Review Article

Emerging and investigational drugs for premature ejaculation

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Abstract: Over the past 20–30 years, the premature ejaculation (PE) treatment paradigm, previously limited to behavioural psychotherapy, has expanded to include drug treatment. Pharmacotherapy for PE predominantly targets the multiple neurotransmitters and receptors involved in the control of ejaculation which include serotonin, dopamine, oxytocin, norepinephrine, gamma amino-butyric acid (GABA) and nitric oxide (NO). The objective of this article is to review emerging PE interventions contemporary data on the treatment of PE was reviewed and critiqued using the principles of evidence-based medicine. Multiple well-controlled evidence-based studies have demonstrated the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) in delaying ejaculation, confirming their role as first-line agents for the medical treatment of lifelong and acquired PE. Daily dosing of SSRIs is likely to be associated with superior fold increases in IELT compared to on-demand SSRIs. On-demand SSRIs are less effective but may fulfill the treatment goals of many patients. Integrated pharmacotherapy and CBT may achieve superior treatment outcomes in some patients. PDE-5 inhibitors alone or in combination with SSRIs should be limited to men with acquired PE secondary to co-morbid ED. New on-demand rapid acting SSRIs, oxytocin receptor antagonists, or single agents that target multiple receptors may form the foundation of more effective future on-demand medication. Current evidence confirms the efficacy and safety of dapoxetine, off-label SSRI drugs, tramadol and topical anaesthetics drugs. Treatment with α1-adrenoceptor antagonists cannot be recommended until the results of large well-designed RCTs are published in major international peer-reviewed medical journals. As our understanding of the neurochemical control of ejaculation improves, new therapeutic targets and candidate molecules will be identified which may increase our pharmacotherapeutic armamentarium.

Keywords: Premature ejaculation (PE); treatment; investigational

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There are multiple psychosexual and pharmacological treatments for premature ejaculation (PE). PE treatment strategies include psychosexual counselling, and daily or on-demand pharmacotherapy, either alone or in combination as part of an integrated treatment program (1). Men with lifelong premature ejaculation (L-PE) are best managed with PE pharmacotherapy alone or in combination with graded levels of patient and couple psychosexual therapy. Men with acquired premature ejaculation (A-PE) should receive etiology specific treatment, e.g., psychosexual counselling or ED pharmacotherapy, alone or in combination with PE pharmacotherapy (1). Men with natural variable PE or PE-like ejaculatory dysfunction should be primarily treated with psychosexual education and graded patient and couple psychotherapy (1).

Pharmacotherapy for PE predomintly targets the multiple neurotransmitters and receptors involved in the control of ejaculation which include serotonin, dopamine, oxytocin, norepinephrine, gamma amino-butyric acid (GABA) and nitric oxide (NO) (2). Of the many studies conducted to investigate the role of the brain in the development and mediation of sexual functioning, dopamine and serotonin have emerged as essential neurochemical factors. Whereas dopamine promotes seminal emission/ejaculation via D2 receptors, serotonin is inhibitory (2). Serotonergic neurons are widely distributed in the brain and spinal cord and are predominantly found in the brainstem, raphe nuclei, and the reticular formation.

Currently, multiple serotonin (5-HT) receptors have been characterized, e.g., 5-HT1a, 5-HT1b, 5-HT2a, 5-HT2b, etc. (3). Stimulation of the 5-HT2C receptor with 5-HT2C agonists results in delay of ejaculation in male rats, whereas stimulation of post-synaptic 5-HT1A receptors results in shortening of ejaculation latency (4), leading to the hypothesis that men with PE may have hyposensitivity of 5-HT2C and/or hypersensitivity of the 5-HT1A receptor (5,6).

Several forms of pharmacotherapy have been used in the treatment of PE (7). These include the use of topical local anesthetics (LA), selective serotonin reuptake inhibitors (SSRIs), tramadol, phosphodiesterase type 5 inhibitors (PDE5i) and alpha adrenergic blockers. The use of topical LA, such as lidocaine, prilocaine or benzocaine, alone or in association, to diminish the sensitivity of the glans penis is the oldest known pharmacological treatment for PE (8).

New therapeutic targets and emerging drugs

Selective serotonin reuptake inhibitors (SSRIs)

The introduction of the SSRIs paroxetine, sertraline, fluoxetine, citalopram and the serotonergic tricyclic antidepressant (TCA) clomipramine has revolutionized the treatment of PE. These drugs block axonal re-uptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of post-synaptic membrane 5-HT receptors. Following acute on-demand administration of an SSRI, increased synaptic 5-HT levels are down-regulated by presynaptic 5-HT1A and 5-HT1B/1D autoreceptors to prevent over-stimulation of postsynaptic 5-HT2C receptors. However, during chronic daily SSRI administration, a series of synaptic adaptive processes which may include presynaptic 5-HT1A and 5-HT1B/1D receptor desensitisation, greatly enhances synaptic 5-HT levels resulting in superior fold increases in IELT compared to on-demand administration (9).

The criteria for the ideal PE drug remain controversial. However, the author is of the opinion that many men may prefer the convenience of "on-demand" dosing copareto daily dosing. Men who infrequently engage in sexual intercourse may prefer on-demand treatment, whilst men in established relationships may prefer the convenience of daily medication.

Dapoxetine

Dapoxetine (Priligy®, Menarini) is the first compound specifically developed for the treatment of PE. Dapoxetine has received approval for the treatment of PE in over 50 countries worldwide. Dapoxetine has not received marketing approval by the US Food and Drug Administration (FDA). Dapoxetine is a potent SSRI (pKi=8nM), structurally similar to fluoxetine, with a pharmacokinetic profile suggesting a role as an on-demand treatment for PE (10). Dapoxetine has a Tmax of 1.4–2.0 h and a terminal half-life of 19 h with a rapid decline of plasma levels to about 5% of Cmax at 24 h, ensuring rapid absorption and achievement of peak plasma concentration with minimal accumulation (11-13). Both plasma concentration and area under the curve (AUC) are dose dependent up to 100 mg, and are unaffected by repeated daily dosing, food or alcohol. Food and ethanol do not have a clinically significant effect on dapoxetine pharmacokinetics (12). No drug-drug interactions associated with dapoxetine, including phosphodiesterase inhibitor drugs, have been reported (14).

Dapoxetine is extensively metabolized in the liver by multiple isozymes to multiple metabolites, including desmethyldapoxetine, didesmethyldapoxetine and dapoxetine-n-oxide, which are eliminated primarily in the urine (11,13). Although didesmethyldapoxetine is equipotent to the parent dapoxetine, its substantially lower plasma concentration, compared with dapoxetine, limits its pharmacological activity and it exerts little clinical effect, except when dapoxetine is coadministered with CYP3A4 or CYP2D6 inhibitors. Co-administration of dapoxetine and potent CYP3A4 such as ketoconazole is contraindicated. Caution should be exercised in coadministration of dapoxetine and moderate CYP3A4 inhibitors and potent CYP2D6 inhibitors such as fluoxetine.

The results of two phase II and 6 phase III trials have been published (15-22). All were conducted prior to the development of the ISSM definition of lifelong PE and instead used DSM-IV criteria and a baseline IELT ≤2 min on 75% of ≥4 sexual intercourse events as inclusion criteria (23,24). An analysis of pooled phase 3 data from five randomised, placebo-controlled, phase III clinical trials comprised 6,081 men with a mean age of 40.6 years (range, 18–82 years) from 32 countries confirms that dapoxetine 30 and 60 mg taken 1–2 h before intercourse is more effective than placebo from the first dose, resulting in a 2.5- and 3.0-fold increases in IELT, increased ejaculatory control, decreased distress, and increased satisfaction (25). Efficacy results were similar among each of the individual trials indicating that dapoxetine is consistently more efficacious than placebo regardless of a subject's demographic

characteristics. Dapoxetine was comparably effective both in men with lifelong and acquired PE (26) and was similarly effective and well tolerated in men with PE and co-morbid ED treated with PDE5i drugs (21).

Several studies have reported that the effects of PE on the partner are integral to understanding the impact of PE on the male and on the sexual relationship (27-30). Female partners have reported parallel improvements in their perception of the man's control over ejaculation and CGIC, their own satisfaction with sexual intercourse, and reduced interpersonal difficulty and personal distress (18).

Following regulatory approval in multiple markets, there have been 3 meta-analyses of dapoxetine randomised clinical trials which confirm moderate efficacy, safety and tolerability as a treatment for PE (31-33) and a 6 published independent post-marketing studies (34-39).

In a open label flexible dose trial of dapoxetine in 19 men with lifelong PE and an arithmetic mean baseline IELT <60 s, 12 weeks treatment with dapoxetine 30 and 60 mg was associated with a 5.4- and 5.9-fold increase in arithmetic mean IELT respectively (34). First dose nausea, which progressively attenuated and disappeared by study end, was experienced by 12.5% and 28.5% off subjects with dapoxetine 30 and 60 mg respectively. Several studies have examined PE pharmacotherapy treatment acceptance, compliance and cessation rates (36,40,41). Mondaini *et al.* reported that in a clinic population 90% of subjects either refused to begin or discontinued dapoxetine within 12 months of beginning treatment (36). Reasons given included: not wanting to take an antidepressant, treatment effects below expectations, and cost. Integrated pharmacotherapy and CBT may achieve superior treatment outcomes in some patients (39). Cormio *et al.* reported that patients treated with a combination of dapoxetine (30 mg) and sexual behavioral treatment for 24 weeks achieved a higher fold increase in IELT tha dapoxetine alone (4.0 *vs.* 1.9 respectively, P<0.0001) (39).

Across the phase III trials of dapoxetine, dapoxetine 30 and 60 mg were well tolerated with similar AE profiles (20). In the integrated analysis of these studies (25), AEs occurred in 651/1,857 (35.1%), 760/1,616 (47.0%), 1,270/2,106 (60.3%), and 341/502 (67.9%) subjects with placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn, and dapoxetine 60 mg qd, respectively. Treatment related side effects were uncommon, dose dependent and included nausea, diarrhea, headache, dizziness, insomnia, somnolence, fatigue, and nasopharyngitis (25).

Severe or serious AEs occurred infrequently (~3% and ≤1%, respectively), and most AEs were of mild to moderate severity (25). Across trials, AE-related discontinuation occurred in 1.7% to 4.0% and 5.1% to 10.0% of subjects receiving dapoxetine 30 and 60 mg, respectively, most commonly because of nausea, dizziness, and diarrhea. Syncope (including loss of consciousness), which appeared to be vasovagal in nature and generally occurred within 3 h of the first dose, was reported in 0.05%, 0.06% and 0.23% of subjects with placebo, dapoxetine 30 mg, and dapoxetine 60 mg, respectively (25). Syncope occurred more frequently when dapoxetine was administered at one of the study sites [onsite (0.31%) *vs.* offsite (0.08%)], appeared to be related to syncope-associated onsite study procedures (e.g., blood draws or orthostatic maneuvers) and occurred almost exclusively with dapoxetine 60 mg, with only one reported episode with the 30-mg dose. Similar observations have been reported with other SSRIs, and these events resolved without sequelae.

Dapoxetine is the only agent for which studies have been adequately powered and designed to assess SSRI class-related effects in a PE population. Dapoxetine was not associated with treatment-emergent anxiety (measured by the Hamilton Anxiety Scale), depression (measured by the Montgomery-Åsberg Depression Rating Scale and the Beck Depression Inventory II), or suicidality (42). Abrupt discontinuation of dapoxetine was not associated with an increased incidence of withdrawal syndrome compared with placebo or continued therapy (measured by the Discontinuation-emergent Signs and Symptoms Checklist) (42). Unlike other SSRIs used to treat depression, which have been associated with high incidences of sexual dysfunction in depressed patients, dapoxetine was associated with low rates of sexual dysfunction in men with PE (42).

In men with normal semen parameters, daily dosing of paroxetine has been reported to induce abnormal sperm DNA fragmentation in a significant proportion of subjects, without a measurable effect on semen parameters. The fertility potential of a substantial number of men on paroxetine may be adversely affected by these changes in sperm DNA integrity (43,44). Manufacturer sponsored 2-year rat genetic toxicology studies of dapoxetine HCl at up to 0.25% of the diet, corresponding to a dose of 158 mg/kg/day, showed no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats (45). However, a recent study suggested that the long-term daily administration of dapoxetine at high dosages (4.0 and 8.0 mg/kg) in rats was associated with a significant inhibition of sperm motility and failure of the

fertilization or successful impregnation of the females mated with dapoxetine-treated male rats (46). As the level of dapoxetine exposure used in this trial far exceeds that achieved in human patients, the significance of this finding is unclear and should not be extrapolated to use in humans.

The ISSM guidelines for the treatment of PE expert committee identified level 1a evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of lifelong and acquired PE (1).

DA-8031

DA-8031 is a potent SSRI which is a potential therapeutic agent in the treatment of PE. Monoamine transporter binding and reuptake inhibition assay demonstrates high affinity and selectivity to the serotonin transporter and low selectivity and affinity to dopamine and norepinephrine transporters (47). In a platelet serotonin uptake study, DA-8031 exhibited significant inhibition at oral doses of 10 and 30 mg/kg in a dose-dependent manner (48). DA-8031 is rapidly absorbed and eliminated after oral administration in rats (48).

Several pre-clinical studies suggest that DA-8031 is a potential candidate treatment for PE. DA-8031 significantly inhibited ejaculation after oral and intravenous administration in both para-chloroamphetamine and meta-chlorophenylpiperazine-mediated ejaculation rat models (47). In electrical stimulation of the sensory branch of pudendal nerve (SBPdn) and para-chloroamphetamine (PCA)-induced ejaculation models, Kang *et al.* demonstrated that DA-8031 administration resulted in inhibition of the expulsion phase of ejaculation by bulbospongiosus muscle activity modulation and impairment of the emission phase by blocking the seminal vesicular pressure rise (49). Treatment with DA-8031 appears to delay the ejaculation latency time without affecting the initiation of mounting behavior or post-ejaculatory interval in rats (48). The mechanism of action of DA-8031 was confirmed by positron emission tomography (PET) of the rat brain which demonstrated reduced serotonin transporter (SERT) occupancy by DA-8031 in the midbrain (50). *In vivo* microdialysis showed that administration of DA-8031 produced a dose-dependent increase in extracellular serotonin levels in the dorsal raphe nucleus (33–81% increase for doses of 10–100 mg/kg) (50).

Human clinical trials are currently being conducted with DA-8031 as a treatment for PE (NCT01798667, Dong-A ST, Seoul South Korea) but results have yet to be reported.

PSD502

The use of topical LA, such as lidocaine and/or prilocaine as a cream, gel, or spray, is well established and is moderately effective in delaying ejaculation (51-56). Data suggest that diminishing the glans sensitivity may inhibit the spinal reflex arc responsible for ejaculation (57). Topical anesthetics may be associated with significant penile hypoanesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used (53).

PSD502 is an aerosolized eutectic mixture of lidocaine-prilocaine delivered as a metered spray which is designed to optimize tissue penetration and onset of effect (58). The spray only penetrates, and hence anaesthetises, the mucosa of the glans penis and not the keratinized skin of the shaft. PSD502 has received marketing approval in Europe. The clinical profile of PSD502 is described in one of two double-blind, placebo-controlled, phase III studies. Dinsmore *et al.* reported that treatment with PSD502 which is applied to the penis at least 5 min before intercourse resulted in a 6.3-fold increase in IELT and associated improvements in PRO measures of control and sexual satisfaction (54). In a second prospective multi-centre placebo controlled trial of 256 men with lifelong PE, Carson *et al.* reported that treatment with PSD502, applied topically to the glans penis 5 min before intercourse, increased the geometric mean IELT from a baseline of 0.56 and 0.53 min in the PSD502 and placebo group respectively to 2.60 and 0.80 min (4.6- and 1.5-fold respectively) (56). There were significantly greater increases in the scores for the Index of Premature Ejaculation (IPE) domains of ejaculatory control, sexual satisfaction and distress in the PSD502 group than in the placebo group. There were minimal reports of penile hypoanaesthesia and transfer to the partner due to the unique formulation of the compound in both studies.

In 2014, PSD502 (Fortacin™) received approval by the European Medicines Agency for the treatment for PE, throughout the European Union. The ISSM guidelines for the treatment of PE expert committee identified level 1a evidence to support the efficacy and safety of off-label on-demand label topical anaesthetics in the treatment of lifelong PE (1).

Phosphodiesterase type 5 inhibitors (PDE5i)

PDE5i, sildenafil, tadalafil, and vardenafil, are effective treatments for ED. Several authors have reported experience with PDE5i alone or in combination with SSRIs

as a treatment for PE (59-72). The putative role of PDE5i as a treatment for PE is speculative and based only upon the role of the NO/cGMP transduction system as a central and peripheral mediator of inhibitory non-adrenergic, non-cholinergic nitrergic neurotransmission in the urogenital system (73).

Although systematic review of studies on the PDE5i drug treatment of PE has failed to provide robust empirical evidence to support a role of PDE5i in the treatment of PE with the exception of men with PE and comorbid ED (74-76), a recent well-designed single study does suggest a potential role for these agents suggesting a need for further evidence based research (69).

In a well-designed study of 42 potent men with lifelong PE, randomized to receive on-demand vardenafil or placebo, Aversa *et al.* reported a 7.5-fold increase in geometric mean IELT following treatment with vardenafil (4.5±1.1 *vs.* 0.6±0.3 min with placebo; P<0.01) and significant improvements in the IPE domains of ejaculatory control, confidence, overall sexual satisfaction, and distress (69). This study suggests that the role of PDE5i should be further evaluated in additional well designed studies. A 2007 review of PDE5i for PE considered preclinical and clinical data to understand potential central and peripheral mechanisms of action of these agents and their overall effectiveness in PE (77). The authors concluded that data were limited but encouraging, and emphasized the need for large, randomized, double-blind, placebo-controlled studies of these agents in men with PE.

In 2 well-designed studies of PDE5i (sildenafil and vardenafil), the overall incidence of AEs was not reported; however, the most common AEs included headache (10–15%), flushing (12–15%), dyspepsia (5–10%), abnormal vision (5%), and rhinitis (5%), which tended to attenuate and disappear with continued use (69,72). These data are similar to those reported in a recent systematic review (78) of the use of PDE5i in men with ED. In that analysis, overall AE rates were 50% with sildenafil and 47% with tadalafil; the overall AE rate for vardenafil was not reported. Common AEs included headache (13–17%), dyspepsia (3.8–10%), flushing (4.8–13%), and rhinitis (3.1–7.9%). The rate of serious AEs was low (1.2–2.5%).

The ISSM guidelines for the treatment of PE expert committee identified some evidence to support the efficacy and safety of off-label on-demand or daily dosing of PDE5i's in the treatment of lifelong PE in men with normal erectile function (LOE 4D). However, off-label on-demand or daily dosing of PDE5i is not recommended for the treatment of L-PE in men with normal erectile function (1). ED pharmacotherapy alone or in combination with PE pharmacotherapy is recommended for the treatment of L-PE or A-PE in men with co-morbid ED (1). Further evidence-based research is encouraged to understand conflicting data (1).

Tramadol

Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action which is thought to include binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of GABA, norepinephrine, and serotonin (79). The major metabolite, M1 has a 200-fold increased affinity for the μ-opioid receptor, which likely accounts for the analgesic effects achieved (79).

The efficacy of on-demand tramadol in the treatment of PE was recently reported (80-85). Although the mechanism of action is not completely described, the efficacy of tramadol may be secondary to anti-nociceptive and anesthetic-like effects, as well as via central nervous system modulation through inhibition of serotonin and noradrenaline reuptake (79,86). Most studies are poorly designed open label trials with a wide range of efficacy. The only double blind trial well-designed study demonstrates superiority to placebo but a mediocre fold increase in IELT of 2.49, consistent with the weak serotonin re-uptake inhibitor activity of tramadol (84). In an open-label crossover comparator study of daily paroxetine (20 mg) and on-demand tramadol (50 mg) in 35 subjects with lifelong PE, superior IELT fold-increases and PRO responses were demonstrated with paroxetine (22- *vs.* 5-fold for tramadol) after 12 weeks of treatment . Although this study was limited by the use of the DSM-IV-TR definition to diagnose PE, 66% of men had an IELT of ≤1 min at baseline, suggesting that the overall population is reasonably representative of the ISSM definition. A large, international, prospective, randomized, placebo-controlled, double-blind trial of tramadol for the treatment of PE (NCT00983151) was recently stopped prematurely, although no reason has been provided; another similar study (NCT00983736) was stopped because of recruitment difficulties.

A recent meta-analysis (87) of 11 controlled studies of tramadol in more than 1,000 patients with osteoarthritis reported that the most common AEs were nausea, vomiting, dizziness, somnolence, tiredness, and headache, and approximately 20% of patients receiving tramadol or tramadol/acetaminophen experienced non-serious AEs. Serotonin syndrome has been reported as an adverse effect

of tramadol alone or in combination with SSRI drugs (88-90).

There have been 4 meta-analyses of tramadol published clinical trial data (91-94). All conclude that tramadol appears effective in the treatment of PE but suggest that these findings should be interpreted with caution given the observed levels of between-trial heterogeneity and the reporting quality of the available evidence. Although the potential for addiction or abuse has not been assessed in men with PE, the risk is regarded as low, based upon the use of low intermittent doses and experience in other patient populations. Tramadol is promoted as having a lower risk of dependence than traditional opioids due to the relatively long half-lives and therefore delayed agonist activity of tramadol (6 h) and the M1 metabolite (9 h), and its noradrenaline reuptake effects (95). In clinical practice, dependence does occur but appears minimal (96). Adams and colleagues (97) reported abuse rates of 0.7% for tramadol compared with 0.5% for non-steroidal anti-inflammatory drugs and 1.2% for hydrocodone, based on application of a dependency algorithm as a measure of persistence of drug use.

The ISSM guidelines for the treatment of PE expert committee was of the opinion that tramadol may be an effective option for the treatment of PE. However, it may be considered when other therapies have failed because of the risk of addiction and side effects. It should not be combined with an SSRI because of the risk of serotonin syndrome, a potentially fatal outcome. Further well-controlled studies are required to assess the efficacy and safety of tramadol in the treatment of PE patients (LOE2) (1).

α1-adrenoceptor antagonists

α1-adrenoceptor antagonists are widely used in the treatment of lower urinary tract symptoms (LUTS) associated with or without BPH (98), but have some adverse effects, including postural hypotension and ejaculatory dysfunction (99). Nonselective α1-adrenoceptor blockers increase urinary flow rate and improve symptoms in men with symptomatic BPH; however, they may be associated with side effects related to peripheral vasodilation, such as postural hypotension, dizziness, and headache (100-102). Conversely, drugs with a high affinity for $\alpha 1_A$-adrenoceptors may be more prostate specific and may maintain the therapeutic response in the treatment of symptomatic BPH with less effect on blood pressure, fewer cardiovascular side effects but a higher incidence of ejaculatory dysfunction (103). α1-adrenoceptor antagonist-mediated abnormal ejaculation may involve two mechanisms. Firstly, the inhibition of α1A-adrenergic receptor expression in the bladder neck, prostate, and urethra caused by silodosin may relax these organs, resulting in retrograde ejaculation (104). Secondly, α1-adrenoceptor antagonists inhibit semen emission, which can result in abnormal ejaculation (105,106).

Several researchers have reported their experience with the selective α1 adrenergic blockers, alfuzosin, terazosin and silodosin in the treatment of PE (107-111). These drugs are approved only for the treatment of LUTS in men with obstructive benign prostatic hyperplasia (BPH). In a double blind placebo-controlled study, Cavallini reported that both alfuzosin (6 mg/day) and terazosin (5 mg/day) were effective in delaying ejaculation in approximately 50% of the cases (107). Similarly, Basar reported that terazosin was effective in 67% of men (108). However, both studies were limited by the use of subjective study endpoints of patient impression of change and sexual satisfaction, and they did not evaluate actual IELT. Additional controlled studies are required to determine the role of α1-blockers in the treatment of PE.

In the study (107) by Cavallini comparing alfuzosin and terazosin with placebo, hypotension was the most common AE leading to discontinuation [4 (4.4%) patients; 2 each with terazosin and alfuzosin]. Other AEs included headache (1 patient with alfuzosin) and headache with epigastralgia (1 patient with terazosin), neither of which resulted in discontinuation. In the study by Başar and coworkers of terazosin versus placebo daily for 1 month (108), published safety data were limited to the finding that none of the patients discontinued treatment because of AEs. These data in men with PE are comparable to what has been observed in men with hypertension or BPH. The most common AEs with terazosin include postural hypotension (3.9%), dizziness (9.1%), somnolence (3.6%), nasal congestion/rhinitis (1.9%), and impotence (1.6%) (112). With alfuzosin, common AEs in men with BPH include dizziness (5.7%), upper respiratory infections (3.0%), headache (3.0%), and fatigue (2.7%) (113).

Silodosin is a new highly selective α1A-adrenoceptor antagonist, and clinical trial data demonstrates significant clinical efficacy and safety for LUTS, even in the elderly (114-116). However, in these studies, abnormal ejaculation was found in a relatively higher percentage of participants (115-118). In a trial to evaluate the superiority of silodosin to placebo and non-inferiority to tamsulosin, Chapple *et al.* reported that abnormal ejaculation, the most common AE, occurred more often in the silodosin than in the tamsulosin group (22.3% *vs.* 1.6%) (116). Similarly, Cho *et al.* reported a reduction or absence of ejaculation in 14% of subjects

treated with silodosin compared to tamsulosin (2.1%) and placebo (1.1%) (119) The presence of ejaculatory dysfunction was associated with significantly more improvement in LUTS. This suppression of ejaculation by silodosin has been confirmed in well-designed studies with control volunteers (105,120). Sato *et al.* evaluated the feasibility of off-label silodosin (4 mg) in 8 patients with PE (109). The IELT was significantly prolonged (from 3.4 to 10.1 min, P=0.003). At study end, all PRO items in the premature ejaculation profile (PEP) significantly improved and all subjects rated their PE as at least "better" (121) on the CGIC. Akin *et al.* compared silodosin 4mg, tamsulosin hydrochloride 0.4 mg, alfuzosin 10 mg, terazosin 5 mg and doxazosin mesylate 4 mg in men with PE and reported that IELT, PEP and quality of life (QoL) responses were statistically improved for all drugs and that silodosin appeared most effective (P<0.05) (111).

These results support the possible use of α1-adrenoceptor antagonists and in particular silodosin as new treatment options for PE and suggest that a placebo controlled study assessing its clinical usefulness would be worthwhile.

Oxytocin antagonists

Oxytocin is a peptide hormone of nine amino acids which facilitates sexual reproduction in mammals (122). An increasing number of studies report the involvement of central and peripheral oxytocinergic neurotransmission in the ejaculatory process. The effects of oxytocin on male sexual behaviour includes a central pathway involved in erection, exerted via oxytocinergic neurons projecting from the paraventricular hypothalamic nucleus (PVH) to the spinal cord, and a peripheral pathway involved in ejaculation, exerted via oxytocin release in the bloodstream (123-125).

In human males, plasma oxytocin levels are elevated during penile erection and at the time of orgasm (126,127). Electrical stimulation of the dorsal penile nerve, produced excitation in about half of the oxytocin cells in the PVH and hypothalamic supraoptic nucleus (SON) of rats (128,129). Systematic administration of oxytocin decreases the number of intromissions required for ejaculation in young adult rats (130), and reduced ejaculation latencies and post-ejaculation intervals in older sexually sluggish rats (131,132). As oxytocin cannot easily penetrate the blood brain barrier, peripherally injected oxytocin's effect on ejaculation is most likely exerted through peripheral oxytocin receptors on the contractility of smooth muscle cells in the testis, epididymis, vas deferens, prostate and penis of rats and humans (133,134). However, since a small proportion of subcutaneously injected oxytocin does cross the blood brain barrier, some effects of systematically injected oxytocin on ejaculation might be mediated by central oxytocin receptors (135).

Several clinical and pre-clinical studies suggest a potential role for highly selective oxytocin receptor antagonists in the treatment of PE (136). In male rats, Argiolas *et al.* demonstrated the central administration of a selective oxytocin-receptor antagonist inhibited ejaculation (137). Clément *et al.* reported that in rodents' brains, oxytocin receptors mediate ejaculation elicited by a dopamine agonist which is dose-dependently inhibited by the intraventricular administration of an oxytocin antagonist whereas systemic administration of an oxytocin antagonist resulted in no significant change (138). In a recent study, the same group demonstrated that a highly selective, non-peptide oxytocin antagonist (GSK557296) inhibits ejaculation both peripherally and centrally (139). Several authors report that copulatory behavior/ejaculation activates oxytocin neurons in rodent brain regions (140,141). Furthermore, in oxytocin receptor knockout mice, there is a decreased incidence of ejaculation and a higher stimulatory threshold required to induce sexual arousal compared with wild type mice (142).

In a randomised placebo controlled study of epelsiban in men with PE, Shinghal *et al.* demonstrated that 50 and 150 mg were well tolerated but did not result in a clinically or statistically significant change in IELT in men with PE, compared with placebo (143). The baseline (mean) IELT for patients pretreatment was 0.52, 0.63, and 0.59 min for placebo, epelsiban 50 and 150 mg, respectively. On-treatment, average geometric least squares means of the median IELT values (mean) were slightly higher in the 50 and 150 mg groups (0.72 and 0.69 min), respectively, *vs.* the placebo group (0.62 min). This study demonstrates that non-CNS penetrant oxytocin receptor antagonists show little effect on ejaculation when given systemically (143). However, the rodent studies reporteed above do show that oxytocin antagonists can delay or prevent ejaculation when injected close to the lower thoracic and lower lumbar spinal cord or when injected directly into the cerebral ventricle strongly supporting the hypothesis that a centrally acting oxytocin receptor antagonist which crosses the blood-brain barrier has the potential to treat PE (137-139).

Ixchelsis (Sandwich UK) is developing IX-01, a small molecule orally delivered oxytocin receptor antagonist that has demonstrated good CNS penetration in preclinical studies.

Modafinil

Modafinil was first identified as a wake promoting agent and is used for the treatment of narcolepsy. Modafinil's mechanism of action is complex and poorly understood and appears to involve induction of changes in brain activation. There is evidence for action on brain catecholaminergic and indolaminergic systems, especially dopaminergic pathways and serotonin pathways, as well as g-Aminobutyric acid (GABA)/glutamate systems, and orexin-containing neurons have been reported (144). It has been shown that dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil (145).

Male sexual behavior in the rat was examined after acute oral administration of d-modafinil in copulation studies with receptive females. D-modafinil (30 and 100 mg/kg) produced a significant delay in ejaculation, accompanied by an increase in the number of intromissions without any change in the mount or intromission latency. The greatest delay in ejaculation was observed in animals with shorter baseline ejaculatory latencies (146).

D-modafinil may delay ejaculation via increases in serotonin release in the brain and/or spinal cord or an action upon the dopamine system (147-150). *In vivo* microdialysis studies demonstrated that d-modafinil induces release of serotonin in the cerebral cortex, central nucleus of amygdala and dorsal raphe, and at the higher doses, in the medial preoptic area (MPOA) and posterior hypothalamus (147,148). Furthermore, low doses of d-modafinil that normally do not alter serotonergic neurotransmission, increased SSRI-induced central serotonin release, suggesting that modafinil works through common pathways that alter mood (151). Further supporting this hypothesis is a recent study that showed that depressive-like behavior in rats was improved with d-modafinil (152).

Several *in vivo* and *in vitro* studies have suggested that modafinil acts via brain dopamine pathways and a role for the dopamine transporter and D2 and D1 receptors have been reported. Neurophysiological studies using brain slices demonstrated that modafinil inhibited dopaminergic neuronal activity via D2 receptors (153). In D2 receptor knockout mice, modafinil-induced wakefulness was reduced, and both D1 and D2 receptor antagonists blocked the modafinil-induced effects, suggesting a role for both the D1 and D2 receptors in the arousal effects induced by modafinil (145). It is possible that d-modafinil acts by a combination of mechanisms that include a direct inhibition of dopamine, an increase in serotonin release, as well as activation of noradrenaline pathways.

Whilst these results are promising, caution must be exercised in the application of the results of animal studies of ejaculation to the humans. Human trials with careful attention to safety and side effect profile are warranted before consideration of modafinil as a potential treatment for PE. The short-acting modafinil d-isomer (NH02D, NeuroHealing, Waban, MA USA) is undergoing pre-clinical trials as an investigational drug for the "on demand" treatment of PE.

Botulinum-A toxin

Botulinum toxin is a protein and neurotoxin produced by the bacterium *Clostridium botulinum*. It is a selective blocker of acetylcholine release from nerve endings which blocks neural transmission when injected into muscle (154). This drug has been widely used as a cosmetic anti-ageing treatment to prevent development of wrinkles by paralysing facial muscles, and as a medical treatment for a diverse range of conditions including strabismus, benign essential blepharospasm, neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, motor and sensory urge and, more recently, chronic prostatic pain. Worldwide experience demonstrated that this therapeutic agent is safe and effective for such indications.

Serefoglu theorised that the rhythmic contractions of bulbospongiosus and ischiocavernosus muscles during the ejection phase of ejaculation may be inhibited by the injection of botulinum-A toxin (155). He subsequently demonstrated that percutaneous injection of either 0.5 or 1 unit Botulinum toxin A into the bulbospongiosus muscle bilaterally significantly increased ejaculatory latency in male rats (0.5 unit: 314.6±193.1 to 507.6±277.8 s, P=0.021; 1 unit: 264.4±129.1 to 598.2±352.5 s, P=0.008) in a dose-dependent manner compared to pre-treatment latency without affecting their ability to achieve mounts, intromissions, or ejaculation (156). Mean ejaculation latency reached its peak 11 days after injection and decreased sharply 14 days after injection at both doses. However, the difference between the post-treatment geometric mean ejaculatory latency for 0.5 or 1 unit of Botulinum toxin and saline failed to reach statistical significance possibly due to the small sample size and/or the high variability in ejaculation latency.

Patents have been granted for the local injection of 25 and 50 units of a botulinum-A toxin into the penis, frenulum, prepuce, or glans penis for treating PE, without any basic or clinical research support (157). However, it is probable that botulinum-A toxin injected into the penis

would immediately diffuse into the systemic circulation limiting its local effect. Similarly, injecting botulinum-A toxin into the prepuce or frenulum of the penis will have little effect on ejaculatory latency because botulinum-A toxin does not exhibit any LA effect.

The current results from these rat studies suggest that botulinum-A toxin injection into the bulbospongiosus muscle may be a safe and effective means to prolong ejaculatory latency without affecting other aspects of sexual behavior. Dose-ranging phase II clinical trials of Botox® (Allergan, Irvine, CA, USA) as a treatment for PE in humans are currently being conduced.

Conclusions

Current evidence confirms the efficacy and safety of dapoxetine, off-label SSRI drugs, tramadol and topical anaesthetics drugs. Treatment with α1-adrenoceptor antagonists cannot be recommended until the results of large well-designed RCTs are published in major international peer-reviewed medical journals. As our understanding of the neurochemical control of ejaculation improves, new therapeutic targets and candidate molecules will be identified which may increase our pharmacotherepeutic armamentarium.

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Footnote

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