

Premature ejaculation: do we have effective therapy?

Ege Can Serefoglu^{1,2}, Theodore R. Saitz¹, Landon Trost¹, Wayne J.G. Hellstrom¹

¹Tulane University, School of Medicine, Department of Urology, New Orleans, LA, USA; ²Medicana International Hospital, Ankara, Turkey

Corresponding to: Wayne J.G. Hellstrom, MD, FACS. Tulane University School of Medicine, Department of Urology, 1430 Tulane Ave. SL-42, New Orleans, LA 70112, USA. Email: whellst@tulane.edu.

Introduction: Premature ejaculation (PE) is the most common sexual dysfunction, with the majority of PE patients remaining undiagnosed and undertreated. Despite its prevalence, there is a current paucity of data regarding available treatment options and mechanisms. The objective of the current investigation is to review and summarize pertinent literature on therapeutic options for the treatment of PE, including behavioral/psychologic, oral pharmacotherapy, and surgery.

Methods: A pubmed search was conducted on articles reporting data on available treatment options for PE. Articles describing potential mechanisms of action were additionally included for review. Preference was given towards randomized, controlled trials, when available.

Results: PE remains an underdiagnosed and undertreated disease process, with limited data available regarding potential underlying mechanisms and long-term outcomes of treatment options. Psychological/behavioral therapies, including the stop-start, squeeze, and pelvic floor rehabilitation techniques have demonstrated improvements in short-term series, with decreased efficacy with additional follow-up. Topical therapies, which are commonly utilized result in prolonged intravaginal ejaculatory latency time (IELT) at the expense of potential penile/vaginal Hypothesia. Oral therapies similarly demonstrate improved IELTs with variable side effect profiles and include selective serotonin reuptake inhibitors (daily or on demand), phosphodiesterase-5 inhibitors, alpha-1 adrenergic antagonists, and tramadol. Alternative therapies such as acupuncture have shown benefits in limited studies. Surgery is not commonly performed and is not recommended by available guidelines.

Conclusions: PE is a common condition, with limited data available regarding its underlying pathophysiology and treatment. Available therapies include topical, oral, behavioral/psychologic modification, or a combination thereof. Additional research is required to assess the optimal treatment strategies and algorithms as well as to better define the mechanisms for PE and its management.

Key Words: Premature ejaculation; sexual dysfunction; treatment



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Introduction

Ejaculatory dysfunction (EjD), erectile dysfunction (ED) and premature ejaculation (PE) are the three main subtypes of male sexual dysfunction (1). It has been more than a century since the initial report regarding PE was published (2), but the definition, classification, prevalence and effective treatment options for PE are still under debate (3). Although PE is classically accepted to be the most common sexual dysfunction (4-8), the number of PE patients who

seek treatment for this condition is low (8,9). Hence, almost 75% of urologists in the U.S. reported seeing less than one PE patient per week (10), and 41.4% of European urology residents denied treating any PE patients (11). Lack of exposure to patients with PE during urology residency training results in a lack of knowledge regarding the principal clinical guidelines for the treatment of PE (11). This highlights a need for increased awareness and education of available, effective management options.

Table 1 Medical therapy options for the treatment of premature ejaculation

Oral therapies	Trade names	Recommended dose
<i>Nonselective serotonin reuptake inhibitor</i>		
Clomipramine	Anafranil®	25 to 50 mg/day or 25 mg, 4 to 24 hrs pre-intercourse
<i>Selective serotonin reuptake inhibitors</i>		
Fluoxetine	Prozac®, Sarafem®	5 to 20 mg/day
Paroxetine	Paxil®	10, 20, 40 mg/day or 20 mg, 3 to 4 hrs pre-intercourse
Sertraline	Zoloft®	25 to 200 mg/day or 50 mg, 4 to 8 hrs pre-intercourse
Citalopram	Celexa®, Cipramil®	20 to 40 mg/day
Dapoxetine	Priligy®	30 to 60 mg, 1 to 3 hrs pre-intercourse
<i>Topical therapies</i>		
Lidocaine/prilocaine cream	EMLA® cream	Lidocaine 2.5%/ prilocaine 2.5%, 20 to 30 minutes pre-intercourse

Historically, treatments for PE were limited to psychological and behavioral therapies; however, more recent reports include pharmacotherapy as a common first-line treatment (*Table 1*) (10). To date, the U.S. Food and Drug Administration (FDA) has not approved any medications for the primary treatment of PE. As such, any medical treatments are currently administered off-label, and patients must therefore be counseled as to the risks and benefits of therapy. Treatments must additionally be individualized according to the type of PE complaint, as well as patient and partner preferences (*Figure 1*).

Psychological/behavioral strategies

Although effective pharmacologic treatments have reduced the popularity of traditional, psychological/behavioral therapies, these methods remain a mainstay treatment in patients with natural, variable PE and premature-like EjD (9,12). In addition, providing basic psychosexual education and therapy to all patients seeking treatment for PE may be of benefit, as PE results in reduced sexual satisfaction and function along with increased levels of personal distress and interpersonal difficulty (13).

Although pharmacotherapy is superior in reducing PE symptoms when compared to psychological treatment alone, behavioral and psychologic therapies offer potential advantages including minimal side effects and ability to improve couples' sexual communication. These therapies may also be used alone or in combination with pharmacotherapy among patients with lifelong and acquired PE (14-16). On the other hand, psychotherapeutic approaches are time-consuming, costly (17,18), and are of

variable efficacy (19). Because of a paucity of well-controlled studies and well-defined treatment protocols there is an overall lack of evidence suggesting beneficial effects of psychotherapy on PE (20,21).

Commonly utilized behavioral methods include the 'stop-start' technique, first developed by Semans (22) and its modification, the 'squeeze' method, proposed by Masters and Johnson (23). These methods inhibit the urge to ejaculate by attenuating sexual stimulus. Masturbation prior to sexual intercourse is widely used by younger men and it has similar efficacy to the 'start-stop' technique (24-26). Another related therapy is pelvic floor rehabilitation exercises, with a recent small, randomized prospective study reporting similar efficacy to on demand dapoxetine in the treatment of lifelong PE (27,28). Overall, behavioral therapies result in success rates of 50-60% in the short term, with significantly reduced efficacy with additional follow-up (17,18). However, the combination of behavioral and pharmacotherapy may result in synergistic improvements, with additional studies required to further elucidate potential beneficial effects (29).

Pharmacotherapy

Topical agents

Topical anesthetic compounds were the first medical treatment proposed for PE (30). Lidocaine-prilocaine creams decrease the sensation of the penis and significantly increase intravaginal ejaculatory latency time (IELT) when applied 10 to 20 minutes prior to sexual activity (31-33). This benefit is further enhanced when lidocaine-prilocaine cream is combined with sildenafil (34). A topical lidocaine-

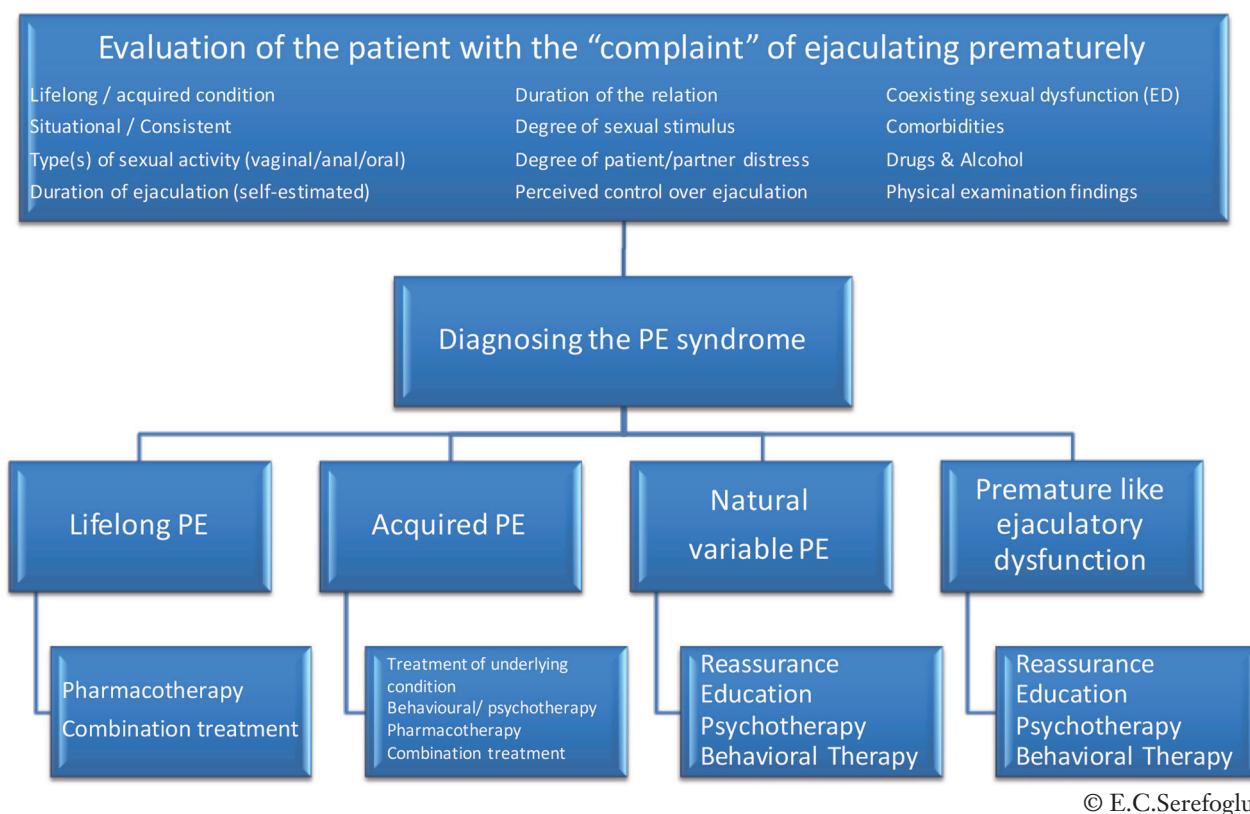


Figure 1 Algorithm for the management of premature ejaculation

prilocaine-containing spray has recently been developed (topical eutectic mixture for premature ejaculation; TEMPE Plethora Solutions Ltd, London, UK), with initial results demonstrating a 6.3-fold increase of IELT and an associated improvement in patient reported outcome (PRO) measures of control and sexual satisfaction (35). As the topical aerosol has minimal local and negligible systemic side effects, it will likely receive appropriate regulatory approval for the treatment of PE in the near future (36). Another topical anesthetic agent available in Korea is SS-cream, a solution that is made from the extracts of nine different herbs (37). In a double-blind, randomized, placebo-controlled study, 82% of patients reported improved sexual satisfaction with mean IELT increase from 1.37 to 10.92 min (38).

Side effects of topical agents include penile hypoesthesia, transvaginal absorption resulting in vaginal numbness, penile/vaginal dermatitis, and difficulties in product application (33,39). However, given the overall efficacy and limited side effects, current PE guidelines recommend topical therapy as a viable treatment option for the management of PE (14,40).

Oral therapies

The quest of finding an oral treatment for PE dates back to 1943 (30). Initial agents to prolong coitus were alpha amino benzoate and phenoxybenzamine, both of which were associated with severe side effects (41-44). Tricyclic antidepressants and ultimately selective serotonin reuptake inhibitors (SSRIs) were subsequently utilized, due to their sustained efficacy on ejaculatory latency and tolerable side effect profile (45-50). The mechanism for delayed ejaculation with SSRIs likely relates to the inhibition of multiple descending pathways associated with the ejaculatory reflex (51). This is supported by studies demonstrating significant variations in cortical serotonergic function between patients with PE and normal volunteers (52).

SSRIs interact with the 5-HT_{2C} receptor causing a delay in ejaculation (53,54). Results may become evident within a few days of treatment onset; however, maximal improvements are usually not evident until 2 to 3 weeks of treatment (55-58). The therapeutic efficacy of daily SSRIs on PE are supported

by multiple, double-blind, placebo-controlled trials (59). Thus, guidelines for lifelong PE often recommend oral SSRIs as first line medical therapy (14,39). Among the available SSRIs, paroxetine has demonstrated greater benefits in regards to efficacy and side effects when compared to fluoxetine, clomipramine and sertraline (60,61).

In addition to known systemic effects, SSRIs are associated with sexual side effects including decreased fertility and ED. Chronic SSRI treatment has a detrimental effect on spermatogenesis, impairs sperm transport, damages the sperm cell membrane, alters sperm DNA and has various effects on hormonal homeostasis (62-66). Given these findings, patients desiring preserved fertility should be considered for alternative therapies to prevent potential impaired spermatogenesis (62-66).

A number of animal studies have demonstrated that SSRIs may not only affect fertility, but also impair erectile function. Angulo *et al.* (67) hypothesize that decreased erectile function with paroxetine is secondary to reduced nitric oxide (NO) production and neuronal nitric oxide synthase (nNOS) expression. Kadioglu *et al.* suggested that sertraline and fluoxetine result in dysregulation of various relaxing factors, most conceivably NO, while paroxetine contributes to erectile dysfunction via different NOS inhibitory activity (68). Unwanted sexual side effects, such as decreased libido, anorgasmia, and erectile dysfunction are limitations associated with serotonergic antidepressants, which may persist beyond cessation of SSRI treatment (69,70).

Dapoxetine is a more recently developed SSRI that is quickly absorbed and rapidly cleared from the body (71). In contrast to other SSRIs, it may be used in an on-demand fashion, given its rapid onset of action. Recent trials with dapoxetine have demonstrated an increase in IELT by a factor of 2.5 to 3 over baseline (36). A recent analysis of five phase III trials of dapoxetine demonstrated that at 12 weeks of treatment the average IELT increased from a baseline of 0.9 to 3.1 minutes with 30 mg dapoxetine and to 3.6 minutes with 60 mg versus an increase to 1.9 minutes with placebo (72,73). Men with lifelong and acquired PE have reported efficacy with dapoxetine (74). Dapoxetine has not been reported to have any drug-drug interactions, including with PDE-5 inhibitors (75); however, dapoxetine has been rarely associated with vasovagal-mediated syncope (76). Although on-demand treatment provides a convenient therapy, a study performed by Waldinger and Schweitzer among lifelong PE patients demonstrated preference for daily over on-demand therapy, as this guaranteed no interference with the spontaneity of sexual activity (77). The

data published on dapoxetine remains a hot topic, given the dynamic nature of the PE drug research field (78).

Another potential treatment option for PE is PDE-5 inhibitors. In one randomized, double-blind, placebo-controlled study involving sildenafil in men with PE, there was no significant change in IELT, however, there was evidence of increased confidence, perception of ejaculatory control, overall sexual satisfaction, and decreased refractory time to achieve a second erection after ejaculation (79). Another randomized, double-blind, placebo-controlled study with sildenafil found the efficacy similar to that of placebo (34). In contrast, other randomized, double-blind, parallel group studies with sildenafil showed significantly improved IELT and satisfaction, with reduced overall anxiety compared to several SSRIs and behavioral therapy (80,81).

Available data on alternative PDE-5 inhibitors, tadalafil and vardenafil, is currently limited (80,81). One report found that vardenafil significantly increased median ejaculatory latency time duration during vibratory stimulation compared to placebo, while both sildenafil and tadalafil showed no significant change (82). In men who have acquired PE with comorbid ED, a PDE-5 inhibitor alone or in combination with a SSRI may provide benefit (83). PDE-5 as monotherapy or as a component of a combination regimen was similarly supported by another recent meta-analysis, that showed an overall positive effect with use in the treatment of PE (84). The use of PDE-5 inhibitors for the treatment of PE will likely continue to increase, as the association between NO and PE is further clarified (85).

Another novel approach postulated to decrease PE is the use of alpha-1 adrenergic antagonists, such as terazosin and alfuzosin (86,87). A recent small study including eight patients who were given alpha-1 adrenergic antagonist monotherapy for PE found that IELT was significantly prolonged from 3.4 to 10.1 minutes ($P=0.003$). All patients felt their PE problem was better controlled when compared with their pretreatment condition (88). These results support further randomized controlled trials to uncover the true efficacy of alpha-1 adrenergic antagonists in PE management.

Opioid analgesics, most specifically tramadol, have proven to be effective for on-demand treatment of PE in several placebo-controlled studies. In two trials, tramadol 50 mg increased IELT, measures of sexual satisfaction, and the sense of ejaculatory control (89,90). Another trial administering 25 mg of tramadol, as needed, increased IELT from a baseline of 1.17 to 7.37 minutes after treatment (90). A subsequent single-blinded, randomized,

controlled trial of 60 patients further confirmed the efficacy of on-demand tramadol (91). Most recently, a multicenter double-blind, placebo-controlled trial of tramadol 62 mg orally disintegrating tablet (ODT) preparation involving 600 patients from 62 sites across 11 countries found significant improvement in IELT, with minimal adverse effects or tolerability issues reported (92). In a subgroup of over 300 men with a baseline IELT <1 minute, results were even more pronounced, with a 2.4-fold increase in IELT observed with 62 mg tramadol ODT (92). Inversely, patients complaining of delayed ejaculation who subsequently discontinue tramadol therapy have reported improvements in sexual function, although the underlying mechanism is not completely understood (93). Given potential long-term effects of tramadol therapy, further studies are needed to determine the risk of drug dependence and potential interactions with combined therapies, including PDE-5 inhibitors (94).

Several less conventional methods have been investigated for the treatment of PE. Sunay *et al.* demonstrated that acupuncture had a significant effect in delaying ejaculation when compared to placebo, although results were inferior to daily paroxetine (95). Additional studies further support the role of acupuncture in the management of PE (96).

Miscellaneous treatments

Surgical therapy is an additional option described for the management of select, refractory cases of PE. Surgically induced penile hypoanesthesia via selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation has been reported by several authors for the treatment of lifelong PE, which is otherwise unresponsive to behavioral and pharmacological treatment (97,98). In one recently published study, surgical foreskin remnant removal resulted in significant increases in IELT, from a baseline of 64.25 seconds before surgery to 731.49 seconds following (99). Further studies are required to better understand the role of surgical management of PE, although most authorities indicate that surgical management is not indicated and should be avoided (14).

As the underlying etiology for PE is frequently multifactorial, management of PE patients can be complex and may require a combination of treatment modalities (100). The physician must consider the severity of symptoms and potential side effects of various therapies when deciding on how to treat a PE patient. A combination of pharmacological, psychological, and behavioral approaches for the man with PE should be

utilized in clinical practice, and when possible, the partner should be included in management (101). Successful treatment of PE patients requires ongoing follow-up to help monitor for improvement and ensure optimal treatment outcomes (102). An all-encompassing and more structured diagnostic approach to PE will help clinicians develop a greater understanding of PE and lead to better treatment outcomes in the future (103).

Conclusions

Data from recent studies has improved understanding of the underlying mechanism for PE and provided evidence-based management options. Further investigations with randomized-controlled trials, using a consistent definition of PE are needed. Currently, clinicians need to consider all treatment modalities when evaluating a man with PE, as each patient may respond differently and experience variable side effects. As our understanding of the mechanism of PE increases, additional and more effective therapies will continue to be developed.

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