Review Article

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Progresses in pharmaceutical and surgical management of premature ejaculation

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Abstract

Objective: Premature ejaculation (PE) is regarded as one of the most common male sexual dysfunctions. This review introduced several pharmaceutical and surgical methods for the management of PE. The definition, etiology, behavioral, and psychological therapy of PE were also discussed.

Data sources: "Premature," "ejaculation," or "sexual dysfuction" were used as the medical subject headings (MeSH) to obtain relevant articles before June 2019 on Pubmed, Google Scholar and CNKI. Most articles used were written in English and several Chinese articles were also cited.

Study selection: Full-text articles of retrospective/prospective/randomized controlled trials were analyzed. Animal experiments and letters were excluded.

Results: There are four PE sub-types: lifelong PE, acquired PE, natural variable PE, and subjective PE. Behavioral therapy, psychotherapy, medication, topical anesthetics, and surgery are currently used for the treatment of PE. However, all the above treatments have limitations. Therefore, novel ways should be investigated to more efficiently control PE.

Conclusions: The pharmaceutical therapy that is currently being used in clinical practice for the management of PE is still the main choice globally due to its good efficacy. Surgery may be a choice for patients who are resistant to medication. However, it should be performed cautiously.

Keywords: Premature ejaculation; Selective serotonin reuptake inhibitors; Penile dorsal nerve neurotomy

Introduction

Premature ejaculation (PE) is one of the most common types of ejaculatory dysfunction, affecting approximately 20% to 30% of the male population.[1] PE is also associated with distress, anxiety, and having a negative relationship with sexual partners.[2,3] Currently, several advancements have been made for the pharmaceutical and surgical management of PE. This review briefly introduces the definition, etiology, behavioral, and psychological therapy of PE. The pharmaceutical and surgical methods that are currently being used in clinical practice for the management of PE were emphasized.

Definitions and classification of PE

The definition of PE is controversial. The American Psychiatric Association has defined PE as a "persistent or recurrent ejaculation with minimal sexual stimulation prior or shortly after penetration and before the person wishes it."[4] The World Health Organization defined PE as "the inability to delay ejaculation sufficiently to enjoy lovemaking, which is demonstrated by either an occurrence of ejaculation before or shortly after the beginning of intercourse, or an ejaculation that occurs in the absence of a sufficient erection to make intercourse possible."[4] The American Urological Association has defined PE as "ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners."[5] These definitions were criticized because they are authority-based rather than evidence-based, and were conceptual and vague.[6] To develop a definition with a definite scientific criteria, the International Society for Sexual Medicine (ISSM) proposed that PE to be defined as "ejaculation that always or nearly always occurs prior to or within approximately 1 min of vaginal penetration from the first sexual experience (lifelong PE

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Table 1: Classification of premature ejaculation.

Items	LPE	APE	Natural variable PE	Premature-like ejaculatory dysfunction
Episodes	From first sexual encounters onwards	At any point in the man's lifetime (had normal ejaculation experience)	Randomly suffering from early ejaculations	At any point in the man's lifetime
Short time intervals between penetration and ejaculation	Yes	Yes	Yes	Yes
Lack of control over ejaculation	Yes	Yes	Yes	Yes
IELT	Short	Short	Normal	Normal/long
Etiology	Neurobiological or genetical problem	Due to urological dysfunctions, psychological factors, or thyroid dysfunction	Normal	Psychiatry disorder
Treatment	Medication, surgery, and psychotherapy	Medication and psychotherapy	Psychoeducation	Psychotherapy and reassurance
References		[7]	[8,10]	[9,10]

LPE: Lifelong premature ejaculation; APE: Acquired premature ejaculation; PE: Premature ejaculation; IELT: Intra-vaginal ejaculatory latency time.

[LPE]; also called primary PE), or a clinically significant and bothersome reduction in latency time, often to about 3 min or less (acquired PE [APE]; also called secondary PE), or 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]

It is now widely accepted that three factors should be considered for the definition of PE: (1) Short time interval between penetration and ejaculation; (2) Lack of control over ejaculation; (3) Distress felt in one or both partners.[7] An important index, the intra-vaginal ejaculatory latency time (IELT) was also proposed to better obtain an objective evaluation of PE.[7]

Although the definition proposed by ISSM was only suited for LPE and APE,[7] several other sub-types of PE have been described, such as natural variable PE[8]and premature-like ejaculatory dysfunction,[9,10] and can be differentiated by their corresponding IELT and etiology [Table 1].

Physiology of ejaculation

The physiology of ejaculation is complicated and obscure. Currently, a two-pathway model is used to explain the physiology of ejaculation. Ejaculation is subjected to both central and peripheral control. For the peripheral control of ejaculation, the pudendal sensory nerves input the sexual stimulating signal, and it is then transferred to the spinal network. After the signal is processed by the spinal network, the sensory information is converted into both a secretory and motor signal output. Somatic, sympathetic, and parasympathetic fibers are involved in signal transduction. The integration and coordination of somatic, sympathetic, and parasympathetic signals are sequentially relayed to the muscles and structures of the pelvis and perineum to facilitate ejaculation.[11] For the central control of ejaculation, the spinal ejaculatory reflex is mediated by the cerebral network. Additionally, the cerebral network controls the final output from all ejaculatory stimuli. Serotonin, dopamine, acetylcholine, adrenaline, neuropeptide, oxytocin, γ-aminobutyric acid and nitric oxide have all been implicated in the regulation of the ejaculatory reflex. The most studied neurotransmitter is 5-hydroxytryptamine (5-HT). Fourteen different 5-HT receptor sub-types have been identified and each of them has a different neuroanatomical location and function. Some sub-types (5-HT1a) reduce ejaculatory latency and other sub-types (5-HT1b, 5-HT2c) prolong ejaculatory latency.[12-14]

Based on ejaculatory physiology, two possible factors may be involved in PE. Penile hypersensitivity, which increases sexual signal input, and may be responsible for peripheral PE.[15] An imbalance of 5-HT synaptic concentration and receptor sensitivity may also disturb the central ejaculatory control and cause central PE[12] [Figure 1].

The "central and peripheral control" model is used to explain the physiology of PE. For peripheral control, the sexual stimulating signal is sent to the pudendal sensory nerves and is transferred and processed in the spinal network. Subsequently, the signal is converted into both a secretory and motor signal output. Lastly, through the integration and co-ordination of the efferent nerve signals, the structures of the pelvis and perineum are triggered to facilitate ejaculation. Penile hypersensitivity, increased sexual signal input, may be responsible for peripheral PE. For this reason, topical anesthetics, α-blockers, and surgical interventions may be used to decrease penile hypersensitivity. For central control, the cerebral network

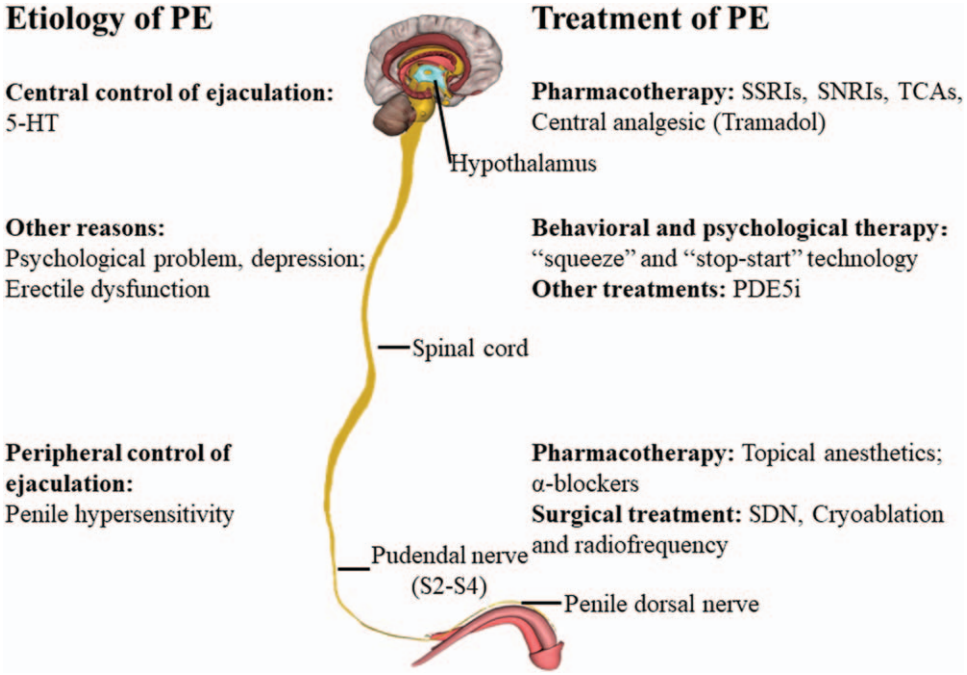

Figure 1: The etiology and treatment of PE. 5-HT: 5-Hydroxytryptamine; PDE5i: Phosphodiesterase type 5 inhibitors; PE: Premature ejaculation; SDN: Selective penile dorsal nerve neurotomy; SNRIs: Serotonin-norepinephrine reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors; TCAs: Tricyclic anti-depressants.

controls the final output from all ejaculatory stimuli. Many neurotransmitters have been implicated in the regulation of the ejaculation process. 5-HT is the most studied. The imbalance of 5-HT synaptic concentration and receptor sensitivity may cause disturbances to the central ejaculatory control and induce central PE. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressant (TCAs), and tramadol target the central control of PE. There are various other reasons for PE, such as psychological problems and depression. Behavioral and psychological therapies are preferred for those reasons. Erectile dysfunction also can result in PE, and phosphodiesterase type 5 (PDE-5) inhibitors may be used to treat such patients.

Etiology of PE

Although PE is regarded as the most common male sexual dysfunction, its etiologies are still obscure. Previously it was recognized as a psychological problem without "organic" changes, but subsequent studies have suggested that PE may be influenced by various somatic disorders and/or neurobiological disturbances.[16] Several genetic studies have indicated that polymorphisms of the serotonin transporter or its promoters are associated with PE.[17,18] In addition, PE is complex with a variety of etiological factors such as depression,[19] erectile dysfunction,[20] metabolic syndrome,[21] chronic prostatitis,[22] and thyroid dysfunction.[23] These findings have further increased the difficulty in the understanding of PE.

Treatment of PE

Behavioral and psychotherapy, medication, topical anesthetics, and surgery are currently used for PE treatment [Figure 1]. Among them, surgery is mostly preferred in China and South Korea, and is gaining attention but not yet widely accepted in western countries.

Behavioral and psychological therapy in PE

Behavioral therapy mainly includes the "stop-start" technique and "penis squeezing" technique. The "stop-start" technique refers to the stimulation of the male to a would-be ejaculation and is then immediately stopped by the partner, this is repeated until the final ejaculation can only be completed with a significant level of stimulation. The "penis squeezing" technique involves squeezing the glans when there is an urge to ejaculate. Theoretically, both methods increase the threshold, delay ejaculation, and ultimately increase sexual self-confidence.[24] However, four randomized controlled studies using psychological therapy provided weak evidence regarding its efficacy in the management of PE.[25] Recently, Fu *et al*[3] reported that 30 mg dapoxetine improved the intra-vaginal ejaculation latency time (IELT) from 1.16 to 4.10 min. However, the combination of behavior therapy and 30 mg dapoxetine increased the IELT from 1.00 to 5.97 min, which was significantly better than a single drug treatment.

Pharmacotherapy

The peripheral ejaculatory reflex has three stages: first, during sexual activity, the glans of the penis is stimulated to trigger the pudendal sensory nerves, which is then transferred to the spinal network. After the signal is processed by the spinal network, the sensory information is converted to both a secretory and motor signal output, which induces contraction of the epididymis, vas deferens, seminal vesicles, prostate, and bladder neck, which in turn,

rhythmically lead to an ejaculation through the distal urethra.[11] Additionally, the ejaculation process is also regulated by the central control. There are multiple treatment options for PE available. SSRIs, topical anesthetic, and PDE-5 inhibitors are widely used.

SSRIs

Currently, LPE is regarded as a neurobiological dysfunction related to disturbances in the neurotransmission of central serotonin and 5-HT post-synaptic receptor function. Thus, SSRIs are a mainstay in the treatment of LPE as advised by ISSM.[26] Although SNRIs and clomipramine (a tricyclic antidepressant) have shown to be clinically beneficial for the treatment of LPE,[27] most LPE patients are treated by SSRIs including dapoxitine (30–60 mg), fluoxetine (20 mg), paroxetine (20 mg), sertraline (50–100 mg), and citalopram (20 mg). These SSRIs are usually taken daily. After receiving treatment for 1 to 2 weeks, serotonin neurotransmission is increased and alterations in specific serotonin receptors will occur in the central nervous system, which is responsible for the central pathway to LPE. However, sex-related side effects such as reduced libido, erectile dysfunction, and non-sex related side effects such as nausea, fatigue, insomnia, constipation, and loss appetite have led to the suggestion that an "on-demand" SSRI with a short half-time should be developed for the treatment of LPE.[28]

Dapoxetine

Dapoxetine is the first new generation of SSRIs, designed specifically for the treatment of LPE and APE.[29] It has the advantages of fast absorption, short half-life, and fast metabolism, etc. In several large global phase III clinical trials, dapoxetine 30 or 60 mg showed significant IELT improvement of more than 3.5-fold and presented with no apparent safety concerns.[30-32] Recently, a randomized placebo clinical trial[33] compared dapoxetine or paroxetine or sildenafil alone with dapoxetine in combination with sildenafil, and the result suggested that drug combination resulted in a better IELF. Furthermore, many studies have confirmed the efficacy of dapoxetine for the treatment of PE [Table 2].[29,34-36]

Table 2: Efficacy of dapoxetine or its combination to delay ejaculation in patients with PE.

Study design (length)	Number of patients	Age	PE types	Instruction	IELT/efficacy	Outcomes	Reference
A non-randomized, open-label, observational study	10,028	Mean: 40.5 years	–	Group A: 30 mg dapoxetine; Group B: clomipramine, paroxetine, fluoxetine, sertraline, topical drugs, condoms, and behavioral counseling	Both well tolerated	Good safety profiles and low prevalence	[30]
A meta-analysis of five randomized clinical trials	6576	≥18 years	LPE or APE	30 or 60 mg	More efficient than placebo	Effective	[29]
Online questionnaire	132	Mean: 42.5 years	LPE	30 or 60 mg	High discontinuation (70. 6%)	Limited efficacy	[30]
Prospective phase II study (1 year)	120	Mean: 40.3 years	LPE	30 or 60 mg	High discontinuation (90%)	Discontinue treatment	[32]
A single-blind randomized placebo-controlled clinical trial (6 weeks)	150	Mean: 34.1 years	–	30 mg	Combined dapoxetine with sildenafil group had the best IELT values	The mean of IELT, satisfaction score and PE diagnostic tool in all groups was significantly improved after treatment	[33]
A prospective randomized controlled study (4 weeks)	120	Mean: 33.7 years	LPE	30 or 60 mg	60 mg more beneficial than 30 mg or acupuncture	Effective and safe	[34]
A prospective, open-label study (12 weeks)	285	Mean: 45.9 years	LPE or APE	30 or 60 mg → 60 or 30 mg → 60 mg → 30 mg	30 and 60 mg all effective	Effective	[35]
A randomized placebo-controlled clinical trial	116	23–49 years	–	30 mg	Increased IELT from 0.86 ± 0. 17 to 4.32 ± 2. 23 min	Effective	[36]

PE: Premature ejaculation; IELT: Intra-vaginal ejaculatory latency time; LPE: Lifelong premature ejaculation; APE: Acquired premature ejaculation.

Dapoxetine may not be appropriate for every patient due to its high dropout rate.[30] In a recent study of 120 patients with PE who were being treated with dapoxetine initially, 90% patients discontinued the treatment within 1 year due to the reasons as follows; efficacy below expectations, cost, loss of interest in sex, and adverse effects.[37] Another research paper published by Park *et al*[38] showed that of 182 patients with PE treated with dapoxetine, only 9.9% of people maintained the treatment for 2 years.

Paroxetine

Paroxetine is another SSRIs drug used to treat depression and is currently also used to treat PE. Simsek *et al*[39] studied 150 patients with PE and compared the effects of paroxetine and dapoxetine in the treatment of PE. Their statistics showed that both dapoxetine and paroxetine increased IELT significantly, but the former was more effective. However, compared with dapoxetine, paroxetine had the lowest dropout rate. Yu *et al*[40] divided 142 patients with PE into three groups according to the pre-treatment IELT: group A: IELT $\leq$30 s, group B: 30 s $<$ IELT $\leq$ 60 s, group C: 60 s $<$ IELT $\leq$ 120 s, all groups were treated with 20 mg/d of paroxetine for 8 weeks. The results showed that: group A increased by 37.9-fold IELT, group B increased by 8.81-fold IELT, group C increased by 3.05-fold IELT, therefore paroxetine may be a better fit for patients with PE with shorter IELT. Furthermore, a meta-analysis by Zhang *et al*[41] based on 19 randomized controlled trials reported that paroxetine had better efficacy than placebo, fluoxetine, and escitalopram with better-tolerated side effects [Table 3].

Other SSRIs

Other SSRIs drugs include citalopram, sertraline, and so on. Related studies have confirmed their efficacy.[54,55] However, none have been approved for treatment in the European Union and needs more large randomized controlled trials to find the optimal dosages of these medications for the treatment of PE.

SNRIs

SNRIs are widely used in the treatment of depression and chronic pain syndromes.[56,57] It has also shown to be clinically beneficial in the treatment of LPE. Dutoxetine is a new orally administered, dual serotonin and norepinephrine re-uptake inhibitor, which can be used to treat PE. Ozcan *et al*[42] compared the efficacy of paroxetine 20 mg with duloxetine 40 mg once a day for a month for patients with PE. The result showed that the IELT of the two groups increased by 126% and 117%, respectively and there was no significant difference in efficacy. Furthermore, both the groups had mild and but generally tolerable adverse effects. Additionally, a study showed that dutoxetine can improve sexual desire and partner satisfaction.[43] However, more clinical trials are needed to determine its efficacy [Table 3].

Tricyclic anti-depressant

TCAs are similar to SSRIs and SNRIs, it treats PE by inhibiting the serotonin and norepinephrine transport, which results in an increased level of 5-HT and norepinephrine in the synaptic cleft. Many clinical trials have demonstrated that clomipramine, one of the TCAs, significantly improved IELT during treatment of PE [Table 3],[44-46] but the drug also has complications such as fatigue, nausea, dry mouth, low blood pressure, and dizziness.[58] Recently, a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group clinical study found that clomipramine 15 mg/d may have a better risk-to-benefit ratio when compared with placebo and clomipramine 30 mg/day.[27]

Tramadol

Tramadol is a promising opioid analgesic for the treatment of PE, it works by binding the μ receptor and inhibiting serotonin and norepinephrine reuptake.[59] A randomized, double-blind clinical trial by Kurkar *et al*[47] showed that tramadol can prolong IELT compared with placebo. The patients were divided into three groups and were given 50 mg tramadol, 100 mg tramadol, and placebo, respectively, every patient received ten doses of each medication for 2 months [Table 3]. The result showed that the mean IELT was 72 at presentation, 82 for placebo, 150 for tramadol 50 mg, and 272 for tramadol 100 mg, indicating that tramadol may have a better therapeutic effect on PE with a larger dose. Another study showed that on-demand 62 mg tramadol was a safe and effective therapeutic dose in the treatment of PE and had fewer complications than the 89 mg tramadol group[48] [Table 3]. Additionally, unlike other types of therapies, tramadol addiction and abuse can occur. Therefore, SSRIs should be considered first before tramadol.

PDE-5 inhibitors

PDE-5 inhibitors can increase nitric oxide release, reduce anxiety, relax the vas deferens, seminal vesicles, prostate smooth muscle, urethral smooth muscle, and reduce central output.[58] It has been approved by the Food and Drug Administration (FDA) for the treatment of erectile dysfunction. Recently, it was discovered that it can be used to treat PE. Therefore, PDE-5 inhibitors may be the gold standard when patients with PE have erectile dysfunction.[60] Abu *et al*[60] conducted a placebo randomized controlled trial and found that after 6 weeks, oral tadalafil 5 mg was found to have a more satisfactory Arab index of PE than the control group [Table 3]. This result was also consistent with other reports[50,61] [Table 3]. Some scholars found that tadalafil combined with other drugs such as lidocaine or SSRIs had better clinical efficacy than single-use, but the incidence of drug-related complications also increased[51,62,63] [Table 3]. Therefore, if the complications are well tolerated, combination therapy may be a better choice for PE, if the complications cannot be tolerated and cause distress to the patients or partners, a single drug can be considered.

Alpha-blockers

Silodosin and naftopidil are both α1-adrenoceptor antagonists and is both effective and safe for the treatment of benign prostate hyperplasia (BPH) and lower urinary

Table 3: Efficacy of other drugs or their combination in the delaying of ejaculation in patients with PE.

Drugs	Number of patients	Age	PE types	Instruction	IELT/efficacy	Outcomes	Reference
Paroxetine	142	18–65 years	LPE	Group A: IELT <30 s, Group B: 30s < IELT < 60s, Group C: IELT >60 s	Both well tolerated	Group A achieved better clinical effects than B and C	[40]
Paroxetine	Not available	Not available	PE	Paroxetine compared with other drugs	Both well tolerated	Paroxetine provided better efficacy than placebo, fluoxetine, and escitalopram with better-tolerated side effects	[41]
Duloxetine	80	Group A: 40 mg duloxetine 32.8 years; Group B: 20 mg paroxetine 32.2 years	LPE	Group A: 40 mg duloxetine, Group B: 20 mg paroxetine	Effective	Effective	[42]
Duloxetine	20	Group A: duloxetine 31.4 years; Group B placebo: 32.7 years	PE	20 mg	Effective	Effective	[43]
Clomipramine	101	20–65 years	LPE	15 or 30 mg	Effective	15 mg has fewer complications with similar IELT	[44]
Clomipramine	30	18–65 years	LPE	25 mg	Effective and safety	Effective and safe	[45]
Clomipramine	35	34.4 years	PE	25–50 mg	Effective	Effective	[46]
Tramadol	180	20–55 years	PE	50 or 100 mg	Effective	Tramadol exhibits a significant dose-related efficacy and side effects	[47]
Tramadol	198	18–65 years	LPE	62 or 89 mg	Effective	62 mg is an effective treatment for PE	[48]
Tadalafil	60	39.2 years	LPE	5 mg	Effective and safety	Effective and safety	[49]
Tadalafil + paroxetine	150	17–49 years	LPE	Group A: 10 mg paroxetine Group B: 10 mg paroxetine + 10 mg tadalafil	Effective	Paroxetine plus tadalafil provided better results in terms of IELT and intercourse satisfaction with mild side effects	[50]
SSRIs combined with PDE-5 inhibitors	971	Not available	PE	–	Effective	SSRIs combined with PDE-5 inhibitors provided favorable effects compared with SSRIs or PDE-5 inhibitors monotherapy and was generally well tolerated	[51]
Silodosin	26	21–76 years	LPE	4 mg	Effective and safety	Silodosin produced a significantly higher IELT compared with naftopidil	[52]
Silodosin	64	Group A: silodosin 4 mg 32.6 years Group B: placebo 33.1 years	PE	4 mg	Effective and safety	Effective and safe	[53]

PE: Premature ejaculation; IELT: Intra-vaginal ejaculatory latency time; LPE: Lifelong premature ejaculation; PDE-5: Phosphodiesterase type 5; SSRI: Selective serotonin reuptake inhibitor.

tract symptoms secondary to BPH.[64-66] The α1-adrenoceptor antagonists may be inhibiting contraction of the vas deferens, seminal vesicles, prostate smooth muscle, and so on, resulting in delay ejaculation[52] [Table 3]. A prospective multi-center clinical trial comparing silodosin with naftopidil in the treatment of patients with PE found that the IELT of the silodosin group was 7.6 min, which was higher than naftopidil group (4.1 min), and no significant clinical complications occurred.[52] Bhat *et al*[53] conducted a randomized controlled trial of silodosin for the treatment of PE, and also demonstrated the efficacy of silodosin [Table 3].

Topical anesthetics

Topical anesthetics have long been used in the treatment of PE. The rationale for using these agents is that they inhibit penile hypersensitivity. Therefore, the peripheral pathway may be blocked by topical agents. Currently, three topical anesthetics are recommended in the treatment of PE,

including eutectic mixture of local anesthetics (EMLA), topical eutectic mixture for premature ejaculation (TEMPE, also known as PSD502), and severance secret (SS) cream. A systematic review and meta-analysis have shown that all of them increased the IELT significantly.[67]

EMLA is one of the topical anesthetics containing 2.5% lidocaine and 2.5% prilocaine. Although it is effective, EMLA should be applied for 20 min before coition and a condom should be used to prevent transferring to partner. The efficacy has been provided by Xia *et al*.[68]

TEMPE is the only topical anesthetic approved by the FDA for the treatment of LPE. Each injection comprises of 2.5 mg prilocaine and 7.5 mg lidocaine and it should be applied 10 to 15 min before initiating intercourse. Two large phase III clinical trials demonstrated its significance ability to delay ejaculation with generally well-tolerated side effects.[69,70]

SS cream is mainly made from a mixture of traditional medicines such as ginseng, cinnamon, scorpion venom, etc.[71] Some of these drugs have a local anesthetic effect and are, therefore, also used to treat PE.[72,73]

In conclusion, topical anesthetics appear to have the ability to increase IELT. They can also be administrated on demand conveniently. However, some female partners may complain of decreased vaginal sensation that causes them to fail to reach orgasm. Furthermore, randomized controlled trials are needed to evaluate the efficacy and safety of topical anesthetics for PE.

Other drugs

Several literatures have associated PE with sex steroid, pituitary, and thyroid hormones, which have all been advocated as potential candidates in the regulation of the ejaculatory process, but the exact mechanisms are still unknown and further studies are required to identify potential targets for treatment.[23] Serefoglu *et al*[74] found that the mice injected with botulinum toxin into the bulbar and corpus cavernosum had increased IELT significantly. The botulinum toxin may interfere with the contraction of muscles in ejaculation reflex to increase IELT. Other drugs such as caffeine,[75] DA8031 (a new type of SSRIs drug),[76] Modafinil,[77] Resiniferatoxin[78] (blocking penile sensory nerves) were also described, but more large-scale, multicenter, randomized controlled trials are needed to determine the advantages and disadvantages of these new drugs in the treatment of PE.

Surgical treatment

Although significant improvements in the treatment of LPE have been made through pharmacotherapy, complications still exist. Topical anesthetics may cause numbness in the patient and his partner(s) and their usage are not convenient.[79] SSRIs usually have to last for a long time and treatment cost is high. Additionally, sexual desire may also be inhibited by SSRIs. The side effects on sperm production, transportation, sperm cell membranes, and DNA also have been reported.[80,81] Is there a simple way to cure LPE? Surgery may be a choice for patients who are resistant to medication treatment.[82] The efforts to explore and find new surgical treatment for PE has never stopped. At least three surgical procedures have been reported in the treatment of PE.[83-86]

Selective penile dorsal nerve neurotomy

Zhang *et al*[87] reported that the number of terminal branches of the penile dorsal nerve among patients with LPE (average 7.16 branches) was higher compared to an average male (average 3.55 branches), this fact provided the "pathological basis" for selective penile dorsal nerve neurotomy (SDN). It was concluded that the number of dorsal nerve branches in patients with LPE is positively correlated with penile sensitivity. Theoretically, SDN may be the solution as it blocks hypersensitive peripheral sexual stimulation signals, inhibits penile hypersensitivity and central excitability, which may help improve ejaculation threshold, and extend IELT.[4] A clinical observation in China reported the effect of SDN in patients with LPE, it showed that the IELT was significantly increased after surgery (0.86 ± 0.32 min *vs*. 6.65 ± 3.90 min).[88] Through a simple surgical procedure [Figure 2], it provides a treatment similar to topical anesthetics. The effect is permanent, no oral medication is needed and no special preparation has to be considered before coitus. Korean doctors preferred to remove the collateral branch to reduce penile sensitivity and increase the IELT and patient satisfaction.[89] They reported that 81.8% of the patients were satisfied after cutting 2 to 3 lateral branches on both sides in 143 patients, the patients experienced an increase in IELT and a reduction of the vibration threshold without loss of sensation. Furthermore, a randomized controlled trial by Liu *et al*[90] showed that SDN was an effective method for patients with PE who were refractory to drugs or refused oral medication.

Currently, guidelines in China does not prohibit the application of a penile dorsal nerve neurotomy for the treatment of LPE as a second-line treatment.[91,92] But this surgery should only be applied to patients who meet the following criteria. A practical guideline published on National Journal of Andrology[92] suggested the indications for SDN in LPE are as follows: (1) IELT $\leq$2 min, lasting more than 6 months; (2) excluded any psychological factor related PE; (3) condition caused distress, anxiety, and other negative emotion changes; (4) penile hypersensitivity, without erectile dysfunction; (5) has strong intentions to undergo SDN; (6) refused behavioral, psychological, and drug treatments.

Cryoablation and radiofrequency

Cryoablation and pulsed radiofrequency are established types of minimally invasive techniques for the treatment of urinary tumor, which can kill tumor cells with precision.[93,94] Some scholars expanded their application based on the hypothesis that performing cryoablation or pulsed radiofrequency on the dorsal nerve reduces hypersensitive peripheral sexual input signals and inhibited penile hypersensitivity. A prospective study by David *et al*[83] evaluated the efficacy of percutaneous computed

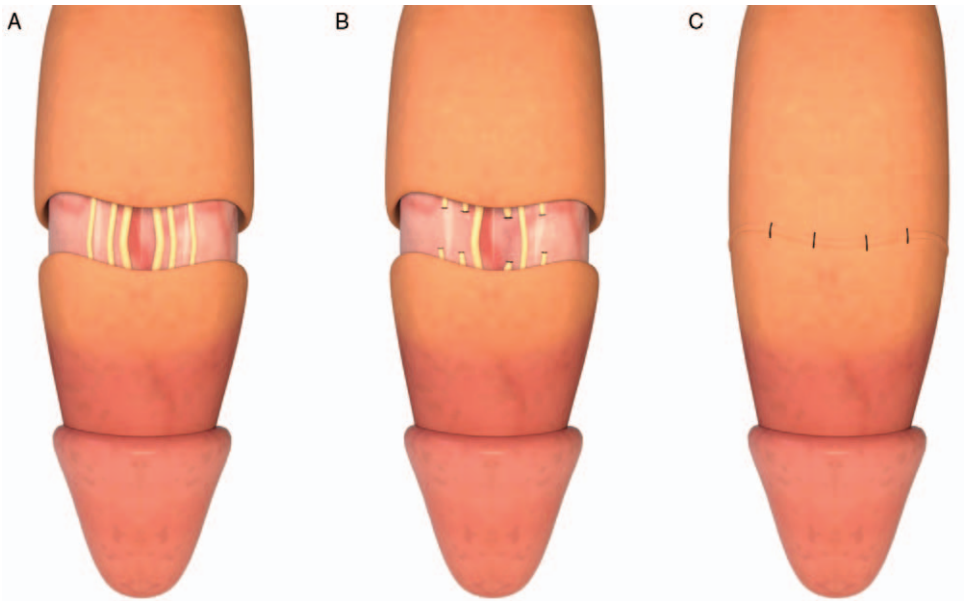

Figure 2: A brief surgical procedure of selective penile dorsal nerve neurotomy. (A) Check the patient's penis foreskin, circumcision can be performed if the foreskin is too long; cut the skin of the penis along the 0.8 to 1.5 cm below the coronal sulcus of the penis, make an incision into both the skin and the sub-cutaneous tissue, and separate 3 to 4 layers of penile fascia to reveal the deep vein of the penis. The dorsal nerve of the penis can be seen on the dorsal artery of the penis. The dorsal nerve of the penis is yellowish and elastic. (B) Retain 3 to 4 branches of the penile dorsal nerve, and remove 3 to 4 cm of remaining penile dorsal nerve branches. (C) Next, suture the surgical site and treat any bleeding, the skin and sub-cutaneous tissue of the suture area should be divided into two layers.

tomography (CT)-guided cryoablation in 24 patients on a unilateral dorsal penile nerve in the treatment of symptomatic PE. The report showed that IELT was increased from a baseline value of 54.7 ± 7.8 s to a maximum of 256.0 ± 104.0 s by day 7, to 182.5 ± 87.8 s by day 90, and 145.9 ± 86.5 s in 1 year. Although four patients experienced a decrease in erectile stiffness, two spontaneously recovered, and two recovered after taking an oral PDE-5 inhibitor. Pulsed radiofrequency (PRF) is often used to treat pain in a variety of areas, which regulates neural activity primarily through electric fields without causing nerve damage.[86,95] Similarly, PRF therapy can modulate the activity of the dorsal nerve of the penis and reduce its sensitivity. Basal *et al*[86] performed PRF for the treatment of PE. Fifteen patients with LPE had increased IELT from 18.5 ± 17.9 s to 139.9 ± 55.1 s after 3 weeks. During the follow-up period, no patients had any erection problem, penile hypoesthesia, or pain after the procedure. Therefore, compared with CT-guided cryoablation, PRF is described as a neuro-modulation technology with the merit of no radiation, no complications, and no nerve injury.

Glandular augmentation with hyaluronic acid gel

This approach refers to the injection of hyaluronic acid gel into the glans, to build a barrier artificially between the dorsal penile nerve and its external environment. Some authors reported the efficacy of this surgery, but a series of complications such as possible sensory loss were also reported.[96-98]

Controversies in surgical treatment with LPE

Most Chinese andrologists are opposed to performing surgery for the management of LPE due to insufficient supporting evidence. Furthermore, possible complications include a loss of sexual desire. However, in both China and Korea, some andrologists insist on performing surgeries as they believe that these procedures are effective for the treatment of LPE. They believe that surgeries are more convenient and are an effective alternative for patients with LPE who reject long-term drug usage. Till now, no large, multi-center, double-blind randomized controlled trials or long-term follow-up data support the safety and efficacy of the surgical treatment of LPE.[99] More high-quality clinical trials and long-term follow-up data are needed to determine the efficacy and safety of surgery for the management of LPE.

Summary

The causes of PE remain unclear. Previously it was recognized as a psychological problem without "organic" changes; however, subsequent studies have suggested that PE may be influenced by various somatic disorders, neurobiological disturbances, genetic changes, metabolism diseases, and penile hypersensitivity. Therefore, there are several methods in use for the treatment of PE. Currently, on-demand pharmacotherapy is still the main choice globally. However, a significant proportion of patients discontinue the treatment within a year due to the following reasons; efficacy below expectations, cost, loss of interest in sex, and adverse effects. Topical anesthetics are an effective alternative but may cause numbness in the patient and his partner(s). Behavioral and psychological therapies are non-invasive methods in the treatment of PE. A combination of an adjusted dosage of drugs taken while undergoing behavioral or psychological therapy may be a better choice for decreasing the complications and optimizing efficacy theoretically. But this combination

should be evaluated by more high-quality studies. SDN is not recommended by the ISSM guideline for the treatment of PE due to insufficient evidence. However, SDN may be a reasonable choice with certain patients. In summary, all current treatment methods for PE have limitations and complication, and other novel methods such as drugs or surgery require further studies to determine their efficacy and safety for the treatment of PE.

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Conflicts of interest

None.

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