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Mini review

Treatment of premature ejaculation☆

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ABSTRACT

Premature ejaculation (PE) is the most common male sexual disorder, and it may have a profound negative impact on a man and his partner's lives. Different organizations and societies have no consensus on the definition and classifications of PE. However, most organizations and societies include in their definitions the intravaginal ejaculation latency time (IELT), the control of ejaculation, and the distress or impact of interpersonal difficulties. Evaluation procedures have been standardized in clinical studies by the development of an objective measurement of IELT (using a stopwatch) and by the introduction of patient-reported outcome (PRO) questionnaires on ejaculation control and sexual satisfaction. The identification of four different patterns of PE—lifelong, acquired, normal variant, and premature-like ejaculatory dysfunction—is critical because of different underlying pathogeneses and consequently different management approaches. The optimal treatment for PE should be individualized, based on a patient's symptoms, expectations, and underlying variant causes. Most lifelong PE patients need pharmacotherapy (possibly in combination with psychosexual counseling) as a first-line treatment because of the underlying neurobiological etiology and the impact of PE on the couple's relationship. The management of acquired PE is etiologically specific and may include pharmacotherapy for erectile function management in men with comorbid erectile dysfunction (ED). Men with natural variable PE complain of early ejaculation in situational or coincidental conditions; the ejaculation is inconsistent and occurs irregularly. Psychoeducation and reassurance are indicated for men with this type of PE. Psychotherapy or sex counseling is the first choice of treatment for men with premature-like ejaculatory dysfunction. All pharmacotherapies such as long-term selective serotonin reuptake inhibitors (SSRIs) or on-demand topical anesthetics are off-label indications, The benefits of pharmacotherapy toward improving ejaculation times should be weighed against their safety profiles. The development of the short-acting selective serotonin reuptake inhibitor (SSRI) dapoxetine hydrochloride (30 mg and 60 mg) for oral on-demand use opened a new era of PE treatment. Other potential pharmacotherapies such as tramadol, lidocaine/prilocaine spray, and phosphodiesterase inhibitors are still under development. Their safety and efficacy profiles should be further evaluated and supported by additional clinical studies.

1. Introduction

Premature ejaculation (PE) and erectile dysfunction (ED) are two common male sexual disorders encountered in daily clinical practice. Unlike ED, the etiology and exact pathogenesis of PE are not well established. There are several different clinical manifestations of PE, ranging from the complaint of a normal phenomenon to a sexual dysfunction syndrome.[1] Therefore, management should be individualized for each person.[2] At the time of preparing this manuscript, there was no authority-approved medicine in Taiwan for treating PE. Therefore, this review focuses on contemporary definitions and classifications of PE, followed by a discussion of the evolution of its treatment and the current treatment recommendations of different guidelines. Some potential management modalities under evaluation by clinical studies are finally discussed.

2. Definition and classification of PE

Premature ejaculation is a self-reported complaint that affects 20–30% of men. This subjective impression may differ from time to time, depending on the patient's psychological and physical condition. The actual prevalence of PE may have a large variation from study to study because of different evaluation modalities and a lack of a consensus on its definition. The stopwatch-measured intravaginal ejaculation latent time (IELT) seems to be one of the most

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objective parameters used to define PE, but loss of control during ejaculation with consequent interpersonal difficulties and distress is also an important criterion for diagnosis.[3–5]

2.1. American Urology Association guidelines and definition

The American Urology Association defines PE as ejaculation that occurs sooner than desired—before or shortly after penetration—causing distress to one or both partners. This guideline unfortunately does not define a cutoff parameter for diagnosing PE and is in accordance with authority-based medicine instead of evidence-based medicine.[6]

2.2. International Society for Sexual Medicine definition

In 2007, the International Society for Sexual Medicine (ISSM) proposed an evidence-based definition of lifelong PE as "a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, 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".[7] This definition only defines lifelong PE and is limited to men engaging in vaginal intercourse. However, because of insufficient evidence-based data to propose a new definition, the ISSM did not define another variant type of PE—acquired PE (i.e., secondary PE, which was proposed in 1943 by Schapiro).[8,9]

2.3. International Classification of Diseases-10 definition

According to the 10th edition of the International Classification of Diseases (ICD-10), which is issued by the World Health Organization, PE is defined as "the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible". However using the criterion of "within 15 seconds of the beginning of intercourse" may underestimate the number of patients in the PE population. In a retrospective study, the IELT occurred within 15 seconds in only 40% of lifelong PE patients.[1]

2.4. Diagnostic and Statistical Manual of Mental Disorders IV definition

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV), which is issued by the American Psychiatric Association, defines premature ejaculation as a "persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity". The definition from the DSM-IV-text revision (DSM-IV-TR) is also based on expert experience and is not supported by randomized clinical studies. However, the newer version of the manual, DMS-V, adopts the criterion of latent time and explains that for PE the "early ejaculation symptom must have been present for at least 6 months and be experienced on all or almost all (approximately 75%) occasions of sexual activity: Persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately one minute of beginning of sexual activity and before the person wishes it".[10]

Among the different organizations and societies, there is a lack of consensus on these definitions and classifications of PE. However, most organizations and societies include in their definitions the concept of latency time to ejaculation, the control of ejaculation, and the distress or impact on interpersonal difficulties. The ISSM also recently adopted a new classification that Waldinger proposed in 2007—in the updated guidelines, the new classification included two other variant types: "natural variable PE" and "premature-like ejaculatory dysfunction".[11] The presence of four different types of PE (i.e., lifelong, acquired, natural variable, and premature-like ejaculatory dysfunction) suggests different underlying pathogeneses and suggests that the treatment approach to these different types of PE should be individualized on the basis of symptoms and expectations.

3. Etiology and risk factors

The exact etiology of PE is still unknown, but implicated in its pathogenesis are several possible risk factors that include a diverse range of biological and psychological factors. Biological factors such as hypersensitivity of the penile glans, disturbance of central serotonin neurotransmission, hyperthyroidism, and local irritation due to prostatitis are linked to the pathogenesis of lifelong and acquired PE.[12–16] Waldinger et al[12] proposed that PE may result from 5-hydroxytryptamine (5-HT) receptor dysfunction. Hyposensitivity of the 5-HT2C receptor and hypersensitivity of the 5-HT1A receptor are hypothesized as major neurobiological factors in PE.[12]

The role of serotonin disturbance in neurobiological ejaculation control can explain only part of the pathophysiology of lifelong PE and acquired PE. The existence of men classified as having the natural variable PE subtype or the premature-like ejaculatory dysfunction subtype may moreover indicate different underlying pathogeneses and suggest that individualized approaches should be used.[4,17] Several psychological factors (e.g., anxiety, an early unpleasant sexual experience or abuse, and adverse familial relationships) may influence sexual dysfunction, including PE.[18,19] Men with PE also reportedly have decreased sexual self-confidence, difficulty in establishing relationships, and distress at not satisfying their partners.[20]

Men with natural variable PE experience early ejaculation in situational or coincidental conditions; the problem may be inconsistent and occur irregularly. They usually experience diminished control of ejaculation with either a short or normal ejaculation time. Men with premature-like ejaculatory dysfunction are preoccupied with an imagined early ejaculation or lack of control of ejaculation, but the actual IELT is in the normal range or even of longer duration.[17]

4. Management of PE

Differences in the underlying pathophysiology and the etiology of the four different types of PE determine the choice of treatment. The management approach should be individualized according to a patient's condition and expectations. The partner's attitude about this syndrome and the intersexual relationship between a couple should also be considered in the management plan.[21] The management of acquired PE is etiologically specific and may include pharmacotherapy for managing erectile function in men with comorbid ED. Behavioral therapy is indicated when psychogenic or relationship factors are present and are often best combined with PE pharmacotherapy in an integrated treatment program. Men with age-related penile hypoanesthesia should be educated, reassured, and instructed in revised sexual techniques that maximize arousal. Masturbation before the anticipation of sexual intercourse is another technique used by many young men.[22]

Most lifelong PE patients need to be treated by pharmacotherapy. They have limited responses to psychological counseling

and behavioral therapy, probably resulting from the neurobiological etiology. Treatment of acquired PE should be individualized (based on the underlying causes) and combining pharmacotherapy with psychological counseling or behavioral therapy has a better response than monotherapy.[9] Psychoeducation and reassurance are indicated for men with the natural variable PE subtype, which may not be a disease condition but only a clinical complaint. Finally, psychotherapy or sex counseling is usually the first choice of treatment for men with premature-like ejaculatory dysfunction.[4]

4.1. Psychological counseling and behavioral approaches

Psychological therapy has been used for many years; however, weak and inconsistent evidence remains regarding the effectiveness of psychological interventions for treating PE.[23] Introduction of the "stop-start" method by Semans in 1956 and the "squeeze technique" proposed by Masters and Johnson in 1970 afforded only short-term success for ejaculation control; the long-term effectiveness of these techniques is still lacking.[24,25] Other clinical psychological interventions have never been verified or duplicated in well-designed clinical studies, and evidence of their effectiveness is weak and inconsistent.[26] However, psychological counseling may help the PE patient and his partner improve their overall relationship, and the effect of psychological counseling or behavioral therapy may be augmented by pharmacotherapy.[21]

Acupuncture has also recently been proposed to treat PE in 90 men.[27] In this randomized study, the IELT was used as the primary endpoint to compare the efficacy of acupuncture to the efficacy of 20 mg paroxetine daily. Sham acupuncture was used as the placebo control. Paroxetine and acupuncture both had better IELT responses, compared to the placebo arm. Acupuncture treatment seemed to be less effective than paroxetine treatment on the mean improvement in the ILET (65.7 seconds vs. 82.7 seconds, $p = 0.001$), but the ejaculation-delaying effect of acupuncture treatment was better than that of the placebo arm (65.7 seconds vs. 33.1 seconds, $p = 0.001$). Long-term effectiveness data unfortunately are not available to support acupuncture as a standard treatment for PE management.[27]

4.2. Pharmacological treatments

Many psychopharmacological compounds and drugs have been used to prolong or delay the ejaculation time; however, these treatments have had limited success. Phenoxybenzamine was the first alpha blocker used to treat PE because of its weak partial agonist and partial antagonist properties against the serotonin 5-HT2A receptor. Inhibition of the contraction of the seminal vesicles and vas deferens resulting from the blockade of alpha-1A receptors may further contribute to impaired ejaculation. An early case study was promising, but no randomized, placebo-controlled studies have been performed to confirm the safety and efficacy profiles of phenoxybenzamine.[28,29] Development of selective alpha-1A antagonists have further confirmed the influence of the alpha-1A receptor on ejaculation function. High-dose tamsulosin (0.8 mg) and silodosin (8 mg) reduce the semen amount or result in secondary anejaculation; however, the use of a selective alpha-1A antagonist for PE treatment is questioned because seminal emission impairment by inhibition of vas deferens or seminal vesicle contractility by alpha-1A antagonist was not able to delay ejaculation in one animal study.[30]

Other centrally acting agents such as the dopamine antagonist thioridazine and the tricyclic antidepressant clomipramine are also helpful in delaying ejaculation. An early pilot study using clomipramine at 25 mg and 50 mg extended the average estimated time to ejaculation after vaginal penetration to 6.1 minutes and 8.4 minutes, respectively.[31] A double-blind and crossover study confirmed the efficacy of clomipramine in prolonging the ejaculation latency time and confirmed its potency over other SSRIs on vas deferens contractions.[32,33] However, the necessity of taking clomipramine 4–6 hours before intercourse and a lack of long-term safety data to support this use have limited its indication to treating obsessive and compulsive behaviors.

4.2.1. Serotonergic antidepressants

The ejaculatory adverse effects, including delayed ejaculation and secondary anejaculation, resulting from the use of SSRIs make these drugs potentially useful in managing PE.[34] In a survey published in 1997, approximately 58% of patients (192 women and 152 men) undergoing regular SSRI treatment had different kinds of sexual dysfunctions, which were detected via the direct questioning of their physicians.[35] Clomipramine, fluoxetine, paroxetine, and sertraline paradoxically seemed to be safe treatment options for PE patients who had previous psychological treatment.[36] In 2004, the American Urology Association recommended topical lidocaine-prilocaine cream and serotonergic antidepressants (which included paroxetine, sertraline, fluoxetine, and clomipramine) as the treatment of choice. However, none of the aforementioned drugs had authority-approved indications for PE treatment (i.e., off-label use). Clomipramine and SSRIs may both delay ejaculation, at the expense of the diminution of libido and a moderate decrease in penile rigidity.[37]

4.2.2. Topical medications

In 1943, the first report of using a topical anesthetic was published by Schapiro, who successfully used a 3% dibucaine (i.e., Nupercaine) solution to treat 33 PE patients.[8] Many commercial topical preparations are available, but they are only indicated for local analgesic purposes and not for PE treatment. Most of these products consist of a mixture of lidocaine and prilocaine in a cream, ointment, gel, or spray formulation and are designed for local anesthesia. Off-label use of these products for PE may cause glans numbness or may even cause ED at an excessive dose. The optimal formulation and therapeutic dosage for the purpose of PE treatment are not yet established. Safety concerns about systemic side effects, especially on cardiac rhythms, from lidocaine and the influence of transvaginal absorption on the female partner need further clarification by using well-designed clinical studies.

A novel aerosolized lidocaine-prilocaine (2.5%) spray, called PSD502, was recently developed to treat lifelong PE.[38] A phase III clinical study that enrolled 300 PE subjects and was conducted in European countries showed that using the topical spray 5 minutes before intercourse improved the mean IELT from 0.6 minutes to 6.3 minutes, which is much better than the placebo arm of 0.6–1.1 minutes. Based on ejaculation questionnaires, the PSD502 treatment arm also showed better scores on ejaculation control and satisfaction, compared to the placebo arm. Only 2.6% of subjects in the PSD502 arm developed local side effects such as genital erythema and ED, and 3.1% of female partners developed a sensation of vulvovaginal burning.[39]

Another topical preparation, called SS cream, consists of nine natural herb extracts. Its exact mechanism of action remains unclear. In a phase III, randomized, placebo-controlled study, 106 subjects with PE were enrolled. The study participants applied either 0.2 g of SS cream or a placebo cream over the glans penis 1 hour before intercourse. The mean IELT was prolonged from 1.37 ± 0.12 minutes to 2.45 ± 0.29 minutes in the placebo group and to 10.92 ± 0.95 minutes in the SS-cream group. There were no systemic side effects; however, 18.49% of subjects in the SS-cream arm developed mild local burning and mild pain.[40] The US Food and Drug Administration does not currently indicate the use of SS cream for PE treatment.

4.2.3. Tramadol

Tramadol is an effective analgesic that combines opioid receptor activation and reuptake inhibition of 5-hydroxytryptamine (5-HT) and noradrenaline. The mechanism of action of the nonopioid component of tramadol is mediated through alpha2-agonistic and serotoninergic activities by inhibiting the reuptake of noradrenaline and 5-HT. This feature and its short half-life (1.7 hours) and rapid absorption has made on-demand tramadol a potential treatment for PE. An early clinical trial confirmed that on-demand 50 mg tramadol and a placebo 2 hours before intercourse improved the mean IELT from 19 and 21 seconds, respectively, to approximately 243 seconds and 34 seconds, respectively ($p < 0.001$).[41] However, in another study involving 35 lifelong PE patients, 3 months of on-demand tramadol (50 mg) treatment did not show greater efficacy over daily paroxetine (20 mg) treatment.[42] Because of the lack of strong efficacy and safety evidence from large-scale clinical studies, the ISSM guidelines do not recommend the use of tramadol for treating PE.

4.2.4. Dapoxetine hydrochloride

Dapoxetine was the first oral pharmacologic agent designed to treat men with PE who were aged 18–64 years. Dapoxetine is a short-acting SSRI with a half-life of 60–80 minutes and a 95% clearance rate after 24 hours. Dapoxetine hydrochloride is rapidly absorbed orally. The time to a maximal plasma concentration is approximately 1–2 hours. The rapid absorption and clearance rate characteristics have made this novel SSRI suitable for on-demand use.[43] An early randomized, double-blind, placebo-controlled study proved that on-demand 30 mg or 60 mg dapoxetine use can extend the IELT by approximately 3 times the baseline IELT. After 12 weeks of treatment, PE patients also had more confidence in their ejaculation control with better overall satisfaction.[44]

The initial dose of dapoxetine is 30 mg, and the tablet should be swallowed along with a glass of water to avoid the bitter taste. The maximal dose of dapoxetine is 60 mg/day. This medication may be taken with or without food. The most common side effects associated with the on-demand use of 30 mg or 60 mg dapoxetine are nausea (11.0% and 22.2%, respectively), dizziness (5.8% and 10.9%), headache (5.6% and 8.8%), diarrhea (3.5% and 6.9%), somnolence (3.1% and 4.7%), fatigue (2.0% and 4.1%), insomnia (2.1% and 3.9%), and nasopharyngitis (3.2% and 2.9%). Most side effects however were transient, mild in their severity, and tolerable by patients.[45]

Orthostatic hypertension and syncope were noted during clinical studies and should be a major safety concern at the time of prescription. An orthostatic test is suggested initially before giving a prescription. To prevent the development of syncope, patients receiving dapoxetine are encouraged to avoid rapid position changes within 3 hours of dosing. Based on an integrated analysis of pooled safety data from clinical trials, the incidence of syncope during clinical studies was 0.19% of subjects receiving the first dose of dapoxetine; this was reduced to 0.08% for subsequent doses. Unlike existing data on SSRIs, the safety data of dapoxetine showed no evidence of mood changes, suicidality, or withdrawal syndrome after treatment.[45] In 2009, dapoxetine received market approval in several European countries (e.g., Sweden, Finland, Spain, Portugal, Germany, Austria, and Italy) and in New Zealand. However, the approval of dapoxetine hydrochloride for treating PE was still being processed in the United States and in Taiwan at the time this review was being prepared.

4.2.5. Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors (PDE5-Is) are indicated for patients with PE and comorbid ED. However, their use in PE patients without ED is not confirmed by clinical studies. In a randomized, placebo-controlled study, 157 lifelong PE patients with ED were enrolled for 8 weeks of treatment with sildenafil or with a placebo. After sildenafil treatment, the IELT was not prolonged (as expected), but the confidence, the perception of ejaculatory control, and overall sexual satisfaction were increased, along with reduced anxiety and a decreased refractory time to achieve a second erection after ejaculation.[46] Without more evidence of the role of nitric oxide in ejaculation, the use of PDE5-Is for PE treatment remains controversial.[47]

4.3. Surgical treatments

No evidence supports using surgical procedures to improve PE. However, several nonrandomized studies have shown some effects on prolonging the ejaculatory latency resulting from surgical procedures such as dorsal nerve neurotomy, frenulectomy for a short frenulum, and hyaluronic acid glans penis augmentation. The side effects of these surgical procedures such as permanent hypoanesthesia and sexual dysfunction should be considered and discussed with patients preoperatively. At present, there are no guidelines to recommend surgical treatment for PE management.[6,9,48,49] Before these surgical procedures can be recommended as part of the standard treatment, additional randomized clinical studies are needed to verify their long-term efficacy and safety profiles.

5. Conclusion

Premature ejaculation is the most common disease encountered in the practice of andrology. The existence of four different types of PE indicates that management approaches should also be individualized. Psychotherapy, sex counseling, and behavioral therapies may be helpful for men with normal variant PE. Men with premature-like ejaculatory dysfunction should receive psychoeducation and sex counseling. Men with lifelong PE should receive pharmacotherapy. The treatment of men with acquired PE should be individualized on the basis of the underlying etiology and a patient's expectations. Behavioral therapies have short-term efficacy, and the response can be augmented by pharmacotherapy. Dapoxetine hydrochloride on demand used 1–2 hours before intercourse was the first authority-approved pill in Europe. Its efficacy and safety were confirmed in clinical trials and in postmarket experience. Nausea and headaches are common side effects but are tolerable, transient, and mild in severity. No topical therapy has been approved for treating PE, but most guidelines recommend using its as an adjuvant tool for men with lifelong PE. However more information is needed on safety data and dosage administration. Regular SSRIs and on-demand tramadol as treatment for PE are off-label uses of these drugs, and their benefits should be weighed against their long-term safety profiles.

Conflicts of interest statement

The authors declare that they have no financial or any conflicts of interest related to the subject matter or materials discussed in the manuscript.

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