REVIEW

CURRENT STATUS AND FUTURE PERSPECTIVES IN THE MANAGEMENT OF PREMATURE EJACULATION – A REVIEW OF THE LITERATURE

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Abstract

Today, new data are emerging regarding the etiology of premature ejaculation (PE), generating also new therapeutic alternatives. Behavioral therapy and sexual counseling, application of topical agents, selective serotonin reuptake inhibitors, tricyclic antidepressants, tramadol, phosphodiesterase type 5 inhibitors, alpha-blockers, oxytocin antagonists or interventional treatment (circumcision, frenulotomy, selective resection of dorsal penile nerves, penile hyaluronic acid injections) are among the therapeutic options proposed and applied for this dysfunction. Some of these alternatives are "off-label" or even still experimental.

Rezumat

Datele noi privind etiologia ejaculării precoce au generat noi alternative terapeutice. Dintre opţiunile terapeutice propuse şi aplicate pentru tratarea acestei disfuncţii, pot fi enumerate: terapie comportamentală şi consiliere sexuală; aplicarea de agenţi topici, administrarea de inhibitori selectivi ai recaptării serotoninei, antidepresive triciclice, tramadol, inhibitori ai fosfodiesterazei de tip 5, alfa-blocante, antagonişti ai oxitocinei; sau tratamentul intervenţional (circumcizia, frenulotomia, rezecţia selectivă a nervilor dorsali ai penisului, injectarea de preparate cu acid hialuronic în penis). Unele dintre aceste alternative sunt "*off-label*", sau în stadiu experimental.

Keywords: premature ejaculation (PE), selective serotonin reuptake inhibitors, tricyclic antidepressants, tramadol, phosphodiesterase type 5 inhibitors, alpha-blockers, oxytocin antagonists, surgery treatment, "off-label", sexual dysfunction

Introduction

Premature ejaculation (PE) is one of the most frequently encountered sexual disorders. Despite its frequency, it still doesn't have a universally accepted definition which translates into heterogeneous data regarding many aspects such as epidemiology, efficacy of various treatments etc. This lack of standardization is generated by the complexity of the subject; various issues related to sexual intercourse and ejaculation such as duration, control, and satisfaction being subjective parameters and was adopted by the International Society for Sexual Medicine (ISSM) [1].
Various treatment alternatives were proposed over the time. Potential targets in the management of PE may be serotonin (5-HT) transporters, receptors for 5-HT(IA) or 5-HT(1B), dopamine, oxytocin, opioids, neurokinin-1, and glutamate in the central nervous system and α(1)-adrenoceptors, phosphodiestrase enzymes, Rho-kinases, purinergic (P2X) receptors, and penile sensory nerves in periphery [2]. Although some of them already confirmed their value, for the others, the evaluation of their therapeutic potential still requires further basic and clinical research.

Behavioural therapy and sexual counselling

Sexual counselling aims to increase awareness of the psychological difficulties that may contribute to

the dysfunction and/or to solve problems in the relationship that may have added to its cause. It may be used alone or associated with behavioural or medical therapy. Behavioural therapy consists in various exercises such as "squeeze technique" proposed by Masters and Johnson in 1970 [3] or Semans' "start-stop method" [4], aiming to help developing tolerance to stimulation and prolonging the intravaginal ejaculatory latency time (IELT).

However, their efficacy in correcting this dysfunction is a subject of debate. Some of the authors reported favourable effects of both methods [5], while others observed no such benefits. A Cochrane Database review by Melnik *et al.* concluded that demonstration of psychological interventions' effectiveness in the treatment of PE is "weak and inconstant". Therefore, the initial success reported by Masters and Johnson couldn't be replicated [6].

A significant proportion of PE men use masturbation before intercourse, together with special positions during sex, interrupted stimulation or having more often intercourse as strategies to manage their dysfunction [7]. The effects consist in desensitizing the penis before the anticipated intercourse and also in learning how to predict arousal evolution and to increase control in a manner similar to the "start-stop" method [5].

However, the masturbation patterns may influence the outcomes, a rapid achievement of orgasm having the opposite effect, as a training to ejaculate very quickly and thus leading to PE aggravation.

Topical agents

The application of topical agents is one of the oldest PE treatment alternative, based on the hypothesis that this dysfunction is secondary to a penile hypersensitivity [8].

It usually involves the application of prilocaine-lidocaine cream or aerosols, all demonstrating optimistic results [9, 10]. A recent meta-analysis which included eight trials assessing their efficacy and safety demonstrated that IELT in the topical anaesthetic agent group was significantly improved by comparison to *placebo* and also significant ameliorations were identified in ejaculatory control, sexual satisfaction and distress [11].

Prolonged application may lead to numbness of the penis and consequently loss of erection. Also, they may generate vaginal wall numbness, thus requiring the use of a condom. Due to their good risk/benefits ratio, topical agents may be considered a useful first-line therapy in PE therapy.

"Off-label" Selective Serotonin Reuptake Inhibitors (SSRI)

Delayed ejaculation was a commonly reported "adverse effect" after SSRIs treatment. In a study evaluating the potential morbidity in men without previous sexual dysfunction, some of the patients in which these effects appeared preferred to maintain the delayed ejaculation, as the couple's sexual satisfaction clearly improved [12].

These observations led not only to the off-label use of SSRIs in PE treatment but it also changed the way PE was understood [13]. Although its' pathophysiology is not entirely clear, evidence indicates that serotonin or 5-Hydroxytryptamine (5-HT) exerts an inhibitory role on ejaculation [14]. PE seems a consequence of disturbances of serotonergic neurotransmission and, apparently, oxytocinergic neurotransmission [15].

The known serotonin receptors are 5-HT1A, whose stimulation precipitates ejaculation and 5-HT1B and 5-HT2C with ejaculation-retarding effects at activation [16].

Effects on ejaculation may begin a few days after drug intake, but usually require 1-2 weeks of administration to be effective, similar to their use for depression treatment [16, 17].

The first double-blind, randomized, *placebo*-controlled study comparing the effects on ejaculation of four SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) in PE patients was published by Waldinger *et al.* The study reported that the IELT improvement in the paroxetine, fluoxetine, and sertraline groups differed significantly from *placebo*, while fluvoxamine did not. The strongest delay was demonstrated by paroxetine, followed by fluoxetine and sertraline [18].

Despite their efficacy in treating PE, these agents may be associated with minor but bothersome side-effects such as fatigue, drowsiness, nausea, vomiting, diarrhoea etc. One major concern is the risk of suicidal ideation and suicidal attempts which imposes prudence and makes them not suitable for young patients (under 18 years of age) or men with associated depression [19]. Another problem is the SSRI discontinuation syndrome (or withdrawal syndrome), a flu-like reaction with various physical symptoms such as headache, gastrointestinal distress, faintness or strange sensations of vision/ touch, associated with abrupt treatment interruption [20].

Only a few studies evaluated the impact of SSRI on the semen quality. Safarinejad *et al.* reported that the use of such drugs in patients with depression may alter the morphology and motility parameters of semen and increase sperm DNA fragmentation, which might be associated with a reduced probability of pregnancy [21]. These findings were later confirmed by Tanrikut *et al.* in a study evaluating the administration of Paroxetine in healthy subjects [22]. Also, Akasheh and co-workers investigated the administration of Sertraline in PE cases and subsequently reported an additional decrease of sperm concentration [23]. These

findings may suggest that administration of these drugs in fertile and planning to conceive men should be performed with caution, however further studies including larger series being necessary.
Prescribing "off-label" treatments may prove difficult due to the restrictions to the physician by the regulatory authorities of different countries and also to the reticence of the patients to accept it.

Dapoxetine

Dapoxetine is the only drug approved for PE therapy by health authorities in European countries as well as in several other countries outside Europe (but not in the US).
It was specifically designed for PE treatment, being a short acting SSRI with rapid absorption following oral administration, peak plasma concentrations at approximately 1 hour and plasma concentrations' decrease to approximately 5% of peak concentrations at 24 hours after a single dose. These pharmaco-kinetic characteristics make it suitable for on-demand treatment of PE [24].
The therapeutic benefits are not only on the IELT, but also on the perceived control over ejaculation. An analysis which combined data from two identically designed, 12-week, double-blind, randomized, *placebo*-controlled trials including 2614 men reported a two-category or greater increase on a 5-point scale with Dapoxetine 30 and 60 mg in 36.3% and 44.5%, respectively by comparison to 15% with *placebo*. Among these men, improvements in IELT and reports of "good" or "very good" satisfaction with sexual intercourse were better than in those with less than a two-category increase in control [25].
Various studies demonstrated the safety of Dapoxetine therapy. In men from the Asia-Pacific area treated with this drug, the treatment-emergent adverse events were 1.7% and 5.1% for the 30 and 60 mg dose by comparison to 0.3% in the *placebo* arm [26]. The most common adverse events reported by McMahon *et al.* included nausea, dizziness and headache. However, the study showed no anxiety, akathisia, suicidal ideation or attempts or mood changes and no discontinuation syndrome following abrupt withdrawal [27].
Although the possible association between this treatment and vasovagal-mediated (neuro-cardiogenic) syncope was suspected [28], the observation was not confirmed by an observational 12-week study on 6712 patients [29]. Syncope and major cardio-vascular adverse events were not reported in the Dapoxetine group but one case of syncope occurred in the non-Dapoxetine group of 3316 men [29].
A one month study comparing 50 mg Paroxetine with 30 and 60 mg Dapoxetine reported similar effects of the first two, while the 60 mg dose demonstrated a larger post-treatment IELT increase [30].
Important issues to be discussed for this treatment category are constituted by the acceptance of treatment and discontinuation rates. Regarding Dapoxetine, Mondaini *et al.* published a study in 2013 reporting a non-acceptance treatment rate of 20%, half of which related to the fear of using a "drug" and a quarter due to treatment cost. Dropout rates were 27% at 1 month, 42.7% at 3 months, 18.7% at 6 months and 2% at 12 months. The main reasons of discontinuation at 6 months were represented by effect below expectations (24.4%), costs (22.1%), side effects (19.8%), loss of interest in sex (19.8%) and lack of efficacy (13.9%). Roughly 10% of the patients continued the treatment after 1 year [31]. By comparison to that, in Paroxetine treated men, the rate of treatment acceptance was only 69.9%, the main reason for refusal being the fear of using an antidepressant drug. The discontinuation rate at 6 months was 30.8%, the main reasons being effects below expectations (75%), loss of interest in sex (15%) and side effects (10%) [32].
Regarding the combined therapy, it becomes quite unanimously accepted that the phosphodiesterase type 5 (PDE5) inhibitors should be used before Dapoxetine (or other SSRIs) in PE patients with comorbid ED, associated with counselling which should be offered to all subjects with sexual dysfunctions [33].
In a prospective, randomized, double-blind, *placebo*-controlled, multi-centre trial which enrolled 118 subjects with lifelong PE without ED, treatment with Dapoxetine 30 mg plus Mirodenafil 50 mg demonstrated better results in terms of IELT, overall sexual act time and premature ejaculation profile (PEP) index score by comparison to Dapoxetine 30 mg alone, while the adverse effects were the same [34].
Recent studies suggested a relationship between a polymorphism in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and the response of patients with premature ejaculation to serotonin reuptake inhibitors. The presence of the short allele of 5-HTTLPR was significantly more frequent in responders, this constituting a premise for further studies in order to better understand these mechanisms [35].

Tricyclic antidepressants

Clomipramine was also used for PE treatment. A double-blind, randomized, four weeks cross-over study followed by drug administration for an additional 3 months evaluated the efficacy of daily Clomipramine. During the course of the double-blind period of the study, no difference was

reported compared to *placebo*. However, during the follow-up period, 45% of cases were found to have derived benefits from the combined treatment [36].
Other well-designed randomized, double-blind, fixed-dose studies reported a significant ejaculation delay in men treated on-demand with 25 mg Clomipramine [37].

Tramadol

Tramadol was initially developed in the 1970s and approved as an analgesic [38], its' mechanism of action consisting in opioid μ-receptor binding but also nor-epinephrine and serotonin reuptake inhibition. This was the argument supporting Tramadol as a potential treatment for PE. The first studies started to emerge in 2008 and emphasized promising results. Salem *et al.* found Tramadol to prolong IELT from 1.17 ± 0.39 minutes at baseline to 7.37 ± 2.53 minutes at the end of the study, significantly higher than the 2.01 ± 0.71 minutes recorded in the *placebo* group [39].
A meta-analysis published in 2013 found 5 randomized controlled trials (RCT) which involved 715 patients comparing Tramadol *versus placebo* or no treatment [40]. Analysed data revealed significantly improved IELT values, satisfaction with sexual intercourse and the ability to control ejaculation, but also the incidence of side effects (although mild or moderate and transient ones) in the study series compared to control.
When compared to SSRIs, Tramadol seems to have a weaker effect. Even more, Alghobary *et al.* reported an initial significant IELT increase after 6 weeks by 7-folds (by comparison to 11-folds in the Paroxetine group), followed by a decline of IELT to 5-folds after 12 weeks (by comparison to a further 22-folds improvement in the Paroxetine group). For this reason, the authors recommended to avoid using Tramadol as a long-term treatment for lifelong PE [41].
The main problems related to the use of this drug nowadays are the non-negligible addiction and abuse risk [40] and the potential alteration of daily activity due to somnolence, one of the most frequent side effects [39].
In order to minimize these potential effects, it was proposed the on-demand administration of Tramadol, which was reported as having a similar efficacy to the chronic intake [42, 43].
Short- and long-term efficacy, tolerability and all other controversies should be clarified by further well-designed studies. For now, Tramadol can be recommended only with prudence, in selected cases [44].

Phosphodiesterase type 5 (PDE5) Inhibitors

Although it is accepted that patients with erectile dysfunction (ED) associated with PE benefit from PDE5 inhibitors, it is still controversial if these drugs may also be used in cases of PE alone. The premise for using them was the hypothesis that the nitric oxide (NO) may have a role as a neurotransmitter in the central and peripheral control of ejaculation, theory which still waits clarification [45]. There are just a few well designed studies evaluating this matter.
The 8-week, double-blind, *placebo*-controlled, parallel group study of McMahon *et al.* found that, despite the lack of intravaginal ejaculatory latency time (IELT) and vibro-tactile stimulation ejaculatory latency time (VSELT) significant improvement, sildenafil increased "confidence, the perception of ejaculatory control, and overall sexual satisfaction, and decreased the refractory time to achieve a second erection after ejaculation", thus having a beneficial effect in these patients [46].
According to another 16-week, double-blind, *placebo*-controlled, cross-over study, Vardenafil significantly increased IELT in addition to the previously described effects [47]. Interestingly, a *placebo*-controlled double-blind study comparing 10 mg Vardenafil, 50 mg Sildenafil and 20 mg Tadalafil in PE therapy reported that all three prolonged VSELT. On the other hand, the statistical significance was solely achieved by Vardenafil [48].
A study evaluating the effects of Sildenafil combined with behavioral therapy showed better results in both prolonging IELT and increasing satisfaction by comparison to behavioral therapy alone [49].

Alpha-blockers

The use of these drugs in PE treatment is based on the fact that ejaculation is under sympathetic control. First data of such an application was published in 1984 by Homonnai, who described the effect of Phenoxibenzamine in blocking ejaculation after 2 to 3 days of administration and suggested its' use as a male contraceptive pill and as treatment in men complaining of premature ejaculation. The effect was fully reversible after cessation of treatment [50].
Since then, the use of various other alpha-blockers in PE therapy was studied: terazosin [51], terazosin *versus* alfuzosin [52], silodosin [53], alfuzosin, tamsulosin, terazosin and doxazosin [54]. Although these drugs seemed rather promising, the designs were disputable, some of them not employing IELT assessment or widely accepted PE questionnaires, others not being prospective and *placebo* controlled.
The study of Akin *et al.* comparing five alpha-blockers reported silodosin as the most effective in correcting PE [54].
Silodosin was also used by Sato *et al.* who also reported favourable effects and described anejaculation, reduced semen volume and discomfort during orgasm as the most frequent

side-effects, but stating that "these problems were not of major concern for the participants" [55]. However, the true impact of these effects are still controversial, other authors suggesting that semen passing through the urethra and contraction of the pelvic floor may contribute to the subjective pleasure of orgasm, which may be adversely affected by Silodosin [56]. Until further studies will clarify these issues, alpha-blockers may only be considered in selected patients.

Oxytocin antagonists

Some theories suggested that oxytocin may be actively involved in regulating ejaculation via peripheral, central and spinal mechanisms [57, 58]. Observations that oxytocin systemic administration in animal models reduces ejaculatory latency time [59] and reverses the inhibitory effects of SSRI [60] generated the hypothesis that oxytocin modulation may offer an alternative pharmacological solution in PE patients. However, the theory is debatable. Walch *et al.* didn't find significant effects on ejaculation time and seminal parameters after intranasal application of oxytocin in normal, healthy men [61]. A study by Shinghal *et al.* assessing the efficacy and safety of Epelsiban, an oral, selective oxytocin receptor antagonist, despite quite promising results in some of the subjects, reported no statistically significant improvements of IELT in men with PE, by comparison to *placebo* [62].
Centrally acting oxytocin antagonists remain possible study candidates for PE therapy.

Interventional treatment

Various surgical interventions such as circumcision, frenulotomy or penile neurotomy have been proposed for PE treatment.
Circumcision was advocated for a long time as a possible definitive surgical treatment for PE due to glans hypersensitivity. However, there are no consistent data sustaining this approach. Recent meta-analyses and systematic literature reviews did not prove a significant difference in PE prevalence in circumcised *versus* not-circumcised men [63, 64]. A study of Alp *et al.* reported a slight IELT increase after circumcision (increment of mean and median IELT of 19 and 19.5 seconds, respectively), however, not enough to be interpreted as a justification for circumcision in men with PE [65]. Even more, the vast majority of PE cases with no satisfactory response to the treatment with topical agents refused circumcision, mostly due to the absence of guarantees and the irreversibility of the procedure creating a permanent body alteration [66].
Frenulotomy is another such surgical procedure. Gallo *et al.* reported a short frenulum in 43% of the patients with lifelong PE, advancing the theory that such a genital anomaly may be involved in the generation of this dysfunction. During follow-up after frenulotomy, the authors reported an increase of mean IELT to 4.11 minutes from 1.65 minutes at baseline and a significant improvement of the PE questionnaire score [67]. The authors suggested that the presence of a short frenulum should be assessed in all patients complaining of PE and frenulotomy should be proposed as first-line treatment in these men.
Other experimental procedures were proposed as a potential surgical treatment of PE. Selective resection of dorsal penile nerves was proposed by Chinese authors. Three studies evaluating about 600 cases reported correction of the ejaculatory dysfunction and prolonged IELT in the majority of cases without alteration of the erectile function [68, 69, 70].
David Prologo *et al.* performed percutaneous CT-guided cryoablation of the dorsal penile nerve reporting significant improvements of IELT at 180 and 360 days [71].
PE blocking therapy by injecting hyaluronic acid (a penile augmentation injectable agent) into the glans penis, thus decreasing the accessibility of tactile stimuli to nerve receptors was initially proposed by Kim and Moon, alone or associated with dorsal-neurectomy [72], with promising results. Abdallah *et al.* used it more recently, reporting the same good functional outcomes [73].
However, all these techniques have a potential risk of permanent alteration of penile sensitivity, further strictly-designed prospective studies being necessary in order to confirm their safety and efficacy.

Treatment patterns

All the comorbidities that may have a role in generating PE (including ED) should be treated first.
The European Association of Urology (EAU) Guideline recommends that pharmacotherapy should constitute the first-line treatment of lifelong PE: Dapoxetine on-demand or other off-label SSRIs and clomipramine in a daily treatment. Topical anesthetic agents may be a viable first-line alternative while behavioral therapies should be used in combination with oral treatment [74].
A survey evaluating the PE management in daily urological practice in Korea reported that perceptional self-diagnosis by the patient himself was employed by 23.5% of the urologists as the diagnosis tool. Moreover, the SSRIs administration was the most frequent treatment in 91.5% of the patients. PDE 5 inhibitors were sometimes used by 40.2% of the urologists, behavioural therapy by 47.6%, topical anaesthetics by 53.7% and surgical modalities such as selective dorsal neurotomyby 54.3% [75].
An evaluation of the training quality of European residents in PE management emphasized that the

majority of respondents follow the established guidelines for PE diagnosis, but not for treatment. The preferred first-line therapy was behavioral in 46.4%, topical anesthetic in 24.3%, andrological referral in 13.6% and prescription of on-demand SSRIs in 12.9% of responders [76].

Treatment perspectives

Two recent studies by Kirecci *et al.* and another one by Otunctemur *et al.* emphasized that PE is associated with decreased plasma melatonin levels, decreased serum NO levels and higher level of seminal NO, all reversed during SSRI treatment in responders. This aspect suggests the serotoninergic interactions with the melatoninergic system and the role of NO in the pathophysiology of this dysfunction [77, 78, 79]. These features create the premises for further studies of the matter and new potential treatments.

Conclusions

Many therapeutic alternatives were proposed, however a significant proportion of them still requiring well-designed studies in order to be confirmed.

On-demand Dapoxetine is the only drug approved by authorities in PE treatment in Europe and several other non-European countries.

Unfortunately, the practice patterns in PE therapy are still influenced by the poor understanding of this dysfunction and false-concepts both in physicians and patients.

However, recent evaluations demonstrated that new data are disseminating, the understanding of PE constantly improving. New etiological theories and treatment pathways that may further change the paradigm of PE management are presently studied.

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