related to ED, constipation, nausea, headache, pruritus (itching), dizziness, somnolence, dry mouth, and vomiting [41,42].

Tramadol could be an option in cases of mild to severe PE owing to its antinociceptive and anesthetic effects [43]. Although there is a risk of abuse and dependence, these events are rare, particularly at small doses when taken intermittently on a short-term basis. However, the possibility of drug addiction and other sexual effects should be considered before prescribing this therapy. Thus, it would be advisable to assess its effectiveness and mechanism of action as an on-demand treatment for PE.

#### *Sprays and creams (topical local anesthetics)*

The treatment of PE with topical anesthetics was first demonstrated some decades ago [44]. Topical local anesthetics are effective in delaying ejaculation in men with lifelong and acquired PE [45]. These anesthetics act by diminishing sensitivity to the glans penis, thereby reducing the spinal and cerebral input of sexually aroused impulses. Currently, there are four local anesthetics for the treatment of PE: TEMPE spray®, EMLA cream®, Promescent spray®, and Stud-100 spray®. However, these local anesthetics are not (yet) available globally. Unlike oral SSRI therapy, topical treatment has almost no systemic adverse effects, and can be used as needed. Two recent meta-analyses confirmed the efficacy and low adverse effect profile of topical anesthetics for lifelong PE [46,47]. However, too much drug application can cause penile paresthesia, numbness, or erectile problems.

Only topical eutectic mixture of prilocaine and lidocaine for PE (TEMPE, also known as PSD502, Plethora Solutions, London, UK) is FDA approved for the treatment of lifelong PE. The spray delivers 7.5 mg lidocaine and 2.5 mg prilocaine base per actuation, with three actuations being a standard treatment. Patients apply the spray to the glans penis 10–15 min before initiating intercourse. Three randomized, double-blind, placebo-controlled studies have shown its efficacy to delay ejaculation [48,49].

Men with lifelong PE who experienced an IELT of 1 min with two or more sexual encounters during a 4-week baseline period were randomized to receive topical TEMPE or placebo in a double-blinded manner for 3 months [50]. The results showed improved ejaculatory latency and sexual satisfaction. In another study, 256 men with PE were randomized from 38 centers in the USA, Canada, and Poland [49]. When applied topically to the glans penis 5 min before intercourse, TEMPE showed significantly improved ejaculatory latency, ejaculatory control, sexual satisfaction, and distress, and was shown to be well tolerated by both patients and partners [49].

Eutectic mixture of local anesthetics (EMLA, Astra Zeneca, Wilmington, DE, USA) cream is a local anesthetic cream containing 2.5% each of lidocaine and prilocaine. To reduce penile sensitivity, EMLA cream should be applied approximately 20 min before sexual intercourse [44].

Promescent (Absorption Pharmaceuticals, Huntington Beach, CA, USA) is a lidocaine spray in a metered-dose delivery system that is only available in the USA as an over-the-counter product [8]. Each spray contains 10 mg of lidocaine in 130 ml of product, with a standard dose of three sprays and a maximum dose of ten sprays. The spray must be applied to the glans penis 10–15 min before intercourse.

Stud-100 spray (Pound International, London, UK) was introduced in 1970 and is the oldest topical anesthetic spray still on the market as an over-the-counter product. The 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 eight sprays (62 mg lidocaine).

In addition to the popularity and availability of these topical agents without the need for a prescription, many female partners complain of vaginal sensation and reduced pleasure sensation. Furthermore, high methodological quality of randomized clinical studies is required to understand the efficacy and safety of topical anesthetics for PE.

#### *PDE5 inhibitors*

The use of PDE5 inhibitors for the treatment of PE is controversial because of insufficient evidence of the ejaculation-delaying effects of such inhibitors [48]. Vardenafil has been the most-studied agent in patients with PE patients with or without ED, and the new PDE5 inhibitor avanafil has not yet been studied in these patients [51–53].

A controlled study involving the effect of tadalafil (20 mg) alone and in combination with fluoxetine (90 mg) in patients with lifelong PE showed that the increase in IELT was greater in patients who received combined treatment with fluoxetine taken once a week and tadalafil taken before sexual relations compared with placebo, fluoxetine, or tadalafil alone [54]. Recently, a combination of tadalafil plus paroxetine improved IELT and intercourse satisfaction compared with paroxetine alone in potent patients with PE; however, combined treatment mildly increased drug adverse effects [55].

The combination of an SSRI and PDE5 inhibitor before intercourse has provided significantly longer ejaculatory latency times compared with SSRI alone for an extended period in patients with PE [56]. In a meta-analysis of these clinical studies, the post-treatment IELT was significantly improved upon combining SSRIs and PDE5 inhibitors [57,58], with reduced adverse events.

Many clinics are now using this combination approach, but PDE5 inhibitors should not be prescribed to men with PE who have a normal erectile function. Additional clinical studies are needed for the use of PDE5 inhibitors in patients with PE.

#### *Other agents*

Thyroid, pituitary, and sex steroid hormones are potential candidates for use in the regulation of the ejaculatory process, but the exact mechanisms are not yet clear, and further studies are required to identify potential targets for such treatment [11]. Low levels of prolactin are linked to a decreased ejaculation [59]. In a recent study, Serefoglu et al. demonstrated that rats injected with botulinum-A toxin into their bulbospongiosus muscle had significantly longer latencies of ejaculation relative to pretreatment [60]. These authors suggested that botulinum-A toxin is a safe and effective treatment that extends ejaculatory latency in rats [60].

The role of  $Ca^{2+}$  in the process of ejaculation, and the clinical efficacy and safety of other  $Ca^{2+}$  channel blockers in the treatment of PE have not yet been studied. In a preliminary report, the possible use of silodosin (an  $\alpha 1A$ -adrenergic receptor blocker) as a new treatment option for PE was recently suggested [61]. Tamsulosin, an  $\alpha 1$ -adrenergic receptor antagonist, is not only an effective treatment for LUTS, but also improved the PE of patients with LUTS and PE [62]. However, in a recent study, the well-tolerated selective oxytocin receptor antagonist epelsiban did not produce a clinical or useful change in IELT in men with PE [63]. In the evaluation of the efficacy and safety of clomiphene as a selective estrogen receptor modulator in the treatment of idiopathic PE, IELT, sexual indexes, and quality of life (QOL) improved in the treated group. A study by Saadat et al. demonstrated that on-demand caffeine (100 mg) can significantly increase IELT [64]. DA-8031 is a newer agent for the treatment of PE with high specificity and selectivity for the serotonin transporter compared with other monoamine transporters and receptors involved in neurotransmission [65]. Several effective techniques and strategies now in the pipeline for PE could provide clinical efficacy with minimization of adverse effects.

#### **Concluding remarks**

PE is a common male sexual dysfunction that can have serious implications for a couple's QOL. PE has multifactorial etiology with coexisting genetics, neurobiological, endocrine, urological, psychological, and interpersonal relational issues. Critical gaps remain in the knowledge of the neuropsychopharmacology of ejaculation, and the treatment of ejaculatory disorders in humans requires improvement. Therefore, the involvement of andrologists, gynecologists, endocrinologists, urologists, psychologists, and psychosexologists with a multidisciplinary viewpoint can be crucial in the management of PE.

The comprehensive analysis of data from the four PE subtypes show that it is only a few men dissatisfied with their ejaculations that have lifelong and acquired PE. The rest are men with subjective and variable PE. However, these guidelines for PE should be re-evaluated and regularly updated by the ISSM every 4 years [66]. With continued research into variable PE and subjective PE, it might be appropriate to expand this unifying definition in the future. The very short IELT in men with lifelong and acquired PE necessitates the use of both oral and local anesthetic drugs to show a significant increase in the clinically significant delay of ejaculation in these men. In patients with severe PE-IELTs of <30–60 s, combination therapy of topical and oral medications can be used and could substantially increase IELT compared with either monotherapy.

The interest in medical treatment for PE is rapidly growing. Most couples do not seek medical help because of embarrassment or perhaps ignorance of effective treatments that are now available. PE therapies are too often focused only on the man. Furthermore, men with PE mostly have associated comorbidities and suffer a significant impact not only on their QOL, but also on the satisfaction of their partner. For instance, ED and PE are not separate entities, but should be thought about from a dimensional perspective that might help sexual healthcare professionals propose a suitable therapy to treat successfully patient-related outcomes in sexual medicine.

Most of the randomized controlled trials have been of uncertain methodological quality because of the limited reporting of methods. Pooled evidence suggests that SSRIs, topical anesthetic creams, tramadol, and PDE5 inhibitors are more effective than placebo at increasing IELT.

Currently, the first-line symptomatic treatment is dapoxetine, but a holistic approach incorporating sex therapy and psychotherapy might be the most appropriate treatment for sexual anxiety and the relative health of the

couple. Many patients with PE can be adequately treated with SSRIs without additional counseling, but it is advisable to inform these men of the type of PE that affects them along with the efficacy and adverse effects of the various treatment options. Combined dapoxetine and sexual behavioral counseling proved to be more efficient than dapoxetine alone in treating patients with lifelong PE, restoring normal ejaculatory function in most patients [6]. Further randomized clinical trials are needed to elucidate the therapeutic potential of such combination in patients with lifelong PE.

The use of tramadol has recently raised hope. However, tramadol has more adverse effects and is less effective compared with SSRIs. Thus, it appears to be a second-line medication. Some alternative treatment strategies, such as daily SSRIs or the pain medication tramadol, are practical and often produce good results; however, the use of these therapies for PE is not approved by the FDA and remains off-label. The efficacy of dapoxetine for PE can be improved by the addition of sexual behavioral counseling. Long-term safety studies, probably in a multicenter format, and those comparing tramadol with SSRIs are needed to determine the effectiveness of tramadol in the treatment of PE. However, this pharmacological aspect has not yet been considered by regulatory agencies because of the lack of scientific evidence, and, thus, the use of dapoxetine with PDE5 inhibitors is discouraged.

Although all current pharmaceutical treatments for PE are 'off-label', some novel oral agents, as well as other topical methods of drug administration, now provide substantial benefit. Topical therapy for PE has become increasingly popular over the past few years, and could become the standard treatment option for patients with PE in the future. The ideal treatment for PE should meet the following criteria: (i) on-demand treatment with a quick rapid onset of action (so as not to affect sexual response); (ii) high rate of efficacy after the initial dose; and (iii) minimal sexual and other adverse effects. The most successful current treatment for PE is combined therapy and counseling. We believe that additional novel drugs will be developed in the near future, and more agents will be approved for the treatment of men with PE.

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**Figure 1.** [QA7] Four known subtypes of premature ejaculation (PE) based upon the duration of the intravaginal ejaculation latency time (IELT) and treatment approaches. Lifelong premature ejaculation (IELT <1 min) is characterized by persistent rapid ejaculation from the beginning of sexual activity and is probably linked to putative genetic factors. Acquired premature ejaculation (IELT <3 min) follows a period of normal ejaculatory function and might be caused by endocrine, urological, or psychological factors. Subjective premature ejaculation (IELT 2–5 min) is usually in men who have a normal ejaculation latency but subjectively report rapid ejaculation. Variable premature ejaculation (IELT 5–7 min) is nonpersistent but with occasional rapid ejaculations. Counseling: this approach, also known as 'talk therapy', involves one-to-one counseling with a mental health provider that includes relation experiences. These sessions can help reduce performance anxiety and find better ways of coping with stress. Counseling is likely to be more effective when combined with drug therapy.

**Figure 2** [QA8]. Current treatment options for premature ejaculation (PE). Topical anesthetics: anesthetic creams and sprays contain a well-established numbing agent, such as lidocaine or prilocaine. Antidepressants are oral medications, but with adverse effects including delayed orgasm. Selective serotonin reuptake inhibitors

(SSRIs), such as sertraline (Zoloft), paroxetine (Paxil) or fluoxetine (Prozac, Sarafem) are useful in delaying ejaculation. Tramadol is an analgesic commonly used to treat pain, but also has delayed ejaculation as a common adverse effect. It can be prescribed when SSRIs are not effective. Phosphodiesterase-5 (PDE5) inhibitors, such as sildenafil (Viagra, Revatio), tadalafil (Cialis, Adcirca), or vardenafil (Levitra, Staxyn), also help in treating premature ejaculation.

Table 1. Efficacy of tramadol in delaying ejaculation in patients with PE

Study design (length)	No. of patients	Age (PE type)	Dose (mg)	Efficacy	Outcomes and safety	Refs
Randomized, double-blind, placebo-controlled, crossover (2 mo)	125	20–55 years (1–10-year duration with PE)	50–100	Dose-related efficacy	Significant dose-related effect and adverse effects	[1]
Randomized, placebo-controlled (28 wk)	300	25–50 years (lifelong PE)	25–50–100	Significant increase in IELT	Small doses effective, safe, and tolerable; somnolence and pruritus	[2]
Single-blind, placebo-controlled, crossover study (2 wk)	60	22–62 years (lifelong PE)	25	Increases in IELT, ability to control ejaculation, and sexual satisfaction score	On-demand use of low-dose tramadol effective for lifelong PE	[3]
Randomized double-blind, placebo-controlled (8 wk)	604	18–65 years (lifelong PE)	62 or 89	Effective on-demand	On-demand 62 mg tramadol in a low and safe therapeutic dose	[4]
Single-blind, placebo-controlled, crossover	60	22–62 years (lifelong)	25	Increase in mean IELT	Promise for rapid ejaculation and proven safety record	[5]
Double-blind, placebo-controlled (8 wk)	64	20–52	50	Increased in IELT	Significantly better in IELT and intercourse satisfaction	[6]

Table 2. Efficacy of dapoxetine or its combination in delaying ejaculation in patients with PE in recent clinical trials

Study type	No. of patients	Age (PE type)	Dose	IELT /efficacy	Effect	Refs
Phase IV, open-label study	286	20–76 years	30 mg or 60 mg or combination PDE5 inhibitor	Increased mean IELT from 1.2–1.0 min at baseline to 4.6–5.3 min at final follow-up visit	Combination effective and well tolerated in patients with lifelong PE or acquired PE	[1]
Baseline to 4, 12, and 24 weeks	50	~34 years (lifelong PE)	30 mg or 30 mg and sexual behavioral treatment	Significant increase	Combination effective	[2]
Five randomized controlled trials	6576	>18 years (lifelong or acquired PE)	30 and 60 mg	More efficient than placebo	Initial dose of 30 mg titrated to maximum dose of 60 mg based on response and tolerability	[3]
Meta-analysis of randomized controlled trials	5934	>18 years	30 and 60 mg	60-mg dose more beneficial than 30-mg dose	Significantly efficacious in patients with PE	[4]
Seven randomized controlled trials	8039	18 years or older	On-demand 30 mg and 60 mg	Significantly higher	Safe and effective (60 mg)	[5]
Secure, online questionnaire	132	Mean: 42.5 years	30 or 60 mg	High discontinuation (70.6%)	Spontaneously discontinue treatment	[6]
Prospective	150	30 and 36 years	On-demand 30 and 60 mg and/or plus paroxetine 20 mg	Increased from baseline to post-treatment by 117%	Effective (60 mg); on-demand dose of 30 mg dapoxetine was no more effective than paroxetine	[7]
Nonrandomized, open-label, observational (PAUSE) study	10 028 [QA9]	Mean: 40.5 years	Group A: 30 mg; group B: clomipramine, paroxetine, fluoxetine, sertraline, topical drugs, condoms, and behavioral counseling	Both well tolerated	Good safety profiles and low prevalence	[8]



**Highlights**

- ✓ Premature ejaculation is highly prevalent, and has considerable effect on the quality of life.
- ✓ The etiologies of lifelong and acquired premature ejaculation are different.
- ✓ The pathophysiological mechanisms of premature ejaculation have not been entirely elucidated.
- ✓ Current treatment options for premature ejaculation are oral, topical and behavioral therapies.
- ✓ The significance of drug discovery, and the use of SSRIs for premature ejaculation are emphasized.

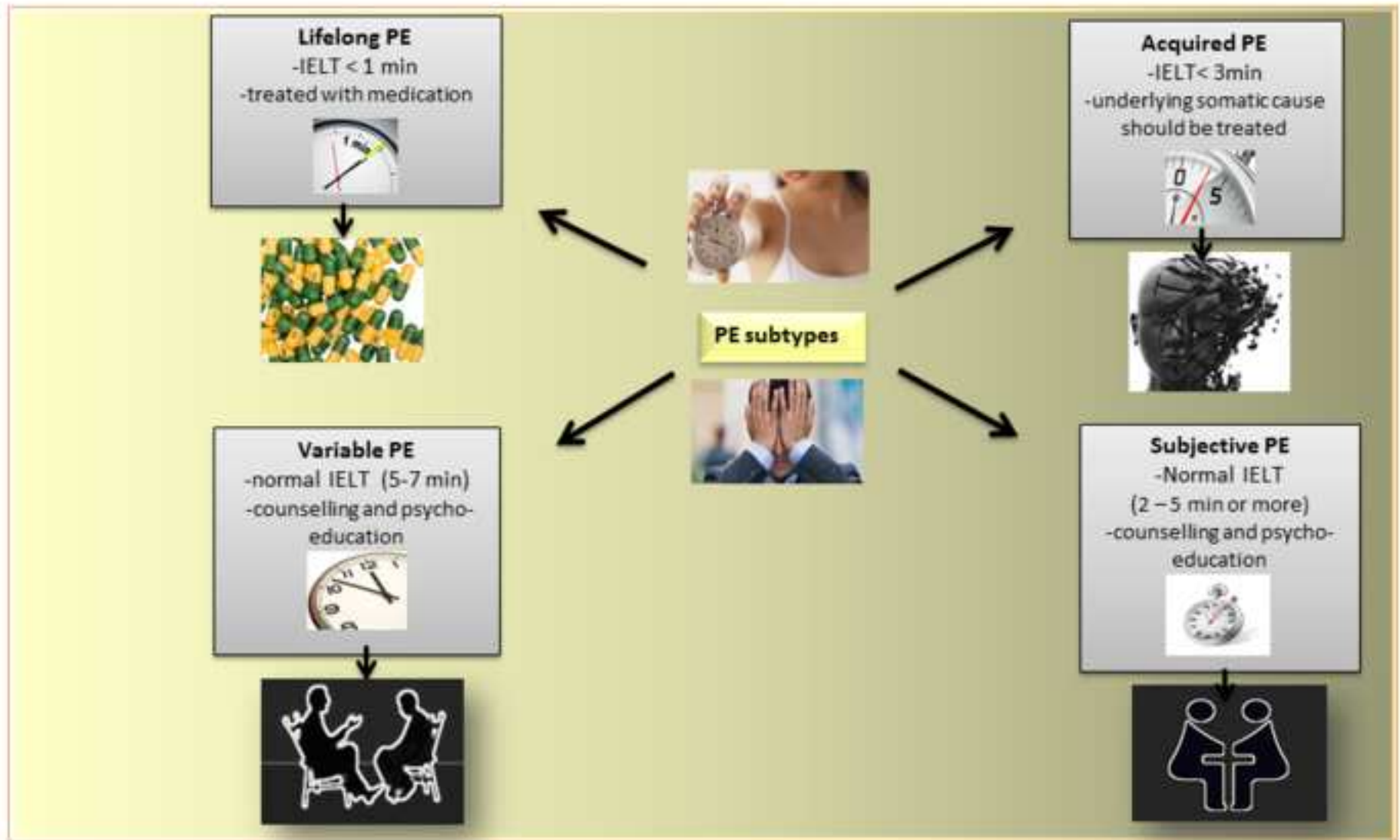


Figure 1

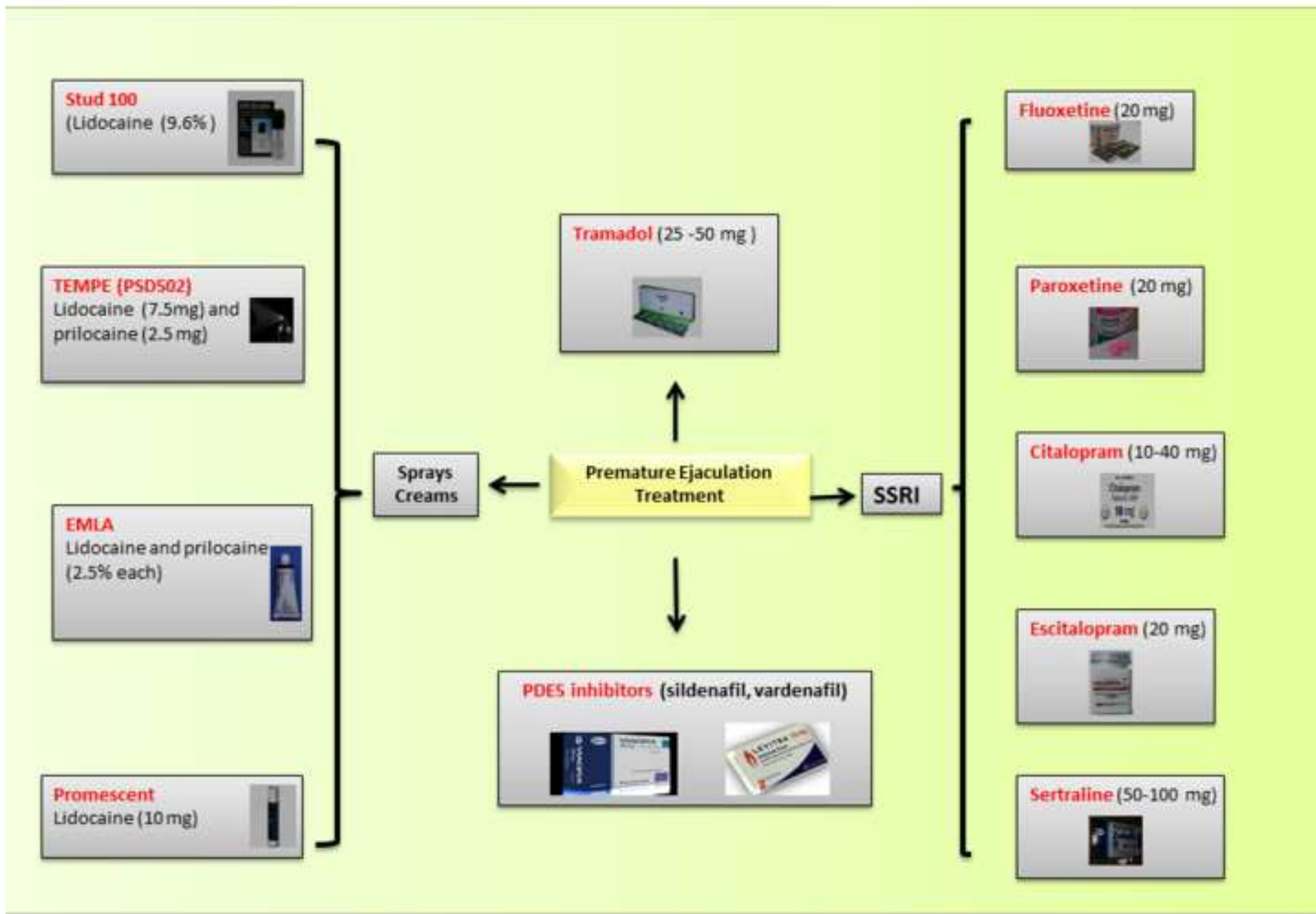


Figure 2