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The pharmacological treatment of premature ejaculation

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Premature ejaculation (PE) is a common sexual dysfunction in men that is characterized by a short time to ejaculation, and a lack of control over ejaculation, and is associated with distress for men and their partners. Lack of knowledge about the aetiology of PE and lack of approved treatments might contribute to its under-diagnosis and under-treatment. The organic factors involved in PE are not well understood but serotonin (5-hydroxytryptamine, 5-HT) is important at the level of the central nervous system in the complex regulatory mechanisms involved in ejaculation. Selective serotonin reuptake inhibitor (SSRI) antidepressants (paroxetine, fluoxetine and sertraline) and the tricyclic antidepressant clomipramine increase ejaculatory control and delay ejaculation in men with PE, suggesting that pharmacological intervention might be useful for PE. These agents are intended for chronic dosing for treating psychiatric disorders because of their pharmacokinetic profile and pharmacodynamic activity, which might result in limitations when used for treating PE. Indeed, these properties might limit the utility of these drugs, whether administered on-demand or chronically, for the episodic treatment requirements of PE. Elevated synaptic 5-HT levels achieved with acute SSRI treatment might be self-limiting because of activation of presynaptic 5-HT_{1A} autoreceptors, and chronic 5-HT_{1A} autoreceptor desensitization might contribute to an increase in side-effects and withdrawal symptoms. Short-acting SSRIs such as dapoxetine, currently under development for the on-demand treatment of PE, might circumvent these limitations and offer better ejaculatory control and sexual satisfaction for men with PE. Phosphodiesterase-5 inhibitors have also been evaluated for treating PE, as have topical anaesthetics and the narcotic analgesic tramadol.

KEYWORDS

5-HT, premature ejaculation, selective serotonin reuptake inhibitor, sexual dysfunction

INTRODUCTION

Premature ejaculation (PE) is a common male sexual dysfunction [1–3]; as a medical condition it remains under-diagnosed and under-treated because of misperceptions by patients and physicians about its causes, and the lack of approved treatments. By contrast with erectile dysfunction (ED), which more frequently affects older men, PE commonly occurs to a similar extent in men of all ages [1,3].

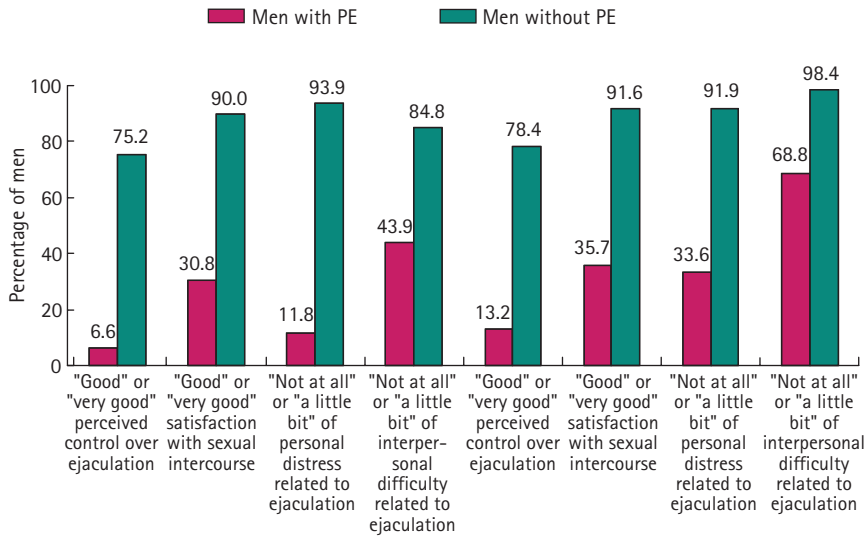
PE is associated with a short ejaculatory latency time, lack of ejaculatory control, decreased satisfaction with sexual intercourse for both the man and his partner, intrapersonal distress, a negative impact on a man's self-esteem and reduced sexual function, and possibly, reduced quality of life (Fig. 1) [4–6]. Recent observational [4,5] and clinical studies [7] identified patients with PE, in part, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) [8], which include components of time, lack of ejaculatory control, lack of satisfaction with sexual intercourse, distress, and interpersonal difficulty:

- Persistent or recurrent ejaculation with minimal sexual stimulation;
  - before, on, or shortly after penetration;
  - before the person wishes it;
- Must also cause marked distress or interpersonal difficulty;
- Cannot be due exclusively to the direct effects of a substance.

Lack of control over ejaculation is a consistent component among all clinical definitions of PE [9–11], and has been shown to be a highly sensitive predictor of this condition [12]. A new definition for PE is being proposed by the International Society for Sexual Medicine, that is anticipated to include some form of these measures.

PE can be classified as either a lifelong condition (present since the onset of sexual maturity) or an acquired condition that develops after an interval of normal sexual function [13]. Some have also proposed that there might be other forms of PE, including natural variable PE, which occurs in specific situations, and premature-like ejaculatory dysfunction, in which men with ejaculatory latency times in the normal range perceive their ejaculation to be premature [14]. Negative conditioning and penile hypersensitivity have been cited as aetiological factors in PE, although neither mechanism has received adequate experimental or evidence-based support to date [15,16]. By contrast with ED, which is primarily a vascular disorder in ageing men [17], there are no recognized organic diseases associated with PE, although recent evidence [18] indicates a role for prostatitis in some men with PE. Notably, the physiology of ejaculation is unimpaired in patients with PE, and it is the lack of voluntary control of, and the short time to, ejaculation after vaginal penetration that can result in associated distress. It has been postulated that PE might have a sensory/neural component involving perturbations in the serotonergic (5-hydroxytryptamine, 5-HT) system [19]. Because individual variability in 5-HT neurotransmission might determine individual ejaculatory thresholds, such alterations could theoretically contribute to the pathogenesis

FIG. 1. Control over ejaculation, satisfaction with sexual intercourse, and personal distress and interpersonal difficulty in men with and without PE [4,5]. The percentage of men with and without PE in two observational studies [4,5] who reported that their control over ejaculation or satisfaction with sexual intercourse was 'good' or 'very good' or reported 'a little bit' or 'not at all' for personal distress or interpersonal difficulty related to ejaculation.



of PE [20]. The neurophysiology and pharmacology of ejaculation and the current and emerging pharmacological treatment options for PE are reviewed here.

NEUROPHYSIOLOGY OF EJACULATION

Normal ejaculation involves the processes of emission and expulsion of semen, which are coordinated by a network of afferent and efferent neural pathways [20,21]. The triggers for ejaculation include tactile stimulation of the glans penis and various supraspinal stimuli. The neural control network for ejaculation involves specific spinal, supraspinal and peripheral neural pathways [22]. Ejaculatory control centres within the spinal cord are responsive to peripheral afferents and supraspinal influences and function to coordinate, in a timely fashion, the sympathetic, parasympathetic, and somatic outputs to the pelviperineal anatomical structures participating in the emission and expulsion phases.

Inhibitory and excitatory control are exerted from supraspinal sites. Certain brain structures have been identified as specifically related to ejaculation and are activated during sexual activity [23,24]. These include discrete regions lying within the posteromedial bed nucleus of the stria terminalis, the posterodorsal medial amygdaloid nucleus, the posterodorsal preoptic nucleus, and the parvicellular part of the subparafascicular thalamus [25]. In the brainstem, the nucleus paragigantocellularis, which contains a high concentration of serotonergic neurones, plays a strong inhibitory role in the control of ejaculation [26,27], and the periaqueductal grey has been shown, in an experimental animal system, to control the expulsion reflex [28]. Midbrain structures also regulate ejaculation, but further investigations are required to reveal additional mechanistic details.

Regulation of the ejaculatory reflex at the level of the spinal cord requires that coordinated neurochemical interrelationships take place at different levels of the neuraxis [29,30]. Several neurotransmitter systems distributed throughout the supraspinal and spinal regions have been implicated in this process, with the 5-HT and dopaminergic neurones playing a primary role [31], and other neurotransmitters, including acetylcholine, adrenaline, neuropeptides, oxytocin, γ-aminobutyric acid, and nitric oxide, acting secondarily [32,33]. Although the hypothesized spinal and supraspinal pathways of the neurotransmitter network involved in the ejaculatory process are documented, the precise role of the various substances in the ejaculatory reflex is difficult to define because of the wide range of sexual variables besides ejaculation that are affected, and because of the heterogeneity of results shown in different species, the variation of activity depending on the site in the CNS where the transmitter acts, and the variety of receptor subtypes putatively involved.

5-HT appears to be a key mediator in the neurophysiology of ejaculation [32–34]. 5-HT neurones express somatodendritic autoreceptors (including 5-HT_{1A} receptors present in the mesencephalic and medullary raphe nuclei), presynaptic autoreceptors (5-HT_{1B} and 5-HT_{1D}), 5-HT signalling receptors (e.g. 5-HT_{2C}), and 5-HT reuptake transporters, each of which mediate different effects on cellular activation and 5-HT signalling [29,35]. In general, activation of 5-HT_{1A} autoreceptors decreases 5-HT release by the presynaptic neurone, providing a negative-feedback mechanism for 5-HT neurotransmission [22,35]. Signal transduction through 5-HT_{1A} and 5-HT_{2C} receptors plays a key role in regulating ejaculation at the central level [36]. Activation of postsynaptic 5-HT_{2C} or 5-HT_{1B} receptors prolongs ejaculatory latency, whereas activation of presynaptic 5-HT_{1A} autoreceptors, which inhibits 5-HT release, decreases ejaculatory latency [30,36]. Subcutaneous administration of the 5-HT_{1B} receptor agonists anpirtoline and m-trifluoromethylphenylpiperazine and systemic, acute administration of the 5-HT_{2C} agonist 2,5-dimethoxy-4-iodoamphetamine have been shown to impair ejaculation in rats [30].

It was suggested that PE might be associated with the presence of low synaptic levels of 5-HT in regions of the CNS that modulate ejaculation, possibly because of variations in 5-HT receptor sensitivity [19]. Thus, a physiological basis for PE might involve an underlying imbalance between 5-HT_{1A} (hypersensitive response) and 5-HT_{2C} or 5-HT_{1B} receptor activity (hyposensitive response) [37], although this hypothesis requires further investigation and confirmation. Overall, based on the current neurochemical knowledge of ejaculation, it appears that increasing central 5-HT is a relevant pharmacological strategy to delay ejaculation.

THE PHARMACOLOGICAL MANAGEMENT OF PE

The management of PE is shifting from a traditional diagnostic and treatment pattern

based on expert opinion to a more experimental, evidence-based approach [4,7,38]. Clinical outcome data using precise endpoints are the cornerstone of evidence-based medicine, but until recently, such evidence was limited for PE. Measurement of intravaginal ejaculatory latency time (IELT) might provide the most objective and quantitative method for assessing the severity and treatment response of PE in clinical studies [7,39]. Some clinical studies including this endpoint have used a stopwatch, operated by the patient or his partner, while others have used estimates of latency based on patient and/or partner recall. However, the use of this variable alone might be insufficient for evaluating patients with PE because the IELT does not reflect important subjective components of this multidimensional condition, e.g. control over ejaculation, and distress. Data from some studies [4,5] indicate that the IELT alone is not sufficient for accurately assigning PE status. In large observational studies that used the DSM-IV-TR as a diagnostic tool for PE [4,5], the patient-reported outcomes of control over ejaculation and personal distress were found to be important measures directly related to PE [12]. For example, results from one study [4] of men in the USA showed that significantly more subjects with than without PE reported having 'very poor' or 'poor' control over ejaculation (72% vs 5%, respectively; $P < 0.001$), and these percentages were similar between trials of men in the USA [4] and those in the European Union [40]. Furthermore, more subjects in the PE group reported 'quite a bit' or 'extremely' for personal distress (64% vs 4%, respectively; $P < 0.001$) compared with the non-PE group. Analyses of these data showed that measures of control over ejaculation and personal distress were reliable, valid, and efficient measures of PE outcomes, and therefore should be used in conjunction with the IELT to assess PE [41,42]. Furthermore, these results in men in the USA were recently confirmed in a similar study of men from five European countries [5].

TABLE 1 A summary of efficacy of SSRIs and clomipramine in all trials and in adequately controlled trials. From [55]. Reprinted with permission from Macmillan Publishers Ltd.

	Mean % (95% CI) increase in IELT	
Agent	All trials (35)	Adequately controlled trials (8)
Placebo	45 (27–87)	47 (29–76)
Clomipramine	512 (234–1122)	360 (201–644)
Fluoxetine	295 (172–506)	295 (200–435)
Paroxetine	1492 (918–2425)	783 (499–1228
Sertraline	790 (532–1173)	313 (161–608)

CLOMIPRAMINE

Clomipramine is a tricyclic antidepressant that inhibits the uptake of noradrenaline and 5-HT by adrenergic and 5-HT neurones [43]. Continuous dosing with clomipramine significantly lengthened the IELT compared with placebo ($P < 0.01$), as measured by stopwatch assessment in a randomized, placebo-controlled crossover trial in 36 men with PE [44]. On-demand dosing with clomipramine significantly increased the IELT compared with placebo or other PE treatments in patients with PE [45,46]. In three double-blind, placebo-controlled crossover studies [46–48], on-demand dosing with clomipramine (25 mg, 12–24 h before intercourse) significantly increased the IELT by about four times that at baseline in men with PE (30, 23 and eight men for each of the three studies); however, only the smallest of these trials used an objective stopwatch technique. In a double-blind, randomized crossover trial in 31 men with PE, clomipramine, sertraline, paroxetine, and sildenafil each significantly improved the IELT compared with behavioural modification (use of the pause-squeeze technique; $P = 0.001$ for each), and there was no significant difference in efficacy between these agents ($P > 0.05$) [49]. However, other analyses have reported that subsets of patients, such as those with the shortest IELT, are less likely to benefit from clomipramine [46,50]. Small studies show that clomipramine also improves patient-reported outcomes. After daily treatment with clomipramine, men with PE reported improved relationship and emotional satisfaction, men and their partners reported increased sexual satisfaction, and the partners reported an increased ability to achieve coital orgasm [51]. Another study also reported significantly improved sexual satisfaction of patients and their partners with clomipramine [48].

Use of clomipramine might be limited by its associated side-effects. During continuous dosing, the adverse event profile of clomipramine in men with PE was reported to be significantly worse than with selective serotonin reuptake inhibitor (SSRI) treatment [44]. Reducing exposure to clomipramine through use of an on-demand regimen did not eliminate potentially annoying nonsexual side-effects, including sleepiness, yawning and nausea, which were significantly worse on the day of dosing and the subsequent day with clomipramine than with SSRI therapy [47].

SSRIs

Based on the role of 5-HT neurotransmission in the physiology of ejaculatory control [22] and possibly in the pathogenesis of PE, and because SSRI antidepressants have the well-established side-effect of delaying ejaculation when used to treat depressed patients [52,53], currently marketed SSRIs such as paroxetine, fluoxetine, and sertraline, which increase synaptic 5-HT concentration via blockade of 5-HT transporters, have been investigated in numerous clinical studies for managing PE. Paroxetine and sertraline have provided significant benefits in patients with PE, either via daily administration or on-demand use before intercourse, and fluoxetine has shown some efficacy for PE as continuously dosed therapy [54,55]. Although none of these agents has received an indication for the treatment of PE, current guidelines from the AUA [11] and recommendations from the Second International Consultation on Sexual Dysfunctions [10] recommend the off-label use of SSRIs for managing PE.

A meta-analysis [55] was conducted that focused on eight randomized, double-blinded studies of SSRI and tricyclic antidepressants for treating PE, that included a stopwatch assessment of IELT. The rank order of efficacy for the increase in IELT with treatment was paroxetine, sertraline, clomipramine, fluoxetine and placebo. A key finding of this analysis was that the efficacy of SSRIs was markedly lower in randomized controlled trials than in less well controlled trials (Table 1). A comprehensive review [56] of SSRIs for treating PE included eight trials of ≈480 men with PE, which evaluated paroxetine, citalopram, sertraline and fluoxetine (Table 2). All studies reported an improvement in IELT, but only three used an

TABLE 2 A summary of randomized controlled clinical trials of SSRI antidepressants for treating PE. Reprinted with permission from [56]

			Measures					IELT†, min		Design	
Drug	Usage, mg	Number*	CE	ROS	IELT	MSS	FSS	BT	AT	RPCDB	SW
Fluoxetine	20 dy	40	–	–	+	–	–	1.2 (1.0)	6.6 (7.7)	+	–
Sertraline	50 dy	37	–	–	+	–	–	0.3	3.2	+	–
Sertraline	50/100 dy then od	24	–	–	+	+	+	0.4 (0.3)	4.5 (2.7)	–	–
Paroxetine	20 dy	130	–	+	+	+	+	1.5 (0.7)	7.7 (4.0)	–	–
Paroxetine	20 dy then od	61	–	+	+	–	–	0.4	5.5	–	–
	20 od	33						0.4	1.5		
Paroxetine	20 dy then od	26	–	–	+	–	–	0.5	5.8 and 6.1 3.2 and 3.5	–	–
	20 od	42						0.3			
Citalopram	20–60	30	–	–	+	–	–	0.6 (0.3)	4.1 (1.9)	–	–
Citalopram	20 dy for 3 months	58	–	–	+	–	–	0.5	3.5	+	+
	20 dy for 6 months	58						0.5	3.3		
Dapoxetine	30 od	2614	+	–	+	+	+	0.9	2.8	+	+
	60 od							0.9	3.3		

*dy, daily; od, on demand; CE, the ability to control ejaculation; ROS, reaching orgasm scores (female); MSS, the rate of male sexual satisfaction; FSS, the rate of female sexual satisfaction; BT, before treatment; AT, after treatment; RPCDB, randomized, placebo-controlled, double-blind study; SW, stop watch; +, used in trials; –, not used in trials. *The number of patients in the trial. †Mean or mean (SD).*

adequately controlled study design, which included the use of a placebo control and a double-blinded study design. Of interest, the most common adverse event across all trials was sexual dysfunction, which included sexual desire and arousal difficulties, delayed ejaculation and anejaculation, absent or delayed orgasm, and ED.

Side-effects have been a major concern with the chronic use of SSRIs in patients with depressive disorders/symptoms, many of which have prompted discontinuation from therapy. The adverse effects of SSRIs include psychiatric and neurological consequences, dermatological reactions, anticholinergic side-effects, changes in body weight, cognitive impairment, drug–drug interactions, and sexual side-effects other than delayed ejaculation (e.g. ED and loss of libido) [57]. Although the rate and mean duration of each type of adverse event varies for each of the SSRIs, patients with comorbidities might be predisposed to certain side-effects [58]. Moreover, when switching between SSRIs, overdosage can occur unless a drug washout period appropriate for the half-life of the first SSRI is implemented [58].

A further limitation of SSRI therapy is that dose reduction or discontinuation of ongoing therapy has been associated with an 'SSRI-discontinuation' syndrome, with patients who have received paroxetine being especially susceptible [59]. This cluster of somatic and psychological symptoms can include dizziness, nausea and emesis, headache, gait instability, lethargy, agitation, anxiety, and insomnia [60,61]. These symptoms are typically reversible upon reintroduction of the SSRI [61]. Less common symptoms include shock-like sensations, paraesthesia, and visual disturbances. Symptoms usually begin within 1–3 days after drug discontinuation and have a median duration of >1 week [59].

SSRI antidepressants with long half-lives might require a washout period to minimize the risk of excessive levels accumulating after multiple doses. Overdose of SSRIs, or more commonly, drug–drug interactions between SSRIs and other agents that enhance CNS 5-HT activity, can lead to serotonin syndrome, a cluster of severe and persistent symptoms that can include myoclonus, hyper-reflexia, sweating, shivering, lack of coordination, and mental status changes [62,63]. Patients receiving continuous-dose SSRI therapy must be made aware of potential drug–drug interactions between SSRIs and their concomitant medications, and schedule their doses accordingly. Given that the dosage and schedule of SSRI administration for PE can vary from the approved regimens for indications such as clinical depression and anxiety, the safety and tolerability profiles of SSRIs in the off-label setting might be altered from those observed when used for approved indications.

CONTINUOUS VS ON-DEMAND ADMINISTRATION OF SSRIS FOR MANAGING PE

Continuous, daily dosing of SSRIs is effective in delaying ejaculation. However, this approach increases exposure to medication, thereby increasing the likelihood of side-effects. Conversely, it was suggested that the efficacy of on-demand administration of conventional SSRIs indicated for the treatment of depression might be limited by inherent neurotransmission feedback mechanisms [37,64]. A few studies evaluated the use of SSRI antidepressants with as-needed dosing, but the study designs were not rigorous [11,47,65,66]. With episodic administration, SSRIs acutely block 5-HT reuptake by 5-HT transporters in presynaptic neurones [63,67], resulting in an increase in synaptic 5-HT levels. However, this increased 5-HT also activates 5-HT_{1A} somatodendritic and presynaptic autoreceptors, ultimately

limiting the increase in 5-HT release into the synapse. Although chronic administration of SSRIs might produce a greater net elevation in 5-HT signalling by preventing the increase in the 5-HT_{1A} receptor-mediated autoregulatory feedback loop in presynaptic neurones [37], these chronic changes in signalling might also be responsible for some of the side-effects associated with ongoing SSRI therapy [11].

Considering the shortcomings of chronic SSRI treatment, an optimal therapy for PE would have a short duration of activity, with clinical efficacy after each dose for on-demand treatment with no need for lead-in dosing [68]. It is possible that on-demand administration of a short-acting SSRI with a sufficiently rapid onset of action could provide an immediate increase in synaptic 5-HT levels, thus overwhelming synaptic feedback control mechanisms (i.e. 5-HT autoreceptor activation) or transporter trafficking, and producing a clinically meaningful effect in the absence of continuous administration. Furthermore, an agent that is rapidly cleared could minimize unnecessary drug exposure when administered on-demand, potentially resulting in a reduced risk for adverse events and less likelihood of drug–drug interactions. Therefore, a serotonergic agent with a rapid onset and rapid clearance could be effective and maximize convenience, while improving safety and tolerability compared with SSRIs with longer half-lives.

DAPOXETINE

Dapoxetine, a short-acting SSRI that is currently under development for treating PE, has a unique pharmacokinetic profile that allows a relatively rapid achievement of high serum concentrations (time to maximum serum concentration 1.29 h) [69,70] and rapid elimination (half-life 1.49 h) after oral dosing, which might contribute to its utility as an on-demand therapy for PE. In two 12-week placebo-controlled trials in the USA [7], of men who met DSM-IV-TR criteria for PE, had an IELT of ≤2 min in ≥75% of intercourse episodes in a 2-week baseline period, and reported a PE severity of moderate or severe (2614 men), on-demand administration of dapoxetine 30 or 60 mg significantly improved outcomes compared with placebo. The IELT was significantly ($P < 0.001$) increased up to 3.6-fold from baseline (vs 1.9-fold for placebo; $P < 0.001$). Patient-reported perception of control over ejaculation and satisfaction with sexual intercourse were also significantly better than with both baseline values and placebo.

The most common adverse events with dapoxetine 30 and 60 mg in these 12-week trials in the USA [7] were nausea (8.7% and 20.1%, respectively, vs 1.9% with placebo), diarrhoea (3.9% and 6.8%, respectively, vs 1.4% with placebo), headache (5.9% and 6.8%, respectively, vs 4.0% with placebo), and dizziness (3.0% and 6.2%, respectively, vs 0.8% with placebo), and 5% of all subjects discontinued because of adverse events. Results from a 9-month, open-label extension study [71] that assessed dapoxetine 60 mg showed that the most common adverse events were nausea (15.4%), dizziness (5.1%) and headache (4.6%), and 6.7% of subjects withdrew for adverse events including nausea (1.6%), dizziness (1%), diarrhoea (0.8%), headache (0.6%) and insomnia (0.5%).

Another SSRI with a short half-life, BMS-505130, has been shown in preclinical trials to be a potent inhibitor of serotonin reuptake [72], although clinical evidence in PE is not yet available.

PHOSPHODIESTERASE-5 INHIBITORS (PDE-5i)

PDE-5i have been used alone [73] or in combination with SSRI antidepressants [72,74] for treating PE. Results for the treatment of men with PE with no concomitant ED have been conflicting. This is probably explained by the lack of any pharmacological rationale for a PDE-5i to affect the central and/or the peripheral control of ejaculation. A randomized crossover study [49] conducted in 31 men showed that sildenafil was superior to clomipramine, sertraline, paroxetine, and the pause-squeeze technique in increasing IELT. In another study [75], as-needed sildenafil increased the time to ejaculation compared with placebo when vibratory stimulation was used to induce ejaculation. Combined therapy with paroxetine and sildenafil increased IELT and increased sexual satisfaction compared with paroxetine alone, but was associated with a higher incidence of side-effects, such as headaches and episodes of flushing [72]. In addition, when behavioural therapy was added to the combined pharmacological therapy (paroxetine and sildenafil), the severity of PE decreased significantly, and based on a four-point scale (0, >5 min; to 3, <1 min), IELT was increased [74]. By contrast with these positive findings, other studies indicated that sildenafil has no effect on sexual function in men without coexisting ED, but causes a decrease in the post-ejaculatory refractory period [76]. Indeed, in one study [77], 28% of patients with ED successfully treated with sildenafil subsequently developed PE; in these patients, subsequent treatment of PE with sertraline was far less effective than in patients with primary PE. Another recent study in men with PE reported that sildenafil did not significantly increase the IELT in comparison with baseline, but did improve measures of control over ejaculation and sexual satisfaction [78]. A recent systematic review [79] of published reports on PDE-5i for treating PE concluded that there is limited evidence to support a role for PDE-5i in the treatment of PE, although some evidence suggests that they might be of benefit for men with both PE and ED.

TRAMADOL

Results from two small studies [80,81] suggest that tramadol, a centrally acting synthetic opioid analgesic that is available in generic form in most countries, might be effective for the on-demand treatment of PE. Although its potential mode of action in PE is not clear, tramadol and its primary metabolite might inhibit noradrenaline and serotonin reuptake in addition to their antinociceptive actions on μ-opioid receptors. Similar to dapoxetine, tramadol is rapidly absorbed and eliminated [82], which are desirable properties for an as-needed dosing regimen. Results from two placebo-controlled studies showed that tramadol 50 mg significantly increased IELT and measures of sexual satisfaction and ejaculatory control compared with placebo ($P < 0.05$ for all) [80,81]. As with all opioids, there might be concerns about the risk of abuse/dependence; however, a recent meta-analysis of the use of tramadol for pain concluded that there was a lack of appropriately designed clinical trials to accurately evaluate this issue [83], which was not mentioned in the two trials in men with PE.

TOPICAL AGENTS

Topical lidocaine/prilocaine formulations effectively cause desensitization, and have been shown to increase the mean IELT [84,85], and several studies [84,86–89] reported

significant increases in ejaculation times in men who used lidocaine/prilocaine cream compared with placebo. For example, results from one recent study [86] (54 men) showed that men with a DSM-IV-TR diagnosis of PE who received a topical eutectic mixture for PE (TEMPE; a metered-mixture of lidocaine and prilocaine) reported a 2.4-fold increase in mean IELT over that observed with placebo (3.8 vs 0.7 min, respectively; $P < 0.01$). Men with PE reported improvements in their ejaculatory control, and both men and their partners reported improvements in their sexual quality of life. The most common adverse event with TEMPE was mild-to-moderate local numbness (12%), which was not associated with discontinuation. Results from previous studies with topical anaesthetics showed loss of erection and numbness in the man and his partner, which have been reported by up to 40% of men in one study [87].

Another topical agent, Severance Secret (SS) cream, has been evaluated in several trials [90,91], and is thought to also act through desensitization, although its exact mechanism is unclear. In clinical trials, SS cream resulted in significant increases in IELT and satisfaction with sexual intercourse in comparison with placebo [90,91]. The most common side-effect of SS cream was a sense of mild local burning/pain at the application site.

CONCLUSION

Although PE affects many men, it remains an under-treated condition, partly because of a lack of understanding of its causes and potential for therapy, and because of its sensitive nature, which might prevent a man from seeking treatment. Among the many neurotransmitter systems involved in ejaculatory modulation, central 5-HT has been implicated as a key mediator of ejaculatory control.

Currently available pharmaceutical therapy for PE involves the off-label use of SSRIs and PDE-5i, as well as topical anaesthetics, each of which have shown varying degrees of efficacy and tolerability. New agents being considered for the on-demand treatment of PE include tramadol and dapoxetine, which might provide an important option for treating PE. Therapy for PE will continue to develop as the understanding of ejaculation expands, including the role of central neurotransmitters (e.g. dopamine and oxytocin) as future targets to delay ejaculation.

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CONFLICT OF INTEREST

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Abbreviations: **5-HT**, 5-hydroxytryptamine; **DSM-IV-TR**, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision; **ED**, erectile dysfunction; **IELT**, intravaginal ejaculatory latency time; **PE**, premature ejaculation; **SSRI**, selective serotonin reuptake inhibitor; **TEMPE**, topical eutectic mixture for premature ejaculation.