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Alternative Treatments for Premature Ejaculation: A Review of Pharmacological Strategies

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ABSTRACT

Introduction and Purpose:

Premature ejaculation (PE) is a common male sexual disorder with a complex etiology involving psychological, neurobiological, and physiological factors. PE is defined as ejaculation occurring earlier than desired, often causing distress. Its etiology is multifactorial and not fully understood. Current standard treatments such as Selective Serotonin Reuptake Inhibitors (SSRIs) and lidocaine-prilocaine creams are helpful but limited, prompting interest in alternatives.

This review presents alternative pharmacological treatments for PE, excluding SSRIs and topical anesthetics, along with their side effects and benefits.

Material and Methods:

This narrative review evaluated pharmacological treatments for PE, excluding SSRIs and topical agents. Literature was searched in databases like PubMed and ScienceDirect for English-language studies published between 2000 and 2025. Selected studies focused on agents such as tramadol, clomipramine, levosulpiride, phosphodiesterase type 5 inhibitors, and α_1-adrenoreceptor antagonists. Inclusion criteria comprised clinical trials, meta-analyses, observational studies, and systematic reviews. Studies focusing solely on SSRIs, local treatments, or non-pharmacological methods were excluded.

Results:

Agents like PDE5 inhibitors, tramadol, silodosin, levosulpiride, and clomipramine showed significant improvements in intravaginal ejaculatory latency time (IELT), patient satisfaction, and outcomes, with acceptable side effect profiles.

Conclusions:
PE treatment should be tailored to individual needs. PDE5Is, α_1-adrenoreceptor antagonists, tramadol, levosulpiride, and clomipramine have shown promising results; however, due to the limitations of current studies, further research is necessary to confirm their efficacy and clarify their clinical roles.

Keywords: premature ejaculation; erectile dysfunction; treatment; definition.

INTRODUCTION AND PURPOSE

Despite the growing interest in men's sexual health, premature ejaculation (PE) remains a challenging and multifaceted clinical condition. Although the phenomenon has been recognized for a long time, its precise definition, etiology, and effective treatment are still the subject of ongoing research efforts [1, 2]. PE not only negatively impacts the quality of sexual life, but can also lead to significant deterioration in partner relationships and reduced self-esteem [3, 4]. The global prevalence of PE is estimated to range between 12.1% and 38.5% [5, 6, 7, 8, 9, 10, 11]. This wide variation is likely due to factors such as the lack of a standardized definition, uncertain etiology, sociological differences, and most importantly differences in investigations like study populations, locations, and research methodologies [12, 13].

It is hypothesized that several factors may contribute to the development of PE, including anxiety, relationship difficulties, genetic component, neurobiological dysregulation, heightened penile sensitivity, sexual dysfunction, also chronic diseases such as neurological, urological, endocrinological and renal disorders [14, 15]. These diverse potential causes reflect the multifactorial nature of the condition. The complexity of PE's underlying mechanisms, spanning both neurobiological and psychological domains, emphasizes the importance of an interdisciplinary therapeutic approach that can address its various contributing factors [16, 17]. Although selective serotonin reuptake inhibitors (SSRIs) and lidocaine-prilocaine topical creams remain among the most commonly used treatments for PE, they were not originally developed for this condition, are often ineffective, and are associated with adverse side effects [18, 19, 20]. There is growing interest in alternative pharmacological treatment options [21].

The aim of this review is to present potential pharmacological therapeutic strategies used in the treatment of PE, excluding selective serotonin reuptake inhibitors (SSRIs) and topical

lidocaine/prilocaine cream. The analysis includes current clinical data on alternative medications and novel, less conventional treatment approaches.

DESCRIPTION OF STATE OF KNOWLEDGE

Despite advances in research on men's sexual health, there is still no universally accepted and standardized definition of premature ejaculation (PE). International Society for Sexual Medicine(ISSM), American Urological Association (AUA), Sexual Medicine Society of North America (SMSNA), European Association of Urology (EAU) and classification systems (ICD-11, DSM-5) offer similar yet not identical descriptions of this condition[22, 23, 24, 25, 26]. Common elements include a short latency time from the beginning of penetration to ejaculation, lack of ejaculatory control, and associated psychological distress or interpersonal difficulties. All of them provide a standardized basis for treatment and further research. [27]

Table 1. Definitions of Premature Ejaculation

Organization / Classification	Definition	References
ISSM	"A male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within 1 minute of vaginal penetration, either present from the first sexual experience or following a new bothersome change in ejaculatory latency, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy."	[22]

AUA/SMSNA	"Lifelong premature ejaculation is defined as poor ejaculatory control, associated bother, and ejaculation within about 2 minutes of initiation of penetrative sex that has been present since sexual debut. Acquired premature ejaculation is defined as consistently poor ejaculatory control, associated bother, and ejaculation latency that is markedly reduced from prior sexual experience during penetrative sex."	[23]
ICD-11	"Male early ejaculation is characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period at least several months and is associated with clinically significant distress"	[24]
EAU	is based on ICD-11	[25]
DSM-5	"A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes. The symptom must be present for at least 6 months and must be experienced on almost all or all (approximately 75%-100%) occasions of sexual activity and causes clinically significant distress. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition"	[26]

Premature Ejaculation(PE), Diagnostic and Statistical Manual of Mental Disorders – fifth edition (DSM-V), International Society for Sexual Medicine(ISSM), European Association of Urology (EAU), American Urological Association (AUA), International Classification of

Diseases, Eleventh Revision (ICD-11), Intravaginal Ejaculation Latency Time (IELT), Sexual Medicine Society of North America (SMSNA)

In summary, while the core symptoms are largely consistent, the definitions differ in terms of ejaculatory latency time, classification of PE types, and consideration of biological and psychological factors. A harmonized definition would facilitate diagnosis and standardize clinical research.[28]

ALTERNATIVE TREATMENT

Table 2. Comparison of Pharmacological Therapies for Premature Ejaculation

Therapy	Mechanism of Action	Efficiency	Quality of Life Influence	Adverse Events	References
PDE5 Inhibitors	Enhances cGMP levels via PDE5 inhibition, promoting smooth muscle relaxation and improving erectile response, indirectly improving PE.	Significantly prolongs IELT and enhances sexual satisfaction; especially when combined with SSRIs.	Improved satisfaction scores; generally well tolerated but side effects may impact adherence.	Headache, flushing, nasal congestion, indigestion, muscle aches, visual disturbances; mild to moderate.	[29,30,31, 32,33]
Tramadol	μ-opioid receptor agonism with serotonin and norepinephrine reuptake inhibition, leading to delayed ejaculatory reflex.	Dose-dependent improvements in IELT and ejaculatory control	High patient satisfaction; enhanced sexual activity; consistent effects across regimens.	Nausea, dizziness, potential dependence with long-term or unsupervised use.	[34,35,36, 37]

Levosulpiride	Selective dopamine D_2 receptor antagonism, reducing dopaminergic signaling and raising ejaculatory threshold.	Improves IELT and sexual satisfaction;	Notable improvement in sexual satisfaction and reduction in distress related to PE.	Generally well tolerated; more studies needed to assess long-term safety.	[38,39]
Clomipramine	Serotonin and norepinephrine reuptake inhibition, mild anticholinergic effects, increasing synaptic 5-HT levels and delaying ejaculation.	Prolongs IELT and improves ejaculatory control; intranasal and oral forms show positive effects.	Enhanced sexual satisfaction and control; best efficacy seen with 15 mg oral dosing.	Gastrointestinal symptoms, mild psychiatric effects, nasal congestion (intranasal).	[40, 41, 42,43]
α_1-Adrenoreceptor Antagonists	Blocks α_1A-adrenergic receptors in smooth muscles of reproductive tract, delaying emission phase of ejaculation.	Significant IELT improvement; most effective with silodosin compared to other α-blockers.	Significant QoL and PEP improvement, especially with silodosin; high satisfaction reported.	Dry ejaculation, mild dizziness, occasional orgasmic discomfort.	[44, 45, 46, 47]

Phosphodiesterase type 5 inhibitors (PDE5Is)

Sexual stimulation initiates the release of nitric oxide (NO) in the corpus cavernosum of the penis. This gaseous signaling molecule activates the enzyme guanylate cyclase, which subsequently increases levels of cyclic guanosine monophosphate (cGMP). Elevated cGMP causes the relaxation of smooth muscle tissue in the corpus cavernosum, allowing for increased blood flow and resulting in an erection. However, the enzyme phosphodiesterase type 5 (PDE5) naturally breaks down cGMP, limiting the duration and strength of the erectile response. PDE5

inhibitors, a class of medications commonly used to treat erectile dysfunction (ED), work by blocking the action of PDE5, thereby preventing cGMP degradation. As a result, cGMP remains elevated for longer, enhancing and prolonging the erectile response to sexual stimulation. [29] In their meta-analysis, Zhang et al. analyzed seven randomized placebo-controlled trials encompassing a total of 471 male participants diagnosed with PE but without erectile dysfunction. The primary outcomes assessed were intravaginal ejaculatory latency time (IVELT) and sexual satisfaction scores. The findings revealed that PDE5Is significantly prolonged IVELT compared to placebo, with a mean difference (MD) of 2.60 minutes (95% confidence interval [CI]: 1.85–3.36; $p < .00001$). Additionally, sexual satisfaction scores improved notably in the PDE5I group (MD: 2.04; 95% CI: 0.78–3.30; $p = .002$). However, the incidence of side effects such as headaches, dizziness, flushing, and nasal congestion was higher among patients receiving PDE5 inhibitors. Despite these adverse events, the study concluded that PDE5 inhibitors are more effective than placebo in managing PE, offering significant improvements in latency time and sexual satisfaction [30] In a prospective clinical study conducted by Wei-Fu Wang et al., 180 men diagnosed with premature ejaculation were assigned to three treatment groups. Group A received sildenafil 50 mg as needed, Group B took 20 mg of paroxetine daily, and Group C practiced the squeeze technique daily. The effectiveness of each intervention was evaluated at 3 and 6 months using measures such as IELT, PE severity grade, and intercourse satisfaction score (ISS), with baseline values serving as the reference. All outcomes, except for intercourse frequency in Group C, showed statistically significant improvements ($P = 0.00$). Sildenafil treatment produced significant enhancements across all measured parameters ($P = 0.00$). At the 6-month mark, discontinuation rates were 1.7% in Group A, 18.3% in Group B, and 36.7% in Group C, while the percentage of patients willing to continue their assigned treatment was 86.7%, 60.0%, and 45.0%, respectively—differences that were statistically significant ($P = 0.00$).)[31] M.J. Mathers and colleagues evaluated therapeutic strategies for PE in a group of 72 men. Participants initially assessed the severity of their symptoms using a scale from 0 (almost never) to 8 (almost always), and their IELT was recorded. Those with a PE score of 4 or above and an IELT under 1.3 minutes proceeded to the treatment phase. Following six weeks of behavioral psychosexual therapy, 49 men still met the criteria and were randomly assigned to receive either vardenafil (10 mg) or sertraline (50 mg) for another six weeks. After a one-week washout period, a crossover design was implemented, switching the medications between groups. Of the original 72 participants, 23 experienced satisfactory results from behavioral therapy alone and did not continue. The remaining 49, with a mean PE score of 5.94 ± 1.6 and an IELT of 0.59 minutes, were randomized. Four participants dropped out. Vardenafil

significantly improved outcomes, reducing the average PE score to 2.7 ± 2.1 ($p < 0.01$) and increasing IELT to 5.01 ± 3.69 minutes ($p < 0.001$). Sertraline was also effective, lowering the PE score by 1.92 ± 1.32 ($p < 0.01$) and extending IELT to 3.12 ± 1.89 minutes ($p < 0.001$).[32] Common side effects include headache, flushing, nasal congestion, indigestion, visual disturbances, and muscle aches. These may impact treatment adherence in some patients.[33] Numerous methodological shortcomings were observed across the analyzed studies, including limited sample sizes, absence of placebo control groups, lack of blinding, and inconsistent definitions of premature ejaculation, all of which weaken the overall credibility and comparability of the results.

Tramadol

Tramadol is a centrally acting analgesic with a dual mechanism of action. Primarily, it binds to μ-opioid receptors in the central nervous system, which contributes to its pain-relieving effects. However, what sets tramadol apart from traditional opioids is its additional ability to inhibit the reuptake of serotonin and norepinephrine, two key neurotransmitters involved in mood regulation and the modulation of pain and sexual function. In the context of PE, tramadol's inhibition of serotonin reuptake increases serotonin availability in synaptic clefts, especially in brain areas associated with sexual reflexes and emotional regulation. This results in delayed transmission of ejaculatory signals and prolongation of latency time.Tramadol also affects noradrenergic pathways, which may further contribute to modulation of sympathetic activity involved in the ejaculatory process. Together, these neurochemical actions make tramadol a potential off-label option for men who do not respond to standard therapies like SSRIs or topical anesthetics [34]

David Bar-Or and colleagues conducted a randomized, double-blind, placebo-controlled multicenter study to evaluate the effectiveness of orally disintegrating tramadol (ODT) in men with lifelong PE. A total of 604 healthy men aged 18–65 years, all meeting DSM-IV-TR diagnostic criteria for lifelong PE and involved in stable, monogamous heterosexual relationships for at least six months, were enrolled. Participants were randomized into three groups: placebo (n = 200), 62 mg tramadol ODT (n = 206), and 89 mg tramadol ODT (n = 198). The study assessed changes in median IELT and improvements across four dimensions of the Premature Ejaculation Profile (PEP). Statistical analyses included Wilcoxon rank-sum tests, ANOVA, and chi-square tests to compare outcomes between groups. Both doses of tramadol significantly increased median IELT compared to placebo: placebo resulted in an increase of

0.6 minutes (1.6-fold), 62 mg tramadol led to an increase of 1.2 minutes (2.4-fold), and 89 mg tramadol extended IELT by 1.5 minutes (2.5-fold) ($p < 0.001$ for all comparisons). Furthermore, significant improvements in all PEP domains were observed in both tramadol groups compared to placebo ($p < 0.05$). ODT was well tolerated, with low rates of treatment discontinuation: 0% in the placebo group, 1.0% in the 62 mg group, and 1.6% in the 89 mg group. However, a limitation of the study was the inclusion of patients with IELT values up to 120 seconds, which may influence the generalizability of the findings to those with more severe forms of PE.[35]

A clinical investigation by Amil H. Khan in Gorakhpur, India, explored the therapeutic potential of tramadol in managing PE among 60 heterosexual, sexually active men who had been in stable relationships for a minimum of three months. All participants were free of additional sexual dysfunctions, including erectile issues. Diagnostic and outcome measures included IELT, DSM-IV-TR criteria, and the Premature Ejaculation Diagnostic Tool, with IELT recorded using a stopwatch operated by the sexual partner. Subjects were randomly assigned into two equal groups. Group A was treated with 100 mg of tramadol daily for four weeks, followed by an as-needed regimen (taken 2 or 8 hours before intercourse) for another four weeks. Group B received an identical placebo under the same schedule. At baseline, IELT was approximately 59 seconds for both groups, and the frequency of intercourse averaged around 2.2 times per week. Following the intervention, Group A experienced notable improvements: IELT rose to 202.5 seconds with daily dosing and 238.2 seconds with on-demand use. Corresponding increases in coital frequency were recorded at 4.32 and 4.86 times per week. The placebo group, however, showed only slight increases, with IELT reaching roughly 95–97 seconds and intercourse frequency rising to about 3.2 times per week. These findings indicate that both scheduled and on-demand tramadol administration can significantly enhance ejaculatory control and sexual activity compared to placebo.[36]

In a 28-week clinical study conducted by Bayoumy I. Eassa in Egypt, the effectiveness of tramadol in treating lifelong PE was evaluated in 300 heterosexual men aged 25–50 years. The first 4 weeks of the study involved placebo administration (starch tablet), followed by 24 weeks of tramadol treatment at varying doses. Patients were randomly assigned to three groups (n=100 each): Group A received 25 mg, Group B 50 mg, and Group C 100 mg of tramadol hydrochloride daily. Key exclusion criteria included secondary (acquired) PE, sexual dysfunction, medical or psychiatric conditions, substance use, and use of drugs affecting sexual performance. Ejaculation control, patient satisfaction, and side effects were assessed throughout the study. The primary outcome was IELT, with pre- and post-treatment comparisons analyzed using paired t-tests (significance set at $p<0.05$). Baseline IELT was approximately 2.8–3.0

minutes across all groups. After 24 weeks of tramadol therapy, IELT increased significantly: Group A (25 mg): 13.17 ± 1.83 minutes, Group B (50 mg): 23.43 ± 1.78 minutes, Group C (100 mg): 36.49 ± 3.25 minutes. The results demonstrated a dose-dependent improvement in IELT. All tramadol-treated groups reported greater control over ejaculation and high satisfaction with the therapy, and the drug was generally well tolerated.[37]All three studies consistently showed that tramadol significantly prolonged IELT and improved sexual satisfaction, [35, 36, 37],however can cause a range of side effects and may lead to dependence, especially with long-term or inappropriate use. Should be administered according to a doctor's recommendations, and patients should be monitored for any signs of misuse or dependence[33]
These studies require larger sample sizes, the inclusion of control groups, and long-term follow-up to assess treatment outcomes, particularly regarding the risk of dependence.

Levosulpiride

Levosulpiride is a selective dopamine D_2 receptor antagonist that has been investigated for its potential in treating PE. Dopamine plays a significant role in sexual function, particularly in facilitating sexual arousal and reducing the ejaculatory threshold. By antagonizing D_2 receptors, levosulpiride may inhibit dopaminergic activity, potentially delaying ejaculation.
A prospective, randomized, open-label study conducted by Bathla et al. compared the efficacy of levosulpiride and paroxetine in treating PE. The study included 36 male participants diagnosed with PE according to DSM-5 , who were randomly assigned to receive either 25 mg of levosulpiride or 12,5 mg of paroxetine once daily for 8 weeks. The efficacy was assessed using the Index of Premature Ejaculation (IPE) scores, which encompass parameters such as ejaculation control, sexual satisfaction, and distress. Statistical analysis using repeated measures MANOVA revealed significant improvements in the IPE scores for both treatment groups over the study period. Levosulpiride demonstrated a significant increase in ejaculation control from Visit 1 (baseline) to Visit 3 (week 8), with a mean difference of 1.944 (SE = 0.707, $p = 0.014$). Sexual satisfaction also improved significantly, with a mean difference of 1.611 (SE = 0.451, $p = 0.002$) at Visit 3. Distress levels decreased significantly, with a mean difference of −1.333 (SE = 0.229, $p < 0.0001$) at Visit 3. The total IPE score showed a significant improvement of 2.222 (SE = 1.031, $p = 0.046$) at Visit 3. These findings suggest levosulpiride is effective in improving PE symptoms, it shows slightly superior efficacy in enhancing ejaculation control and sexual satisfaction. [38]
A systematic review and meta-analysis by Arshad et al. evaluated the efficacy of levosulpiride

in treating PE. The analysis included four randomized controlled trials with a total of 203 participants. The findings indicated that patients treated with levosulpiride had significantly higher odds of improving IELT compared to those receiving a placebo. Specifically, the odds ratio (OR) for IELT improvement was 100.81 (95% confidence interval [CI]: 13.12–774.90), with no observed heterogeneity ($I^2 = 0\%$). Furthermore, the odds of achieving an IELT greater than 5 minutes were significantly higher in the levosulpiride group (OR: 38.88; 95% CI: 5.12–295.29), as were the odds for an IELT between 1 and 5 minutes (OR: 32.84; 95% CI: 4.15–259.75).These results suggest that levosulpiride may be an effective off-label option for managing PE, particularly in patients who are sensitive to the side effects of SSRIs. However, the limited number of studies and potential biases highlight the need for further research to confirm these findings and establish standardized treatment protocols.[39]

Clomipramine

Clomipramine, a tricyclic antidepressant (TCA), is primarily used in the treatment of mood disorders, such as depression and obsessive-compulsive disorder (OCD). However, it has also shown promise in the management of PE. Clomipramine works by inhibiting the reuptake of serotonin (5-HT) and norepinephrine (NE) in the brain, thereby increasing their availability in the synaptic cleft. The enhanced serotonergic transmission is thought to be central to its therapeutic effects on premature ejaculation. Serotonin plays a key role in the regulation of sexual behavior, including ejaculation. An increased level of serotonin in the brain can delay the ejaculatory reflex, which is beneficial for men experiencing premature ejaculation. Furthermore, clomipramine has mild anticholinergic effects and affects the dopaminergic system. These effects are less well-understood but may contribute to its overall impact on sexual function. The inhibition of norepinephrine reuptake may also play a role in reducing anxiety and improving sexual performance, which could be particularly useful in men whose PE is exacerbated by performance anxiety.[40]

In a multicenter, randomized, double-blind phase III study conducted by Choi et al., the efficacy of 15 mg clomipramine administered on-demand before intercourse was evaluated. The study included 159 patients across five centers in Korea- placebo group of 53 men and intervention group of 106 men. After 12 weeks of treatment, a significant increase in IELT was observed in the clomipramine group compared to placebo (mean IELT: 4.40 ± 5.29 min vs. 2.68 ± 2.03 min; $p < 0.05$). Additionally, there was a significant improvement in the PEDT score ($p < 0.001$),

and adverse effects such as nausea (15.7%) and dizziness (4.9%) were mild to moderate in severity.[41] In another study-a randomized, double-blind, placebo-controlled by Kim et al. assessed the efficacy and tolerability of two doses of clomipramine (15 mg and 30 mg) in 101 men with PE. The medication was taken orally 2–6 hours before intercourse over a period of 4 weeks. Both doses significantly increased IELT compared to placebo; however, the higher dose (30 mg) was associated with a higher incidence of side effects (57.6%) compared to the 15 mg dose (32.4%). The most common adverse effects were gastrointestinal symptoms and mild psychiatric disturbances. Based on these results, the authors concluded that the 15 mg dose offered a more favorable benefit-to-risk profile.[42] Shavakhabov et al. conducted a study using an intranasal form of clomipramine. In this study, 54 patients received a nasal spray for 8 weeks: group A with 5 mg of clomipramine hydrochloride, applied one hour before intercourse and group B received a placebo spray. The results showed a significant increase in IELT (in group A from 28.3 ± 2.3 seconds to 82.6 ± 4.2 seconds and in group B from 30.8+1.9sec. to 43.6seconds), as well as an improvement in CIPE scale scores (in A group from 28.9 ± 3.6 to 40.3 ± 8.1 points, in group B from 30.1+4.1 points to 32.4+6.1 points) . Adverse effects were minimal-only two patients (3.7%) reported mild nasal congestion.[43]

These studies are hindered by constraints such as limited participant numbers, brief study periods, and insufficient post-treatment monitoring. Moreover, inconsistencies in reporting adverse effects and non-uniform study protocols emphasize the necessity for more comprehensive, rigorously designed clinical trials.

α_1- adrenoreceptor antagonists

α_1-adrenoreceptor antagonists (α_1-blockers), such as silodosin, tamsulosin, alfuzosin, terazosin, or doxazosin, are primarily used to treat lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). These medications exert their effects by selectively blocking α_1A-adrenergic receptors, which are predominantly located in the smooth muscles of the bladder neck, prostate, seminal vesicles, and vas deferens. By inhibiting these receptors, α_1-blockers reduce smooth muscle contractions, leading to improved urinary flow. Interestingly, this mechanism also impacts ejaculatory function. The contraction of smooth muscles in the vas deferens and seminal vesicles is essential for the emission phase of ejaculation. By relaxing these muscles, α_1-blockers can disrupt the normal ejaculatory process, leading to conditions such as anejaculation or reduced semen volume. While these effects are often considered side effects in the context of BPH treatment, they have prompted research into the potential

therapeutic use of α_1-blockers for PE. By delaying the emission phase, these medications may help prolong the IELT, offering a potential treatment avenue for men with PE.[44]

Akin et al. evaluated the effects of various α-blockers on PE according to the DSM-IV-TR. In a study involving 108 men, who were randomly assigned to five treatment groups: silodosin, tamsulosin, alfuzosin, terazosin, or doxazosin for 2 weeks. Among these, silodosin at a dose of 4 mg (group 1) yielded the most significant improvement, with IELT increasing from 18.8 ± 12.9 seconds to 151 ± 53.9 seconds ($p < 0.001$). While the other α-blockers also extended IELT, the improvements were comparatively smaller. Significant post-treatment gains were also observed in Premature Ejaculation Profile (PEP) scores and Quality of Life (QoL) assessments across all groups, with the silodosin group showing the most pronounced changes- PEP scores decreased from 12.4 ± 3.3 to 6.8 ± 2.1 and QoL scores improved from 3.7 ± 0.7 to 2.1 ± 0.8 ($p < 0.001$). A total of 85.7% of patients in the silodosin group reported symptom relief. Reported side effects were generally mild, including dry ejaculation and light dizziness.[45] The study by Hodeeb et al. included 160 patients in a randomized, double-blind, placebo-controlled trial. Men treated with 4 mg silodosin experienced a significant increase in IELT—from 248.4 ± 83.7 seconds to 559.3 ± 159.9 seconds ($p < 0.001$). At the same time, PEP scores improved, indicating better ejaculatory control and increased sexual satisfaction. Reduced ejaculate volume was submitted in 13,75% of patients, which resolved after discontinuation of the medication.[46] Additionally, in a Japanese pilot study by Sato et al., the off-label use of 4 mg silodosin administered on demand (2 hours before intercourse) was evaluated in eight men with PE. The mean IELT significantly increased from 3.4 minutes to 10.1 minutes ($p = 0.003$). All participants reported improvement on the Clinical Global Impression of Change (CGIC) scale, and PEP scores showed significant improvements in ejaculatory control and overall sexual satisfaction. Although 25% of patients experienced anejaculation and 87.5% reported some degree of orgasmic discomfort, these effects were not considered problematic. No systemic adverse effects were observed.[47]

All three studies indicate that silodosin may be an effective and well-tolerated pharmacological alternative for the treatment of PE. The drug significantly prolongs ejaculatory latency, improves ejaculatory control and sexual quality of life, and is associated with a relatively mild side effect profile.

DISCUSSION

According to scientific society guidelines, the first-line treatments for PE are selective serotonin reuptake inhibitors SSRIs and topical anesthetics [2, 16]. While these therapies are generally effective, they can be associated with undesirable side effects and show variable efficacy among patients [18, 19]. Furthermore, current pharmacological options for PE are used off-label, as no drugs have been specifically developed and approved for this condition.[20]This highlights the need to explore alternative treatment strategies, particularly for individuals who do not respond adequately to first-line therapies[21, 28]. Understanding the precise etiology of PE could facilitate the development of more targeted and causal treatments. However, the lack of a standardized and universally accepted definition of PE complicates both diagnosis and management.[1, 14, 15, 27, 28] Moreover, systemic organ-related disorders, such as diabetes, depression, and cardiovascular disease, increase the risk of, or may contribute to, the development of ejaculatory disorders.[15, 16, 48, 49, 50]. Recent studies have provided evidence for the potential efficacy of alternative pharmacological interventions for PE. Nonetheless, it is important to consider that differences in study populations, geographic settings, and research methodologies may impact the consistency and comparability of the findings, limiting the generalizability of conclusions regarding these emerging treatments.

PDE5Is primarily used to treat erectile dysfunction, have shown encouraging efficacy in managing PE. These agents function by enhancing nitric oxide-mediated cGMP accumulation, which facilitates prolonged smooth muscle relaxation and blood flow, thereby potentially delaying ejaculation.[29] In a meta-analysis by Zhang et al., PDE5Is significantly improved IELT and sexual satisfaction scores compared to placebo, although a higher frequency of side effects such as headache, flushing, and nasal congestion was observed [30]. Additional clinical evidence supports these findings. In a prospective study by Wei-Fu Wang et al., sildenafil (50 mg as needed) demonstrated significant improvements in IELT, PE severity, and intercourse satisfaction, outperforming both daily paroxetine and the squeeze technique. Patients treated with sildenafil also had the lowest discontinuation rate and the highest willingness to continue therapy (86.7%) [31]. Similarly, M.J. Mathers et al. found that vardenafil significantly increased IELT and reduced PE severity in men who had not responded to behavioral therapy alone. These results were comparable to those achieved with sertraline, though vardenafil showed a greater

increase in latency time [32]Studies suggest that combining PDE5is combined with an SSRI compared with an SSRI alone may enhance therapeutic effects, especially in men with both PE and mild erectile dysfunction. This strategy can lead to longer IELT, better ejaculatory control, and fewer side effects due to lower individual doses. These studies consistently demonstrate that PDE5 inhibitors are effective in improving ejaculatory latency and sexual satisfaction in men with PE.[30] Notable weaknesses in studies methodology such as small sample sizes, short follow-up durations, and lack of placebo controls, no blinding undermine the reliability and generalizability of the findings. Additionally, treatment protocols, and definitions of PE complicates cross-study comparisons and highlights the need for more standardized, rigorously controlled trials.

Tramadol, a centrally acting analgesic with dual action as a μ-opioid receptor agonist and serotonin-norepinephrine reuptake inhibitor, has emerged as a potential off-label treatment for PE. Its ability to increase synaptic serotonin levels appears to delay the ejaculatory reflex, making it beneficial for patients unresponsive to first-line therapies.[34] Clinical trials, including a large multicenter study by Bar-Or et al., demonstrated that orally disintegrating tramadol significantly increased IELT and improved patient-reported outcomes with good tolerability [35]. Similar findings were confirmed in trials by Khan et al. and Eassa et al., which showed dose-dependent improvements in IELT and sexual satisfaction with both daily and on-demand use of tramadol [36, 37]. Despite these promising results, tramadol carries a risk of side effects and potential dependence, particularly with long-term use. Tramadol administration should be closely monitored and reserved for selected patients who do not respond to conventional treatments [37] Therefore, more studies requires investigation. Levosulpiride, a selective dopamine D_2 receptor antagonist by modulating dopaminergic pathways involved in sexual arousal and the ejaculatory reflex. A randomized, open-label study by Bathla et al. demonstrated that levosulpiride significantly improved ejaculatory control, sexual satisfaction, and distress scores in men with lifelong PE, with slightly better efficacy than paroxetine [38]. Additionally, a meta-analysis by Arshad et al. further supported levosulpiride's effectiveness, showing a markedly higher likelihood of IELT improvement compared to placebo, with favorable odds ratios for both modest and substantial latency gains [39].The studies's open-label design, small group of patients, possible biases and no placebo group limit the generalizability of these results. Further studies with double-blind, placebo-controlled designs are recommended to confirm these findings.

Clomipramine due to its ability to enhance serotonergic and noradrenergic neurotransmission, mechanisms thought to delay the ejaculatory reflex.[40] Several clinical trials have confirmed

its effectiveness. The study by Choi et al. showed that on-demand 15 mg clomipramine significantly increased IELT and improved PEDT scores compared to placebo, with generally mild side effects [41]. Kim et al. further supported these findings, reporting that both 15 mg and 30 mg oral doses were effective, although the higher dose was associated with a greater incidence of adverse effects, suggesting the 15 mg dose had a more favorable safety profile [42]. Additionally, Shavakhabov et al. demonstrated that intranasal clomipramine also significantly prolonged IELT and improved satisfaction scores, with minimal adverse events [43]. Short period, limited number of observations and no lifelong evidence in these studies suggest that further large-scale, placebo-controlled trials are required to more clearly determine the long-term efficacy and tolerability of clomipramine in the treatment of PE. Nonetheless, existing evidence supports both oral and intranasal clomipramine as effective pharmacologic options, particularly the 15 mg oral dose, which offers a promising balance between clinical benefit and tolerability.

α_1-adrenoreceptor antagonists, particularly silodosin, have emerged as promising pharmacologic options for PE, owing to their ability to relax smooth muscles involved in the emission phase of ejaculation. This mechanism, while initially considered a side effect in BPH treatment, has been repurposed to therapeutically delay ejaculation.[44] Clinical studies confirm the potential of silodosin in improving ejaculatory latency and patient-reported outcomes. For instance, Akin et al. found that silodosin led to the most substantial improvement in IELT and quality-of-life metrics among five α-blockers tested, with a favorable safety profile despite the absence of a placebo group [45]. Hodeeb et al. corroborated these findings in a randomized, double-blind, placebo-controlled trial, demonstrating a significant increase in IELT and improved satisfaction with few adverse effects [46]. Similarly, Sato et al. observed notable IELT gains using on-demand silodosin[47]. However these findings support the need for larger, controlled studies to assess long-term safety and efficacy. The relatively small and unbalanced group sizes reduce the statistical power and may limit the generalizability of the findings.

SUMMARY/CONCLUSIONS

Given the multifactorial nature of PE, which involves both psychological and physiological factors, treatment should be tailored to the individual. Patient preference, comorbid conditions, and risk of side effects must be taken into account when selecting the most appropriate therapy.

While selective SSRIs and topical anesthetics are considered first-line treatments for PE, their variable efficacy and potential side effects highlight the need to explore alternative pharmacological strategies. Promising results have emerged for several agents, including PDE5Is, α_1-adrenoreceptor antagonists, tramadol, levosulpiride, and clomipramine, which have shown potential in improving intravaginal ejaculatory latency and sexual satisfaction.

However, despite encouraging clinical outcomes, many of the studies evaluating these alternatives suffer from limitations such as small sample sizes, short treatment durations, and inconsistent methodologies. These weaknesses limit the generalizability of the findings and emphasize the need for more comprehensive and standardized clinical trials.

To move the field forward, future research should focus on developing universally accepted definitions and outcome measures for PE, which would enhance comparability across studies. Moreover, a deeper understanding of the underlying pathophysiological mechanisms of PE is essential for identifying new, targeted therapeutic options. While alternative pharmacologic treatments hold promise, rigorous and well-designed studies are necessary to confirm their safety, efficacy, and appropriate role in clinical practice.

Disclosures

Author`s contribution:

Conceptualization: PB; Methodology: MS; Software: WF; Check: IK, JW, PK; Formal analysis: DK; Investigation: GP; Resources: PF; Data curation: KD; Writing -rough preparation: MS; Writing -review and editing: PB; Visualization: WF; Supervision: PB; Project administration: DK; Receiving funding:GP

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