

The drug treatment of premature ejaculation

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Abstract: The management recommendation for both acquired premature ejaculation (APE) and lifelong PE (LPE) are similar, such as a behavioral/psychotherapy, a pharmacotherapy and a combination of these treatments. For the drug treatment for PE, gold standard is selective serotonin reuptake inhibitors (SSRIs) including dapoxetine or paroxetine. The drug treatment for PE is still developing and some new promising therapeutic options have been proposed. Topical anesthetics, tramadol, and alpha-1 blockers will be the next strategies of the drug treatment for PE in the future.

Keywords: Premature ejaculation (PE); drug; selective serotonin reuptake inhibitors (SSRIs); alpha-1 blocker

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Introduction

International society of sexual medicine (ISSM) published the guideline for premature ejaculation (PE) in 2010 and updated it on 2014. The managements recommended for both acquired PE (APE) and lifelong PE (LPE) are almost same, such as a behavioral/psychotherapy, a pharmacotherapy and combination of these treatments (1). For the pharmacotherapy for PE, gold standard is selective serotonin reuptake inhibitors (SSRIs) including dapoxetine or paroxetine. For some patients, topical therapy with local anesthetics including Lidocaine/Prilocaine might be effective (1).

Off-label SSRIs and tricyclic antidepressants (TCAs)

There is a high level evidence to support the efficacy and safety of off-label daily dosing of the SSRIs and a serotonergic TCA: paroxetine (2), sertraline (3), citalopram (4), fluoxetine (5), and a serotonergic tricyclic, clomipramine (6,7). And as the off-label on-demand dosing, clomipramine (8) and paroxetine (2) are used for the treatment of LPE and APE. A meta-analysis showed that paroxetine was the strongest among several SSRIs in delaying ejaculation, showing 1,492% IELT increase from baseline (9). Delaying ejaculation

effect appears from 5 to 10 days after drug administration; however, the maximum effect will take 2–3 weeks of treatment (10).

Adverse effects are mild and not long over two weeks, including mild nausea, diarrhea, fatigue, yawning, or perspiration (11). Systematic analysis of randomized clinical trials (RCT) of SSRIs in patients with depression suggests that youth but not adults have a small risk of suicidal ideation or suicide attempts (12,13). Physicians should be careful, when they prescribe SSRIs to young PE patients aged 18 years or younger and to those with PE and a suicidal ideation (14). Rapid dose reduction or sudden cessation of daily dosed SSRIs should be avoided, which may be associated with an SSRI withdrawal syndrome (15). As the other possible adverse effect, SSRI might affect sperm motility, therefore men who concern their fertility should not take SSRIs (16).

On-demand administration of off-label SSRIs 3–6 hours prior to intercourse is modestly efficacious and well tolerated (8). However On-demand usage of off-label SSRIs is associated with a less effectiveness in delaying ejaculation than daily treatment (2,8,17). Therefore, on-demand off-label SSRIs may be combined with low-dose daily treatment (2). So far, on-demand dosing of dapoxetine seems to be effective and safe; however in unavailable countries with dapoxetine, daily dose of off-label SSRIs (especially paroxetine) seems to be the most effective. In some countries, the government authorities

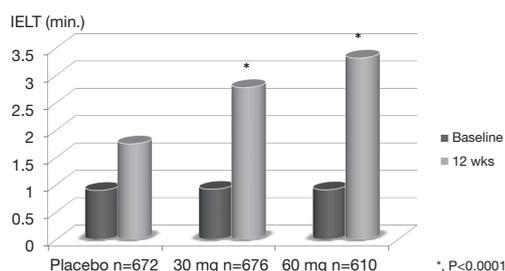


Figure 1 IELT with on-demand dosing of dapoxetine (18). IELT, intravaginal ejaculatory latency time.

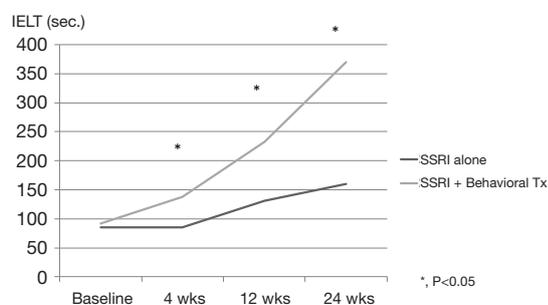


Figure 2 The combination of dapoxetine and behavioral treatment provides better results than dapoxetine alone (24). IELT, intravaginal ejaculatory latency time; SSRI, selective serotonin reuptake inhibitor.

might not allow the off-label prescription of SSRIs. This complicates PE treatment in countries where there is no approved medication and the regulatory authorities advise against off-label prescription.

Dapoxetine

Dapoxetine has been approved for treating PE in over 50 countries. It has a pharmacokinetic profile supporting a role as an on-demand treatment for PE, rapid-acting and short half-life (18-20). Pryor *et al.* reported the first RCT for dapoxetine (dapoxetine 30 or 60 mg taken 1-2 hours before intercourse) with placebo, which shows significant improvement in dapoxetine group and dose dependency (Figure 1) (18). Dapoxetine is similarly effective both in men with LPE and APE (20-22). Moreover, it is well tolerated in men with PE and comorbid erectile dysfunction (ED) treated with phosphodiesterase type 5 inhibitors (PDE5i) (23). Cormio *et al.* reported the importance of behavioral management as the combination with dapoxetine, which clearly showed significant improvement in the combination

with behavioral treatment group (Figure 2) (24). Adverse-events in on-demand usage of dapoxetine were uncommon, including dizziness, nausea, diarrhea, and headache (18,23). They led to the study discontinuation only in 4% (30 mg) and 10% (60 mg) of subjects.

Topical anesthetics

The use of topical anesthetics to reduce the sensitivity of the glans penis is probably the oldest known form of treating PE (1). There is a high evidence to support the efficacy and safety of off-label on-demand topical anesthetics in the treatment of LPE (1). The use of topical anesthetics such as lidocaine and/or prilocaine as a cream, a gel, or a spray is well established and is moderately effective in delaying ejaculation (25-28). Diminishing the glans sensitivity is thought to inhibit the spinal reflex arc responsible for ejaculation (29). Dinsmore *et al.* reported that PSD502, a lidocaine-prilocaine spray, which is applied to glans penis 5 minutes before sexual intercourse, showed a 6.3-fold increase in IELT (25). However, topical anesthetics are related with significant penile hypoanesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used (27).

PDE5i

PDE5is are effective treatments for ED, and some authors have suggested that PDE5is alone or in combination with SSRIs as a treatment for PE (30-33). Systematic reviews of multiple studies suggested the supportive role of PDE5i in men with PE and comorbid ED (34,35). The treatment of LPE with PDE5i in men with "normal" erectile function is not recommended and further evidence-based research is encouraged to understand conflicting data (11). Recently Sun *et al.* reported the meta-analysis of PDE5i for PE with concomitant ED, which showed a significant improvement with PDE5i alone compared with both of placebo and SSRI alone (36). It also suggested that the combination of PDE5i with SSRI showed a clear improvement compared with SSRI alone in PE with ED patients. However, PDE5i use showed the relatively significant increase of adverse event compared with placebo; moreover, combination with SSRI showed an increase of adverse event compared with SSRI alone (36).

Tramadol

Tramadol has been investigated as a potential off-label

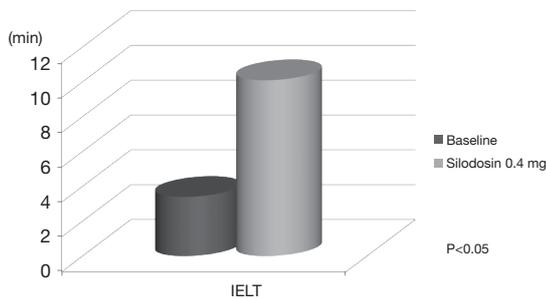


Figure 3 The efficacy of silodosin on acquired PE (48). PE, premature ejaculation; IELT, intravaginal ejaculatory latency time.

therapy for PE, with several studies demonstrating efficacy improving IELTs with varying doses of daily or on-demand tramadol therapy (11). Although the mechanism of action is not completely understood, the efficacy of tramadol may be secondary to anti-nociceptive and anesthetic-like effects, as well as via central nervous system modulation through inhibitions of serotonin and noradrenaline reuptake (37,38). Recent meta-analysis showed the efficacy of tramadol for PE, showing the significant improvement in several settings such as compared with placebo, paroxetine daily and on demand, PDE5i, topical anesthetics, and a behavioral management (39). Tramadol may be an effective option for the treatment of PE. However, the risk of addiction should be noted. It should not be combined with an SSRI because of the risk of serotonin syndrome, a potentially fatal outcome (40). Further well-controlled studies are required to assess the efficacy and safety of tramadol.

Alpha-1 adrenoceptor antagonist (alpha-1 blocker)

Recently Lee *et al.* reported that PE in Korean policemen is associated with ED and lower urinary tract symptoms (LUTS) including prostatic disease, which might be the important disease background for the PE (41). Alpha-1 adrenoceptor antagonist (alpha-1 blocker) is widely accepted as the first-line treatment for LUTS caused by benign prostatic hyperplasia. One of adverse events of alpha-1 blocker is ejaculatory disorder, and we previously demonstrated that alpha-1A blocker, tamsulosin, showed significant decrease of seminal emission compared with alpha-1A/D blocker, naftopidil (42).

For the treatment of PE, Beretta reported the first study with non-selective alpha-blocker, which showed that IELT in PE patients was significantly increased after

phenoxybenzamine administration (43). Selective alpha-1 blocker, terazosin, showed the significant improvement of PE compared with placebo, in the patients' reported outcome (44).

Hsieh *et al.* reported that alpha-1 blockers (phenoxybenzamine, prazosin, WB-4101, chloroethylclomidine and yohimbine) all inhibit the contractile response of the rat seminal vesicle to electrical nerve stimulation. As phenoxybenzamine is effective in treating PE, the comparable *in vivo* potencies of WB-4101 (alpha-1A blocker) and yohimbine (alpha-2 blocker) strongly suggest that they have clinical therapeutic potential for PE (45). In our study, although the volunteers with naftopidil (high affinity with alpha-1D as well as alpha-1A) showed no decrease of ejaculatory volume, those with tamsulosin (high affinity with alpha-1A) showed significant ejaculatory volume decrease (42). This study clearly showed that the mechanism of ejaculatory disorder induced by alpha-1 blocker is the relaxation of seminal tract including seminal vesicle and ejaculatory through subtype A of alpha-1 adrenoceptor. Therefore, subtype A of alpha-1 adrenoceptor plays an important role in an ejaculatory event evoked by sympathetic nerve stimulation. Another recent publication also showed the efficacy of tamsulosin for PE in the patients with LUTS and PE (46).

Silodosin is a new alpha-1 blocker that has more powerful affinity with the alpha-1A adrenoceptor. In another study, we demonstrated that silodosin showed a surprising reduction of ejaculatory volume to 0ml, a complete dry ejaculation (47). Sato *et al.* reported an interesting study suggesting that silodosin prolonged IELT with 3-fold longer than baseline in APE patients, although it is a preliminary outcome in small number of patients (n=8) (Figure 3) (48).

Conclusions

The drug treatment for PE is still developing and some new promising therapeutic options have been proposed. Tramadol maybe stronger than SSRIs; however, it has a problem in the safety issue including addiction, which preventing this as the first-line treatment. Super selective alpha-1A blocker might be the next therapeutic strategy, although it leads to the dry-ejaculation. The large-scale RCT will be needed for these new options.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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