Review – Sexual Medicine

The Role of Phosphodiesterase Type 5 Inhibitors in the Management of Premature Ejaculation: A Critical Analysis of Basic Science and Clinical Data

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Abstract

Objectives: To assess the usefulness of the phosphodiesterase type 5 inhibitors (PDE5-Is) in the treatment of premature ejaculation (PE) and to describe possible mechanisms to explain their effect.

Methods: A MedLine search was performed for peer-reviewed articles on the role of PDE5-Is in managing PE. No meta-analysis method was used.

Results: Five manuscripts that examined the efficacy of PDE5-Is in the treatment of PE were retrieved. Three studies used sildenafil as monotherapy and two used it in combination with a serotonin selective reuptake inhibitor (SSRI). Three studies demonstrated a beneficial effect of sildenafil in the treatment of PE, as measured by intravaginal ejaculatory latency time (IELT) and by different questionnaires assessing the patients’ subjective feelings of ejaculatory control, sexual satisfaction, and anxiety. One study showed the superiority of sildenafil compared to other modalities. Two studies showed that combination therapy of paroxetine and sildenafil was better than paroxetine alone. One study did not demonstrate a beneficial effect of sildenafil in prolonging IELT, but showed that sildenafil improved patients’ perception of ejaculatory control. Another study showed that topical anesthetics were better than sildenafil in the treatment of PE but did not use IELT or a validated questionnaire to measure the efficacy of treatment. Several possible mechanisms could explain effectiveness of the PDE5-Is for treatment of PE: centrally, through the effect on the nitric oxide/cyclic guanosine monophosphate pathway; peripherally by causing relaxation of smooth muscle in the vas deferens, seminal vesicles, prostate, and urethra and inhibition of adrenergic transmission; or locally by inducing peripheral analgesia. Another possibility might be prolongation of the duration of erection.

Conclusions: Encouraging evidence supports the role of PDE5-Is for treating PE. Possible therapeutic mechanisms of action of PDE5-Is are multiple and complex and include central and peripheral effects. A large population, multicenter, randomized, double-blind, placebo-controlled study is needed to elucidate the efficacy of PDE5-Is in the treatment of PE.

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1. Introduction

1.1. Prevalence of premature ejaculation

Ejaculatory dysfunction, erectile dysfunction (ED), and decreased libido are the major components of male sexual dysfunction. The introduction of oral pharmacologic therapy for ED has focused much attention on this pathology compared to others. Premature ejaculation (PE), however, is actually more prevalent, involving up to 31% of men aged 18–59 [1], and is considered to be the most common among male sexual disorders. PE is more prevalent in young men and in men who lack sexual experience and frequency. The risk of PE does not vary significantly with age, and men with PE are at risk for suffering from psychological disturbances, such as depression and anxiety [2].

1.2. PE definitions

There is no universally accepted definition of PE. The 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines PE as “persistent or recurrent onset of orgasm and ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it,” which causes “marked distress or interpersonal difficulty” [3]. This definition consists of the four elements of PE: ejaculatory latency, control, distress, and sexual satisfaction. DSM-IV divides PE into lifelong PE, which had been present from the onset of sexual life, and acquired PE, in which the dysfunction developed after a period of normal sexual function. PE can be further divided into global (regardless of partner or situation) and situational (only with certain partners or circumstances). Some authors suggested defining PE as a syndrome, rather than a complaint, comprising quantification of the ejaculation time, inability of ejaculatory control, and a description of severity of PE in terms of psychological distress [4,5]. Still, the absence of an agreed-on definition causes wide variations in patient selection for studies on PE.

1.3. Physiology of ejaculation and PE pathophysiology

The physiology of ejaculation is still not clearly understood. Ejaculation involves three stages: emission, ejection, and orgasm. Emission consists of contractions of seminal vesicles (SVs) and prostate with expulsion of sperm and seminal fluid into the posterior urethra and is mediated by sympathetic nerves (T10–L2). Ejection is mediated by somatic nerves (S2–4) and involves pulsatile contractions of the bulbocavernous and pelvic floor muscles together with relaxation of the external urinary sphincter.

Ejaculation is a complex integration of actions that occur in the central and peripheral nervous systems. Structures in the central nervous system (CNS) that are involved in ejaculation include the medial preoptic area (MPOA), nucleus paragigantocellularis (nPGi), stria terminalis, amygdala, and thalamus. Whereas the MPOA is involved in stimulation of emission and ejection, the nPGi has an inhibitory influence. Descending serotonergic pathways from the nPGi to the lumbosacral motor nuclei inhibit ejaculation. The MPOA can inhibit the nPGi, which results in ejaculation [6].

Many neurotransmitters are involved in the control of ejaculation, including norepinephrine, serotonin, acetylcholine, oxytocin, γ-aminobutyric acid (GABA), and nitric oxide (NO) [7]. Serotonin (5-hydroxytryptamine [5-HT]) has an inhibitory effect on ejaculation [8]. The serotonin receptors 5-HT1a and 5-HT2c were associated with ejaculation [9]. 5-HT1a is a presynaptic autoreceptor that inhibits serotonin secretion and thus may stimulate ejaculation, whereas the 5-HT2c receptor is postsynaptic and its activation is related to inhibition of ejaculation [9,10]. NO has a central effect, mostly in the MPOA, in promoting penile erection, and it may inhibit seminal emission [11].

Given the obscurity of ejaculation physiology, it is not surprising that PE pathophysiology is equally poorly understood. Historically, PE was considered as being a problem with psychological causes, such as anxiety, early sexual experiences, sexual conditioning, and sexual technique [12]. It was speculated that anxiety activates sympathetic output and thus leads to earlier emission and rapid ejaculation [13]. Currently, a speculated neurogenic cause is either a hyposensitivity of 5-HT2c receptors or a hypersensitivity of the 5-HT1a receptors [6]. Other causes might be a hyperexcitable ejaculatory reflex, resulting in faster emission and ejection, prostatic pathologies such as inflammation or infection [14], high fasting serum leptin levels [15], hyperthyroidism [16], and genetic predisposition [17].

1.4. Current treatments for PE

PE can be treated with behavioral techniques, topical anesthetics, α-adrenergic receptor antagonists, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs). Phosphodiesterase type 5 inhibitors (PDE5-Is), for example, sildenafil,
tadalafil, and vardenafil, inhibit PDE5 both centrally and peripherally and lead to the accumulation of intracellular cyclic guanosine monophosphate (cGMP) [18]. Although used successfully in the management of ED, novel applications include alleviating PE. In this review, we discuss the role of PDE5-Is in the treatment of PE and the possible mechanisms of action of its therapeutic effects.

2. Methods

We searched MedLine for peer-reviewed studies published from January 1, 1990 to February 28, 2007 on treatment with PDE5-Is for patients suffering from PE and on the pathophysiologic explanation of the action of PDE5-Is on ejaculatory function. We used the key words “premature ejaculation,” “rapid ejaculation,” “sildenafil,” “tadalafil,” “vardenafil,” “PDE5-I,” and “medical treatment of PE.” The search was restricted to publications in the English literature, and letters to editor were excluded. The results of the individual studies are presented and discussed; no meta-analysis or integration of the results was carried out.

Of 111 articles retrieved from the systematic search, we focused our analysis on the five that appeared in English, which examined the role of PDE5-Is in the management of patients with PE. These articles were selected for the quality of their methodology and the importance of the results presented. We assessed each study protocol in terms of patient characteristics, definitions of PE used, the study’s primary and secondary end points, and its outcomes. We obtained additional information from data of European and International Society for Sexual Medicine guidelines.

3. Results

Five manuscripts were found concerning the use of PDE5-I in PE (Table 1). Two were placebo-controlled studies [19,20]. None fulfilled the criteria of a level 1 study (double-blind, placebo-controlled, randomized study). Four articles were comparative, using one or two treatment modalities [20–23]. Three reports assessed therapy with sildenafil as monotherapy [19–21] and two as combination therapy with an SSRI [22,23].

In a prospective, randomized, double-blind crossover study, Abdel-Hamid et al assessed the efficacy of as-needed clomipramine, sertraline, paroxetine, or sildenafil and the pause-squeeze technique in 31 men with lifelong PE without ED [21]. PE was defined as patient self-reported intravaginal ejaculation latency time (IELT) < 2 min and lack or little control over ejaculation. Sildenafil (50 mg) was given 3–5 h before intercourse. IELT was measured by the patient using a stopwatch, and the patient answered a questionnaire and received a sexual satisfaction score and an anxiety score. Although all regimes

Table 1 – Studies assessing the efficacy of PDE5-Is in the treatment of PE

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Patients, n</th>
<th>Design</th>
<th>Duration, wk</th>
<th>Lifelong vs. acquired PE</th>
<th>PE definition</th>
<th>Study end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Hamid et al. [21]</td>
<td>Clomipramine, sertraline, paroxetine, sildenafil, pause-squeeze technique</td>
<td>31</td>
<td>Double-blind</td>
<td>28</td>
<td>Lifelong</td>
<td>Lack of control, IELT &lt; 2 min</td>
<td>Stopwatch IELT, sexual satisfaction score, anxiety score</td>
</tr>
<tr>
<td>Salonia et al. [22]</td>
<td>Sildenafil + paroxetine vs. paroxetine alone</td>
<td>80</td>
<td>Open-label</td>
<td>26</td>
<td>Both</td>
<td>IELT ≤ 1 min</td>
<td>Stopwatch IELT, IIEF domain, intercourse frequency, satisfaction score</td>
</tr>
<tr>
<td>Chen et al. [23]</td>
<td>Behavioral treatment, lidocaine, paroxetine + sildenafil, paroxetine + placebo</td>
<td>138</td>
<td>Open-label</td>
<td>36</td>
<td>Lifelong</td>
<td>IELT &gt; 50% of time</td>
<td>Stopwatch IELT, PE</td>
</tr>
<tr>
<td>McMahon et al. [19]</td>
<td>Sildenafil alone, sildenafil + DMA cream, DMA cream alone, placebo</td>
<td>157</td>
<td>Double-blind</td>
<td>8</td>
<td>Lifelong</td>
<td>Both</td>
<td>Self-reported improvement</td>
</tr>
<tr>
<td>Atan et al. [20]</td>
<td>Sildenafil alone, sildenafil + DMA cream, DMA cream alone, placebo</td>
<td>94</td>
<td>Double-blind</td>
<td>8</td>
<td>Both</td>
<td>Both</td>
<td>Self-reported improvement</td>
</tr>
</tbody>
</table>

PDE5-Is = phosphodiesterase type 5 inhibitors; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; IIEF = International Index of Erectile Function; DMA = lidocaine, paroxetine + placebo; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

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showed prolongation of IELT, the effect of sildenafil was significantly greater (from 1 to 15 min, effective in 90% of patients) and was correlated to improvement in the sexual satisfaction score and the anxiety score. The relation between IELT and the questionnaires was not evaluated. The effect of sildenafil remained during the washout period in 29% of patients. The incidence of side effects was similar among groups and included headache, flushing, and nasal congestion in 18% of the patients who received sildenafil.

Salonia et al [22] compared the efficacy of sildenafil and paroxetine to paroxetine alone in the treatment of 80 potent men with nonorganic PE as defined by an IELT of <1 min. Eighteen of them had secondary PE. Forty men received 10 mg paroxetine daily for 21 d and then 20 mg as needed for 6 mo, whereas the other 40 men received the same, only with the addition of as-needed 50 mg sildenafil 1 h before intercourse. IELT, which was measured using a stopwatch, was significantly longer after 6 mo for the patients who received sildenafil (from a mean of 0.33 min to 5.3 min vs. 4.2 min in patients who received paroxetine alone, \( p < 0.05 \)). There were also improvements in intercourse frequency and in sexual satisfaction, as was measured by the International Index of Erectile Function (IIEF) questionnaire. Side effects were more frequent in the group that received the combination therapy, with 20% complaining of headache and 15% of flushing. Nevertheless, 90% of the patients were willing to continue therapy.

Chen et al [23] examined the efficacy of sildenafil as adjuvant therapy with paroxetine in potent patients with primary PE. Patients who reported that PE occurred in >50% of intercourse attempts and had a self-reported IELT <3 min (measured qualitatively using a questionnaire) were enrolled. All 138 patients received psychological and behavioral counseling in addition to topical lidocaine treatment. Patients who remained dissatisfied after 3 mo were then treated with paroxetine daily for 30 d and then on an as-needed basis. After an additional 3 mo, 25–100 mg sildenafil was added 1 h before intercourse to dissatisfied patients. Of the 58 patients who received adjuvant sildenafil, 56 were satisfied (97%) compared to 42% who were satisfied with paroxetine alone and 28% who were satisfied with topical lidocaine.

In a randomized, 8-wk, double-blind, placebo-controlled multcenter study, McMahon et al [19] assessed the efficacy of 50–100 mg as-needed sildenafil in 157 potent men with lifelong PE, defined according to DSM-IV criteria and with IELT <2 min in 75% of intercourse attempts. IELT, which was measured using a stopwatch, was prolonged in patients who were taking sildenafil, but the difference was not statistically significant. The patients were asked to answer the Index of Premature Ejaculation (IPE) questionnaire. There was no significant difference in the overall IPE score, but patients who were taking sildenafil had significantly higher scores on questions assessing ejaculatory control and confidence as well as overall sexual satisfaction. Sildenafil also significantly shortened the refractory time after orgasm. The correlation between IELT and the IPE questionnaire was not evaluated.

Atan et al [20] compared the efficacy of sildenafil alone, sildenafil with topical EMLA cream, topical EMLA cream alone, and placebo in 84 potent patients with lifelong and acquired PE. PE was defined according to the DSM-IV definition, and improvement was determined solely on the basis of patients’ statement after eight attempts at intercourse. IELT was not measured. Twenty patients received placebo for 2 mo, 20 patients received 50 mg sildenafil 45 min before intercourse, 22 patients received sildenafil and topical EMLA cream before intercourse, and 22 patients received EMLA cream alone. There was no significant improvement in PE between sildenafil alone and placebo. Only the groups that received EMLA cream with or without sildenafil showed significant improvement in PE. Only the patients who received sildenafil experienced side effects, which included headaches (26%) and flushing (26%).

We found no peer-reviewed publications on the role of tadalafil or vardenafil in the treatment of PE, other than abstracts presented at international conferences [24,25].

4. Discussion

4.1. Possible mechanisms of actions of PDE5-Is in PE

The physiology of ejaculation and the pathophysiology of PE are still not fully understood. Likewise, the mechanisms of action of PDE5-Is in the treatment of PE still need to be elucidated. Nevertheless, several possible mechanisms could explain their effects in PE, as has been demonstrated in animal and human studies. PDE5-Is may exert their influence both centrally and peripherally. We will describe the presence and affects of the NO/cGMP pathway, the presence of PDE, and the possible actions of PDE5-Is in each nervous system.
4.1.1. Central mechanisms
The NO/cGMP pathway seems to play a role in sexual behavior via a central effect, as nitric oxide synthase (NOS) and guanylate cyclase are present and active in areas of the CNS that are responsible for sex drive and sexual behavior [26]. Some authors have demonstrated that NO donors increase cGMP in the hypothalamus, and infusion of NO donors to the extracellular environment in the MPOA of rat’s brain induces erection and copulatory behavior [11]. NO decreases central sympathetic output to the periphery [27] via a cGMP-dependent mechanism or through interactions with other neurotransmitters [28]. Specifically, a decrease of sympathetic tone by NO activity in the MPOA is related to inhibition of ejaculation [29]. PDE5 has been demonstrated in the CNS [30], and PDE5-Is can cross the blood–brain barrier into the brain [31]. Administration of sildenafil intrathecally in rats increases NO and cGMP in the MPOA [32]. Moreover, incubation of rat hippocampal slices with vardenafil results in an increase in extracellular environment in the MPOA of rat’s brain [33].

4.1.2. Peripheral mechanisms
4.1.2.1. Relaxation of smooth muscle in the VD, SVs, prostate, and urethra. Because the NO/cGMP and NO/cyclic adenosine monophosphate (cAMP) signaling pathways are involved in relaxation of corporal smooth muscles, they could also affect smooth muscle in the VD, SVs, prostate, and urethra. Many lines of evidence support the presence and activity of the NO/cGMP and NO/cAMP signaling pathways in the VD, smooth muscles, prostate, and urethra. Nitrergic innervation and NO synthase activity have been detected in human VD, SVs, prostate, urethra, and skeletal muscles [34–37]. NO and NO-donating agents have been shown to inhibit seminal emissions in rats [38], whereas NO inhibitors decrease the latency to emission in rats [39] and reduce the contractile response of guinea pig VD and human SVs [40,41]. Moreover, one study on knockout mice demonstrated that mice homozygous for a deletion in the gene for endothelial NOS (eNOS) have shorter latency times with much less stimulation than wild-type mice [42]. Elevation of intracellular cGMP and cAMP leads to relaxation of smooth muscle in rat and guinea pig VD [40,43] and in human SVs [44]. PDE5 activity has been demonstrated in the VD, SVs, prostate, and skeletal muscles [45–48], and sildenafil has been shown to cause selective potentiation of nitrergic transmission in urogenital smooth muscle in mice [49].

Another way in which PDE5-Is can prolong latency is by inhibiting adrenergic transmission. PDE5-I was able to reverse adrenergic tension in human prostatic strip preparations [50], and adrenergic transmission in human VD was inhibited by sildenafil [51]. Medina et al described a mechanism that is independent of the NO/cGMP pathway. They demonstrated that sildenafil also has a direct inhibitory effect on smooth muscle of human VD by activation of pre-junctional large conductance Ca2+-activated K+ channel [51].

4.1.2.2. Induction of peripheral analgesia. One presumed cause of PE is penile hypersensitivity, leading to the suggested treatment modality of topical anesthetics. Sildenafil may mimic this effect given that activation of the NO/cGMP signaling pathway by sildenafil was shown to induce a state of peripheral antinociception [52]. Another explanation for peripheral analgesia could be mechanical. PDE5-Is cause cavernosal congestion by maximal dilatation of blood vessels supplying the corpus cavernosum, leading to an increase in intracavernosal volume and, therefore, to increased pressure on nerve receptors, thus causing hypoesthesia of the glans penis and prolongation of ejaculatory latency time. This theory, however, is highly controversial [53].

4.1.2.3. Prolongation of the duration of erection. To date, many studies have demonstrated the effect of different PDE5-Is in prolonging the duration of erection, as part of the rationale of this treatment modality in ED. Some works have correlated the duration of erection with the ejaculation latency time in such a manner that the longer the duration of erection, the more prolonged the ejaculatory latency time [54]. Therefore, PDE5-Is might have a beneficial effect on PE by improving the duration of erection.

4.2. Clinical aspects
4.2.1. Overall effectiveness of using PDE5-Is for treating PE
Of the five studies we reviewed, three found PDE5-Is to be helpful in the treatment of PE, whereas two did not. Three reports assessed the efficacy of sildenafil as monotherapy [19–21]. One found that sildenafil was superior to other treatment modalities, such as clomipramine, sertraline, paroxetine, and the pause-squeeze technique in terms of IELT and sexual satisfaction [21]. The other two studies, which were placebo-controlled, found no significant advantage to treatment with sildenafil in PE. One study did not demonstrate any difference between sildenafil and placebo in terms of improvement in stopwatch-measured IELT but did show significant changes in ejaculatory control, confidence, and overall sexual satisfaction in favor of sildenafil as
assessed by the IPE questionnaire [19]. The other study did not show any advantage of sildenafil over placebo but rather that topical anesthetics were better in treating patients with PE; IELT, however, was not measured and the noted improvement was based only on the patients’ responses toward treatment and not according to any validated questionnaire [20].

Two studies assessed PDE5-Is as part of a combination therapy with SSRI [22,23]. Both of them showed that sildenafil with paroxetine is superior to paroxetine alone in the treatment of PE. Salonia et al demonstrated improvements in stopwatch-measured IELT, sexual satisfaction, and frequency of intercourse with sildenafil and paroxetine [22]. Chen et al showed that the combination of sildenafil and paroxetine was efficient in 97% of patients so treated compared to 42% of patients treated with paroxetine alone [23].

4.2.2. Differences in PE definitions

The European and International Society for Sexual Medicine guidelines state that the inclusion criteria for studies on management of PE must ensure that participants have PE and no other sexual dysfunction, such as ED, and that the IELT measurement as a specific entry criterion is not a necessity [55]. The definition of PE, as reflected by the inclusion criteria, was varied among the studies we reviewed. All but one defined PE using IELT, either measured by stopwatch or self-reported. Two studies defined PE as IELT < 2 min [19,21], one study defined PE as IELT < 3 min [23], whereas another defined it as IELT < 1 min [22]. Two studies used the DSM-IV criteria for defining PE, one in addition to a measured IELT [19], whereas the other one based its definition solely on the DSM-IV [20]. Two more investigations, which used IELT as a criterion, used also a question on the subjective feeling of control [21,23]. The variation in criteria is not surprising in light of the lack of a widely accepted definition of PE, but it seems reasonable to include patients with IELT < 2 min together with a subjective feeling of lack of ejaculatory control.

4.2.3. Issues and controversies regarding IELT

The European and International Society for Sexual Medicine guidelines state that outcome measures should include IELT, ejaculatory control, and sexual satisfaction [55]. Only one study did not use IELT as an end point, but rather patients’ self-reported statements on improvement or no improvement [20]. All the other studies used IELT and different questionnaires to assess the patients’ subjective feeling of improvement. IELT in three studies was measured using a stopwatch [19,21,22] and in one study based on the patients’ estimations [23].

Although the measurement of IELT by a stopwatch is the most accepted tool because it is considered to be “objective,” many authors find this modality to be controversial, first, due to the inconvenience of the use of a stopwatch during intercourse, second, because it may decrease the quality of the sexual intercourse, and third, because it may not be acceptable to all patients or their sexual partners. We believe that the IELT as estimated by the patient and his partner is comparable to stopwatch-measured IELT and far more convenient.

4.2.4. Overall effectiveness instruments and general questionnaires

Different types of questionnaires have been used to assess the patients’ sense of improvement. Two studies used questionnaires developed originally for ED patients. Abdel-Hamid et al [21] used an Arabic questionnaire to assess anxiety and the first nine items of the sexual satisfaction questionnaire designed originally for ED patients [56] to assess sexual satisfaction. Salonia et al [22] used the IIEF questionnaire and a general efficacy question. The other two studies used novel instruments: Chen et al [23] used a modification of a question from the Center for Marital and Sexual Health (CMASH) Ejaculatory Function questionnaire on PE, and McMahon et al [19] used the IPE and a general efficacy question. In another PE study [57], we used the Index of Ejaculatory Control (IEC) 10-item questionnaire, which was validated and designed to assess the patient’s feeling of control, sexual satisfaction, and distress specifically in PE patients [58].

Given that PE may be psychogenic, at least in part, and possibly related to anxiety while part of its definition are feelings of lack of ejaculatory control, bother, and distress, there is considerable room for a placebo effect in all studies on the management of PE. For this reason, any well-constructed study aimed at assessing the effect of PDE5-Is on PE must be placebo-controlled. In our recent randomized, double-blind, placebo-controlled, crossover study, we compared sildenafil with placebo in 61 potent men with PE [57]. We showed that patients receiving sildenafil had prolonged IELT compared with those who received placebo, as measured by a specially designed visual scale Ejaculatory Latency Time Questionnaire (ELTQ). Significant improvements were also observed in the IEC score for patients who received sildenafil. The number of patients responding positively to the global assessment question (“Did you have better control over your
ejaculation?”) while on sildenafil was significantly higher than those on placebo ($p < 0.01$).

Although ED with PE is considered as an indication for treatment with PDE5-Is [59], we found no studies that specifically evaluated this condition, and the studies we did review excluded patients with ED.

5. Conclusions

There are limited but encouraging results to support the use of PDE5-Is in the treatment of patients with PE with or without additional SSRIs. The physiologic effects of PDE5-Is in the treatment of PE are multiple and complex, including central and peripheral effects, mainly via augmentation of the NO/cGMP signaling pathway.

Although IELT is an accepted tool for assessing PE, currently available IELT measurement methods are not ideal because inherent subjective difficulties in measurement can cause bias in the evaluation of the results. New convenient and efficient technology to measure IELT, which will be less dependent on the attention of the sexual partners, would be very useful. In addition, there is a need to perform studies to evaluate the correlation between stopwatch-measured IELT and existing questionnaires.

Finally, the inability to reach decisive clinical conclusions is derived from the lack of agreed-on definitions for PE and well-accepted outcome measures to monitor treatment efficacy. The lack of conclusive evidence emphasizes the need for a large population, randomized, double-blind, placebo-controlled study to assess the efficacy of PDE5-Is in the management of PE.

Conflicts of interest

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