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Advances in treating premature ejaculation

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Abstract

In spite of its high prevalence and long history, the ambiguity regarding the definition, epidemiology and management of premature ejaculation continues. Topical anesthetic creams and daily or on-demand selective serotonin reuptake inhibitor (SSRI) treatment forms the basis of pharmacotherapy for premature ejaculation today, in spite of low adherence by patients. Psychotherapy may improve the outcomes when combined with these treatment modalities. Tramadol and phosphodiesterase type 5 inhibitors have a limited role in the management of premature ejaculation. Further research is required to develop better options for the treatment of this common sexual disorder.

Introduction

Although premature ejaculation was first described over a century ago [1], the ambiguity regarding its definition, epidemiology and management continues [2]. Recently, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3] (published by the American Psychiatric Association) defined premature ejaculation and, contrary to previous versions of this manual, it included the parameter of approximately one minute intravaginal ejaculatory latency time (IELT). The DSM-5 also listed potential exclusionary conditions, to include nonsexual mental disorders, severe relationship distress or other significant stressors and substance/medication use or other medical disorders, which may result in early ejaculations. These criteria were intended to eliminate cases of premature ejaculation resulting secondarily from psychological and/or medical factors. However, the sexual complaints of patients who seek treatment for premature ejaculation are varied, and a significant amount of them do not fulfill the criteria of the definition in DSM-5 [4,5]. Therefore, the concerns of these men must also be addressed by health care providers and available therapeutic options must be offered. The aim of this review is to summarize the contemporary advances in premature ejaculation treatment and provide a broad insight into the efficacy and safety of these options.

Psychotherapy

Historically, premature ejaculation was considered to be a psychological or partner-related condition due either to anxiety or to conditioning towards rapid ejaculation based on rushed early sexual experiences [6,7]. Therefore, psychotherapy was the initial treatment modality proposed for premature ejaculation, although its utility is limited in today's practice.

Psychotherapy may help men improve their sexual skills and enable them to control their ejaculation. Moreover, broadening the sexual knowledge of a man with premature ejaculation may aid him in increasing his sexual self-confidence and reduce performance anxiety. More importantly, psychotherapy may resolve psychological and interpersonal problems which may be the cause and/or result of premature ejaculation [8,9]. Unfortunately, the majority of the psychotherapy studies dealing with premature ejaculation do not meet the criteria for high level evidence-based studies [8], so it is now recommended that psychotherapy be used in conjunction with pharmacotherapy [10].

The initially developed and most frequently used behavioral treatments include the "squeeze" technique, which was later modified to become the "stop–start" method [6,11]. Both of these techniques were suggested to assist men in identifying their excitement levels by a series of graduated exercises. These exercises begin with self-stimulation, moving on to partner hand stimulation, then to intercourse without movement, and finally to stop/start thrusting. This treatment modality is hypothesized to result in an increase in IELT, but there are no reliable data to support this claim [6,12-14]. Two recently published meta-analyses concluded that there is weak and inconsistent evidence regarding the effectiveness of psychological interventions for the treatment of premature ejaculation, confirming the need for future research in this field [15,16].

Topical anesthetics

Hypersensitivity of the glans penis is another one of the proposed etiological factors underlying the pathophysiology of premature ejaculation [17]. Therefore, the use of topical anesthetics to diminish the sensitivity of the glans penis was one of the first pharmacological treatment alternatives for premature ejaculation [7].

Lidocaine-prilocaine cream is the most studied local anesthetic for treating premature ejaculation. A randomized, double-blind, placebo-controlled trial demonstrated that 5% lidocaine-prilocaine cream significantly increased the IELT when applied for 20 minutes prior to sexual intercourse [18]. Another controlled study showed that a combination of sildenafil and lidocaine-prilocaine cream is superior to placebo, and either as monotherapy, in the treatment of premature ejaculation [19]. A recently developed lidocaine/prilocaine-containing spray (topical eutectic mixture for premature ejaculation; TEMPE Plethora Solutions Ltd, London, UK) has been shown to increase IELT 6.3-fold and improved patient-reported outcome measures of control and sexual satisfaction [20]. Another topical anesthetic agent developed for premature ejaculation is SS-cream, which is made from the extracts of nine herbs [21]. A well-controlled study showed that SS-cream increased IELT from 1.37 to 10.92 minutes and 82% of patients reported improved sexual satisfaction [22]. Frequently reported side effects include penile hypoanesthesia and transfer to the partner, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used [23].

Selective serotonin reuptake inhibitors

Disregulation in central serotonergic neurotransmission is hypothesized as one of the etiologic factors underlying premature ejaculation [24,25]. Serotonin is the most important neurotransmitter in the control of ejaculation and its impact on ejaculation has been demonstrated in animal and human models [26-28]. The introduction of tricyclic antidepressants and SSRIs for the treatment of premature ejaculation has revolutionized our understanding of this problem and completely altered its management. These drugs block the axonal re-uptake of serotonin from the synaptic cleft and increase 5-HT neurotransmission through enhanced stimulation of post-synaptic membrane 5-HT receptors. Today, most premature ejaculation patients are treated either with on-demand SSRIs (dapoxetine) or with daily dosing of paroxetine, clomipramine, sertraline, fluoxetine or citalopram [25,29-38] (Table 1).

Daily treatment with paroxetine 10-40 mg, clomipramine 12.5-50 mg, sertraline 50-200 mg, fluoxetine 20-40 mg, and citalopram 20-40 mg is usually effective in delaying ejaculation [29-31,34,37,39]. Among these agents, paroxetine seems to exert the most pronounced delay in ejaculation, increasing IELT approximately 8.8-fold over baseline [40]. Improvement in IELT may occur within 5-10 days of starting treatment, but a minimum of 2-3 weeks is necessary to observe the maximal therapeutic effect [41]. Reported side effects are usually minor, may start within the first week of treatment and may gradually disappear within 2-3 weeks [42]. These side effects include fatigue, yawning, mild nausea, diarrhea, insomnia, and constipation [42]. Hypoactive desire and erectile dysfunction are also reported [43]. Of note, SSRIs must be used with caution in premature ejaculation patients who desire fertility, as these drugs are associated with impaired sperm parameters [44-46].

Premature ejaculation patients may not adhere to SSRI treatment. Salonia *et al.* [47] reported that 30% of patients refused to begin treatment (paroxetine, 10 mg daily for 21 days followed by 20 mg as needed) and another 30% of those that began treatment discontinued it. Reasons given for discontinuing treatment included not wanting to take an antidepressant, treatment effects below expectations, temporary loss of interest in sex because of relationship issues and side effects [47].

Dapoxetine is a rapid acting SSRI with a short half-life that was the first approved oral medication for the treatment of premature ejaculation. Its pharmacokinetic profile enables its on-demand use [32,33,35,48,49]. In several well-controlled studies, dapoxetine 30 mg or 60 mg (taken 1-2 hours before intercourse) is shown to increase IELT 2.5- and 3.0-fold and improve the patient-reported outcome measures [35,50,51]. Treatment related side effects were uncommon, dose dependent and included nausea, diarrhea, headache, and dizziness [35,49]. It should be remembered that many men with premature ejaculation may prefer the convenience

Table 1: Medical treatment options for premature ejaculation [58]

Therapy type	Drug	Trade name	Dose	IELT fold increase
Topical therapy	Lidocaine/prilocaine cream [29]	EMLA® cream	25 mg/gm lidocaine, 25 mg/gm prilocaine	4-6
Oral therapy	Dapoxetine [35,49,31,39]	Priligy®	30-60 mg on demand	2.5-3
Oral therapy	Clomipramine [30,34,38]	Anafranil®	12.5-50 mg/day or	6
			12.5-50 mg on demand	4
Oral therapy	Fluoxetine [56,64,23,66–68]	Prozac®, Sarafem®	20-40 mg/day	5
Oral therapy	Paroxetine [36–38,60]	Paxil®, Seroxat®	10-40 mg/day or	8
			10-40 mg/day on demand	1.4
Oral therapy	Sertraline [59,64,61-66]	Zoloft®	50-200 mg/day	5
Oral therapy	Citalopram [67–68]	Celexa®, Cipramil®	20-40 mg/day	2
Oral therapy	Tramadol [69]	Zertane®	62 mg ODT on demand or 89 mg ODT on	2.4
			demand	2.5

of daily treatment which does not interfere with the spontaneity of having sex [52]. Similar to daily SSRI treatment, 20% of premature ejaculation patients do not start on-demand dapoxetine, mostly because of the fear of using a "drug" and the cost of the treatment [53]. Of the patients who initiated dapoxetine treatment, 90% discontinued this treatment within 1 year. The main reasons were effect below expectations (24.4%), costs (22.1%), side effects (19.8%), loss of interest in sex (19.8%), and no efficacy (13.9%) [53].

Using antidepressants is not without risks. Although risk of suicidal ideation among young adolescents with depressive and/or anxiety disorders slightly increases with SSRI treatment [54], such a risk was not detected in SSRI studies on adult men with premature ejaculation [35,36-38]. However, physicians must be aware of this risk while prescribing antidepressants to patients with premature ejaculation.

Tramadol

Tramadol is a centrally acting opioid analgesic and several studies have demonstrated that it may increase IELT when administered daily or on-demand [57]. Several well-controlled clinical studies confirmed that 25-100 mg tramadol treatment results in a 2.4-12.6-fold increase in IELT from baseline [58-60,64]. Although tramadol may be considered an effective option for the treatment of premature ejaculation, the risk of addiction and its side effects limit its wide-spread use. Somnolence, pruritus, dizziness, dryness of mouth, nausea and vomiting are frequently seen undesirable effects with the use of tramadol, the severity of which were dose-dependent [60]. More importantly, combining tramadol with an SSRI may result in potentially fatal serotonin syndrome, thus this medication should only be used with caution in selected patients [61].

Phosphodiesterase type 5 inhibitors

Although the efficacy of phosphodiesterase type 5 inhibitors in treating premature ejaculation has been studied by several authors [62-65], they also have a limited role in the management of premature ejaculation in men who have co-morbid erectile dysfunction [66-67]. Men who have conditioned themselves to ejaculate rapidly because of a softening erection may experience improvements in their premature ejaculation under phosphodiesterase type 5 inhibitor treatment.

Other drugs and treatments

Dopamine and oxytocin appear to have a stimulatory effect on ejaculation [68-69]. When administered into the cerebral ventricles of male rats, oxytocin has been demonstrated to shorten ejaculation latency and post-ejaculatory refractory period [70]. Similarly, systemic oxytocin administration has been demonstrated to shorten ejaculation latency and post-ejaculatory interval in sexually active male rats [71]. In an attempt to understand the potential role for anti-oxytocin drugs in the treatment of premature ejaculation, several studies have demonstrated that central administration of selective oxytocin-receptor antagonists inhibit sexual behavior, including ejaculation, in male rats [72,73]. A recent study demonstrated that a highly selective, non-peptide oxytocin antagonist may inhibit ejaculation when administered both peripherally and centrally [68], which may be a promising alternative for the treatment of premature ejaculation. However, future well-designed human trials are necessary to confirm that oxytocin receptors are future targets for pharmacotherapy of premature ejaculation.

Various treatment alternatives have been introduced for treating premature ejaculation. In a randomized placebo-controlled trial, acupuncture therapy has been demonstrated to be effective in delaying ejaculation, compared to placebo [74]. However, the authors also noted that acupuncture was less effective than daily paroxetine treatment.

Several other authors investigated the impact of ablation and modulation of the dorsal penile nerve [75,76]. Prologo *et al.* [75] demonstrated that unilateral CT-guided

percutaneous cryoablation of the dorsal penile nerve resulted in a significant increase in IELT and improved patient-reported outcome measures as well. Recently, Basal *et al.* [76] assessed the role of percutaneous pulsed radiofrequency ablation of bilateral dorsal penile nerves in the treatment of premature ejaculation. Similarly, they noted mean IELT was significantly increased among men with lifelong premature ejaculation. In spite of these promising results, the invasive and irreversible nature of these procedures must be considered before recommending these modalities to premature ejaculation patients, and further clinical trials are required to assess their safety and long term efficacy.

Conclusion

Topical anesthetic creams and daily or on-demand SSRI treatment form the basis of pharmacotherapy for premature ejaculation today, in spite of low adherence by patients. Psychotherapy may improve the outcomes when it is combined with these treatment modalities. Tramadol and phosphodiesterase type 5 inhibitors have limited roles in the management of premature ejaculation. Further research is required to develop better options for the treatment of this disorder.

Abbreviations

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; IELT, intravaginal ejaculatory latency time; SSRI, selective serotonin reuptake inhibitor.

Disclosures

Ege Can Şerefoğlu is serving as a consultant for Allergan Company.

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