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REVIEW

Current therapeutic strategies for premature ejaculation and future perspectives

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Premature ejaculation (PE) is a common sexual disorder in men that is mediated by disturbances in the peripheral and central nervous systems. Although all pharmaceutical treatments for PE are currently used 'off-label', some novel oral agents and some newer methods of drug administration now provide important relief to PE patients. However, the aetiology of this condition has still not been unified, primarily because of the lack of a standard animal model for basic research and the absence of a widely accepted definition and assessment tool for evidence-based clinical studies in patients with PE. In this review, we focus on the current therapeutic strategies and future treatment perspectives for PE.
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INTRODUCTION

Normal male sexual activity includes sexual libido, penile erection, ejaculation and orgasm, with ejaculation and orgasm composing the final stage of the sexual response cycle.

Ejaculation is a tightly coordinated activity with different ejaculatory organs and a spinal reflex initiated by genital and/or brain stimulation through the peripheral sensory receptors and regions, afferent pathways, the central nervous system ejaculatory centre of the brain (namely, sensory and motor areas located in the para-ventricular nucleus of the hypothalamus and the medial preoptic area). The spinal ejaculatory centre, located at the T_{12}–$L_{1\text{-}2}$ spinal cord level (paragigantocellular), and its efferent pathway modulate the function of the ejaculatory organs. Ejaculation is also mediated by a complex interaction of central serotonergic and dopaminergic neurons with the secondary involvement of cholinergic, adrenergic, oxytocinergic and GABAergic neurons.

Ejaculation consists of two main phases, the emission phase and the expulsion phase. The emissions include seminal fluid and secretions of the prostate and bulbourethral glands. In this phase, the contraction of accessory ejaculatory organs induces the accumulation of semen in the posterior urethra. Expansion of the posterior urethra creates a feeling of emission and sensory information that is transmitted to the spine *via* dorsal nerve sensory pathway and along the spinal cord up to the brain ejaculatory centre during the sexual arousal phase. The expulsion phase consists of the highly regular rhythmic contraction of striated muscles and the relaxation of smooth muscles in the ejaculatory ducts. The ejaculated semen can be divided into a number of components by serial biochemical analysis.[1] These include secretions from the seminal vesicles, prostate and bulbourethral (Cowper's) glands and spermatozoa.

Ejaculatory dysfunction may arise due to a problem in any of these steps and encompasses premature ejaculation (PE), retarded ejaculation, anejaculation, retrograde ejaculation and painful ejaculation. However, PE is the most common type of ejaculatory dysfunction.

During the past four to five decades, the lack of a globally accepted definition has led to difficulties in determining the prevalence of PE, which has been cited as ranging from 4% to 66%.[2,3] Defining PE remains controversial. The most recent definition of PE adopted by the International Society for Sexual Medicine is 'a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy'.[4] PE is also classified as either primary (lifelong) or secondary (acquired). Primary PE has a disease onset at the time of the initial sexual experience and persists throughout an individual's entire life. Ejaculation occurs too quickly, either before vaginal penetration or less than 1 min afterwards. Secondary PE has either a gradual or a sudden onset and occurs in an individual with a previous history of normal ejaculation. Ejaculatory latency is short but not usually as brief as in primary PE.[5]

Historically, PE was considered a psychological rather than a physiological problem and was treated by behavioural therapy and psychotherapy. Semans[6] first reported the 'start–stop' technique in 1956, which was modified with psychotherapy by Masters and Johnson[7] in 1970. Although such therapies may be initially useful for some couples, they are rarely successful in long-term follow-up.[8,9] At present, attempts to explain the cause of PE rely on various biological and psychological theories; however, most of these theories

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are not evidence-based by now. Psychological theories highlight the impact of early sexual experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity and other psychodynamic explanations. Factors cited in biological explanations include evolutionary theories, the sensitivity of the penis, central neurotransmitter levels and receptor sensitivity, a certain degree of arousability, the speed of the ejaculation reflex and the sex hormone levels. Common flaws in most of these studies that generated these hypotheses include methodological problems and a lack of interoperability in the definition of PE.

Studies on the aetiology of PE must necessarily rely on research in animal models, which are crucial to investigating the anatomy, physiology, cell biology, biochemistry, pathophysiology and pharmacology of PE, all prerequisites for developing new therapies for the treatment of PE. However, experimental animal models of PE have not yet been developed well to investigate the aetiology, pathophysiology and relevant pharmacology of PE. These fields of study will hopefully stimulate researchers to seek new methods to develop an experimental model of PE in the near future.

Recently, increasing evidence from psychopharmacological studies has suggested that PE may be related, at least in part, to diminished serotonergic neurotransmission. Aided by this recognition of the existence of a neurobiological component underlying the aetiology of PE, the management, especially the pharmacological treatment, of PE has advanced over the past decade. Nevertheless, to date, no oral or topical agent has been approved by the US Food and Drug Administration for the management of PE; however, drug therapy is still often the preferred first-line therapy.

NON-PHARMACOLOGICAL TREATMENT

As mentioned above, PE is often considered a psychological rather than a physiological problem, and, as such, behavioural psychosexual therapy remains a popular treatment choice. The earliest method of behavioural therapy was described by the urologist Semans[6] in 1956. In 1970, sex therapists Masters and Johnson[7] reported a similar manoeuvre that differs slightly from that of Semans. Their technique involves requesting the partner to squeeze the penile fraenulum immediately after cessation of penile stimulation, which can partially restrain erection, and then the female partner restarts the stimulation at least 30 s later.[8] In fact, the primary goals of traditional psychosexual treatment for PE are to increase the male's self-confidence in sexual activity, reduce anxiety, resolve any interpersonal difficulties and improve couple communication. Ejaculation is actually a spinal reflex under strong control from higher central nervous centres, the same as urination and defecation, so control can be learned and is significantly influenced by past experiences. Although behavioural therapy has been shown to have a 45%–65% success rate, the benefits are generally short-lived, and the problem typically reoccurs.[9,10] However, some researchers have demonstrated that the patients with PE occupy the far left edge of a normal distribution curve of ejaculatory latencies, suggesting serotonin receptor sensitivity as a genetic explanation for psychosexual therapy failure.[11]

Currently, pharmacotherapy and psychotherapy are often proposed in combination for treatment of severe PE. The severe PE patient requires more therapeutic methods than drugs alone.[12] Two reports have described combination therapy with psychological and medical components administered independently. When clinicians and sex therapists work together as one team to manage severe PE patients, better results could be obtained.[12,13]

PHARMACOLOGICAL TREATMENTS

Pharmacological modulation of the ejaculatory threshold provides a novel and refreshing approach to the treatment of PE and is completely different from the psychosexual and behavioural treatment model. Because penile hypersensitivity and hyperexcitability have been suggested to contribute to the aetiology of PE, topical desensitizing agents and oral selective serotonin reuptake inhibitors (SSRIs) have been introduced as new therapeutic options. These agents have revolutionized the treatment of PE and are becoming increasingly popular. However, SSRIs were all initially developed to treat other diseases, such as depression and pain; thus, their use in treating PE is considered 'off-label', as they have not yet been approved by the US Food and Drug Administration for this indication. A systematic review and meta-analysis revealed 79 publications on drug treatment for PE involving 3034 men between 1943[14] and 2003.[15] A recent meta-analysis showed that, in spite of a trend towards more evidence-based research on drug treatments, the majority of studies for PE still lack adequate design and methodology.[16]

Current and widely accepted pharmacological treatment options for PE include antidepressive agents, topical desensitizing agents, phosphodiesterase type 5 inhibitors (PDE-5Is) and α-receptor blockers.

Antidepressive agents

Several studies in male rats have shown that 5-hydroxytryptamine (5-HT) and other serotonin receptors are involved in the ejaculation process.[17,18] Activation of 5-HT_{2C} receptors can delay ejaculation, whereas the activation of 5-HT_{1A} receptors speeds up ejaculation. PE has been attributed, in part, to decreased central serotonergic neurotransmission, 5-HT_{2C} receptor hyposensitivity and/or 5-HT_{1A} receptor hypersensitivity.[19] Thus, 5-HT_{2C} receptor agonists, such as SSRIs and serotonergic tricyclic antidepressants, should theoretically help delay ejaculation.

Clomipramine. Clomipramine is a tricyclic antidepressant that inhibits the uptake of noradrenaline and 5-HT by adrenergic and 5-HT neurons, respectively.[20] In 1973, Eaton[21] published his novel report on the efficacy of clomipramine, and numerous subsequent publications have confirmed its effectiveness in treating PE. A meta-analysis has shown that daily use of clomipramine increases intravaginal ejaculatory latency time (IELT) by 4.6-fold, which is not statistically different from the effect of sertraline or fluoxetine.[15] In three double-blind, placebo-controlled crossover studies,[22–24] on-demand use of clomipramine (25 mg; 12–24 h before intercourse) significantly increased the IELT by approximately fourfold in PE patients. However, only the smallest of these three trials used an objective stopwatch technique for measuring the IELT. In addition, after daily treatment with clomipramine, men with PE reported improved relationship and emotional satisfaction, and their partners reported an increased ability to achieve coital orgasm.[25]

The most common adverse side effect of clomipramine is nausea on the day of sexual intercourse and the following day. With chronic use, adverse events of clomipramine were reported to be significantly more severe than with SSRIs.[26]

SSRIs. The ability of SSRIs to delay ejaculation was first discovered serendipitously as a result of the use of these drugs in the treatment of depression in men in the 1970s.[27] At present, four different SSRIs are commonly used in the treatment of PE: fluoxetine, sertraline, paroxetine and citalopram. SSRIs increase synaptic 5-HT concentrations *via*

blockade of the 5-HT transporter and activation of the 5-HT_{2C} receptor, as previously mentioned, can delay ejaculation.[19] The extent of such delay depends on the type, dosage and frequency of SSRI administration. Other SSRIs, specifically fluvoxamine[28] and venlafaxine,[29] have not proven useful for delaying ejaculation. Although none of these agents has been approved for treating PE, the current American Urological Association guidelines[30] and the recommendations of the International Consultation on Sexual Dysfunction[31] suggest the off-label use of SSRIs for managing PE.

A prolongation of delay IELT can be induced by SSRIs as soon as 2–3 days after the first oral treatment in patients with PE, and this delay tends to plateau after 3–4 weeks at a six- to eightfold increase in the IELT.[32,33] Although the effects of such drugs are well established, some fundamental questions remain regarding dosing regimen (daily versus on-demand) and efficacy (which SSRI is superior).

In one study where it was used daily, paroxetine was shown to be the most effective SSRI (8.8-fold increase in the IELT), followed by sertraline (4.1-fold) and fluoxetine (3.9-fold). Each of these increases was significantly higher than that induced by placebo (1.4-fold).[34] A meta-analysis of the use of SSRIs for PE included data from eight randomized, double-blind studies of SSRIs and tricyclic antidepressants for the treatment of PE, including the IELT assessment with stopwatch. The rank order of efficacy, as defined by the increase in IELT, was as follows: paroxetine, sertraline, clomipramine, fluoxetine and placebo.[15] However, the author has highlighted the unreliability of IELT and the absence of patient-reported outcomes as clear weaknesses of this meta-analysis.

Only a small number of studies have evaluated on-demand use of SSRIs, and according to the existing data, it is difficult to compare the efficacy of on-demand use and daily use of SSRIs. In 2004, Waldinger *et al.*[23] investigated the ejaculation delay induced by fixed-dose on-demand treatment with paroxetine and clomipramine in a randomized, double-blind study of 30 PE patients. On-demand treatment of paroxetine (20 mg) did not cause clinically relevant delay in ejaculation, but daily use of the same SSRIs for 6 weeks significantly increased the IELT by 146 s. More well-designed, head-to-head trials are required for the assessment of SSRIs used on-demand.

SSRIs may cause side effects such as fatigue, mild nausea, diarrhoea or heavy perspiration. SSRIs have different short-term and long-term adverse effects. The most common short-term adverse effects are yawning, mild nausea, excessive sweating, fatigue and loose stool. Priapism[35] and loss of bone mineral density[36] are the most common with long-term treatment. Bleeding[37] has only rarely been reported in patients with PE, but in patients with depression, it is well known; thus, this adverse effect also requires attention. A reduction in sexual desire and a moderate reduction in penile rigidity have been reported.[38] These adverse effects are usually mild and gradually disappear within 2–3 weeks of use in most patients. Similar to clomipramine, however, patients should be informed of all these possible side effects before beginning treatment. A sudden reduction or cessation of long-term treatment with an SSRI can lead to 'SSRI discontinuation syndrome', a group of physical and psychological symptoms including nausea, vomiting, dizziness, headache, ataxia, drowsiness, excitement, anxiety and insomnia. These symptoms begin 1–3 days after drug cessation and typically continue for more than 1 week. Side effects are usually reversible with SSRI reintroduction.[39] Because of the SSRI discontinuation syndrome, it is still recommended that SSRIs are gradually withdrawn over 3–4 weeks, with the exception of fluoxetine.[40]

SSRI overdose or, more commonly, interaction between SSRIs and other agents, can enhance 5-HT activity in the central nervous system to the point of causing the 'serotonin syndrome', a group of serious, persistent symptoms including myoclonus, hyperreflexia, sweating, shivering, discoordination and mental status changes.[39] Patients receiving long-term SSRI treatment for PE must be aware of potential drug interactions between SSRIs and other concurrent drugs in order to reschedule the doses and timings of different drugs.[39]

Acute SSRI administration. The 5-HT transporter blockade induced by acute administration of all current SSRIs leads to higher 5-HT levels in the synapse and in the space around the cells.[41] Increasing 5-HT levels activates 5-HT_{1A} autoreceptors, resulting in less 5-HT being released into the synaptic cleft within minutes.[42] A higher 5-HT concentration increases activation of presynaptic 5-HT_{1B} autoreceptors, which alone can reduce the release of 5-HT. Under normal physiological conditions, the net effect of acute administration of SSRIs is little to no increase in 5-HT neurotransmission and minimal or no stimulation of postsynaptic 5-HT receptors.[43] Given this background, on-demand SSRI treatment would not be expected to result in acute stimulation of 5-HT postsynaptic receptors. Consequently, one would expect minimal increase in synaptic 5-HT levels and, thus, little or no synaptic stimulation of 5-HT receptors. Little or no activation of postsynaptic 5-HT receptors should then result in no clinically relevant ejaculation delay.[43]

Chronic SSRI administration. In contrast to their acute administration, chronic use of currently available SSRIs causes some physiological changes that delay ejaculation. Ongoing blockade of 5-HT receptors that mediate serotonin reuptake results in a persistent increase in 5-HT levels in the synapse and in the space around the cells. As opposed to the acute administration of SSRIs, this ongoing blockage leads to desensitisation of the 5-HT_{1A} autoreceptors in a few weeks,[44] in addition to possible desensitisation of 5-HT_{1B} autoreceptors[45] and therefore less inhibition of 5-HT release into the synapse. The net effect of the chronic administration of SSRIs is an increase in the 5-HT released into the synapse and enhanced 5-HT neurotransmission, thus resulting in a stronger activation of the 5-HT receptors compared with that observed in acute SSRI administration.[46] These data predict that daily treatment of SSRI will stimulate the 5-HT postsynaptic receptors, leading to a clinically relevant ejaculation delay after 1–2 weeks of continuous intake.[43]

Tramadol

Tramadol is a synthetic opioid analgesic active in the central nervous system with a C_{max} of 300 $\mu g\,l^{-1}$ after a single oral dose of 100 mg.[47] Tramadol is registered as a central analgesic, has been used for many years and has a widely accepted safety profile, despite the fact that its mechanism of action is not fully understood. Based on animal experiments, at least two different mechanisms are likely: one enantiomer exerts a major weak μ-opioid effect, while the other inhibits norepinephrine and serotonin reuptake, activating descending monoaminergic inhibitory pathways.[48,49] Tramadol's inhibition of the reuptake of norepinephrine and serotonin may explain its ability to delay ejaculation.[49] However, its induction of 5-HT_{1A} and 5-HT_{2C} also requires further investigation.

Two recently published studies assessed the effectiveness of on-demand use of tramadol for the treatment of PE.[49,50] Safarinejad and Hosseini[50] reported on-demand use of tramadol (50 mg) to have a significant impact on IELT delay in PE patients. In a double-blind, placebo-controlled study, on-demand use of tramadol 50 mg, taken 2 h before sexual intercourse, was associated with a clinically significant

ejaculation delay in the treatment of PE. Of those taking tramadol, 28% reported adverse effects. The most common side effects were nausea (15.6%), vomiting (6.2%) and dizziness (6.2%) but these were all mild. In another study by Salem *et al.* evaluating on-demand treatment with 25 mg Tramadol,[49] the treatment group experienced a 6.3-fold increase in IELT compared with a 1.7-fold increase in the placebo group. In this study, 13.3% of patients reported adverse effects, including dyspepsia and mild sleepiness.[49] Although tramadol is an interesting on-demand PE drug and preliminary results are encouraging, further studies are needed. Tramadol also has a weak n-opioid agonistic effect; consequently, long-term follow-up study is necessary to assess the risk of opioid addiction with this drug.

PDE-5Is

At least 30% of men with PE also suffer from erectile dysfunction (ED).[51] Patients suffering from ED may ejaculate soon after erection and before the failure-to-maintain phase of the erection sets in.[52] Some experiments have shown a relationship between ejaculation function and PDE-5. Mancina *et al.*[53] demonstrated the expression of PDE-5 in all human and rabbit vas deferens muscles. Kriegsfeld *et al.*[54] showed that ejaculation can be inhibited by nitric oxide in non-genetically altered mice, and this effect most likely is modulated by reduced sympathetic nervous system activity. PDE-5Is have also been successfully used in the management of the subgroup of ED patients with comorbid PE.

PDE-5I has been used alone[55,56] or in combination with SSRIs[57] for the treatment of PE. Although the only double-blind, placebo-controlled, parallel group study of sildenafil citrate for the treatment of PE showed no significant improvement in IELT and vibrotactile stimulation compared with placebo, the sildenafil group had a statistically significant increase in ejaculation control (1.8 ± 0.3 versus 1.5 ± 0.3, $P<0.05$).[55] In another study, on-demand sildenafil use increased ejaculation time as induced by vibratory stimulation compared with that in the placebo group.[56] Two studies of vardenafil for PE showed that it increases IELT and reduces the post-ejaculation refractory period in men with lifelong PE.[58,59]

A double-blind, prospective, crossover study compared the effectiveness of sildenafil with the squeeze technique and on-demand use of two different SSRIs (paroxetine and sertraline) and clomipramine in patients with primary PE. Sildenafil demonstrated a 15-fold increase in IELT compared with two- to fourfold increases for the other groups.[60] Another study examined the combination of paroxetine and sildenafil and demonstrated that combination therapy increased IELT and sexual satisfaction but that this therapy resulted in a higher incidence of side effects.[57] In general, studies have shown that PDE-5Is alone or in combination with SSRIs may increase the IELT of patients with ED and concurrent PE.

However, other studies have indicated that sildenafil does not affect the sexual function of men without comorbid ED, but rather leads to a reduction in the post-ejaculation refractory period.[61,62] A recent systematic review of published reports of PDE-5I for PE found limited evidence to support the use of PDE-5I in treating PE, although some data suggest that these medications may benefit men with both PE and ED.[62] In short, these studies failed to demonstrate any significant benefit in patients with PE in the absence of comorbid ED.

α1-adrenoceptor antagonist

Ejaculation is controlled by the sympathetic nervous system. Therefore, α-blockers have also been hypothesized to be effective in the treatment of PE. Some animal studies have demonstrated stimulation of the hypogastric nerve to reduce the pressure on the seminal vesicle.[63] In one study, treatment with an α1-adrenergic receptor antagonist resulted in significant improvement in 50% of primary psychogenic PE patients resistant to psychotherapy.[64] Another very small study with short-term follow-up also suggested that treatment with an α1-receptor blocker may be beneficial for patients with PE and concurrent lower urinary tract symptom.[65]

Topical agent

Xin *et al.*[66, 67] proposed that the aetiology of PE is hypersensitivity of the penis, and, thus, one of the goals of PE treatment is to reduce the sensory perception of the penis and the penis biothesiometry studies have shown patients with PE to have higher penile sensitivity, which is not age-dependent. Schapiro[14] described using local anaesthetic agents for PE in 1943, the first documented topical therapy for PE. The topical agents were originally used 'off-label' in the treatment of PE. Compared with systemic therapy, local treatment is appealing because these agents could be used on-demand and minimal systemic side effects. However, the application of topical agents does result in a number of adverse events, including penis hypoaesthesia, ED, female genital anaesthesia and skin reactions. Topical agents currently available for PE treatment include severance secret cream (SS-cream), lidocaine cream, prilocaine cream and lidocaine spray.

SS-cream. SS-cream (CJ Co. Ltd, Seoul, Korea), developed at Yong-Dong Severance Hospital in Korea, is made from the extracts of nine natural products. It is applied to the penis 1 h before sexual intercourse and washed off prior to intercourse. SS-cream is available only in Korea and is not approved for use in other countries. Studies have reported both the latency and the amplitude of somatosensory-evoked potentials measured at the glans penis to be increased relative to baseline after local application of SS-cream,[68] which also have shown penile vibration threshold increase.[69] Xin *et al.*[70] reported the ejaculation latency to be significantly prolonged—more than 2 min—in 89.2% of patients using SS-cream. In a multicentre, double-blind study involving 106 cases, the use of 0.2 g SS-cream was reported to increase the mean IELT measured by stopwatch from a baseline of 1.37–10.92 min, compared with 2.45 min with placebo ($P<0.001$); this treatment was also 27 times more effective than placebo in enhancing sexual satisfaction ($P<0.001$).[71] The main disadvantage of SS-cream is the unpleasant odour and colour, which makes it unacceptable to many patients. A novel formulation, named 'Renewal SS-cream', is a new local agent composed of the two principal components of the original SS-cream. In rabbits, the renewed SS-cream delays the latency of spinal somatosensory-evoked potential more effectively than does the original SS-cream.[72]

Lidocaine–prilocaine cream. Lidocaine and prilocaine form a liquid eutectic mixture when mixed with equal parts by weight, resulting in a higher concentration of anaesthetic at the time of application. The eutectic mixture of local anaesthetics (AstraZeneca, London, UK) is a cream containing 2.5% lidocaine/prilocaine for topical usage with the ability to anaesthetize intact skin. It is available in some countries.

However, published studies of lidocaine and prilocaine cream are scarce. The largest double-blind clinical trial of lidocaine–prilocaine cream enrolled 42 cases in two groups. Treatment resulted in a 5.6-fold increase in IELT. However, only 29 of the initial 42 participants completed the study. A total 16% of patients with adverse effects reported penile numbness, retarded ejaculation, penile irritation and decreased

vaginal sensitivity.[73] Another placebo-controlled study reported the optimal application time to be 20 min prior to intercourse.[74]

Lidocaine spray. Another topical agent, lidocaine, has been available for more than 25 years in some countries. Both 9.6% lidocaine and 9.6% lidocaine mixed spray are available. Although manufacturers claim that the spray had the ability to delay ejaculation, reliable data from clinical trials are absent; therefore, its efficacy and safety cannot be assessed.[75]

FUTURE PERSPECTIVES ON THE TREATMENT FOR PE

Curing PE remains a distant goal. The ideal treatment for PE would be a novel medication that is rapid-acting and effective on an on-demand basis, without sexual side effects (e.g., diminished libido and ED) and without generalized side effects (e.g., nausea, insomnia and headache).

On-demand therapy of SSRIs

Although chronic administration of SSRIs has been successful in the treatment of PE, side effects, such as dry mouth, headache and dizziness, have presented a problem.[24] Therefore, it is understandable that patients are reluctant to accept the continued and long-term administration of SSRIs.[17,76] To minimize these side effects and better target the patient's needs in a cost-effective manner, the on-demand use of SSRI has been proposed.[24] Some studies have evaluated the use of SSRI antidepressants and 'as needed' dosing, but the study designs were not rigorous.[28,77] In recent years, however, several pharmaceutical companies have become interested in on-demand treatment of PE with SSRIs that have a short half-life and a very short period to attain maximum concentration. An example of such a drug is dapoxetine.

Dapoxetine. Dapoxetine is a new agent designed for the purpose of treating PE. Dapoxetine ((+)-(S)-N,N-dimethyl-(a)-[2-(1-naphthalenyloxy)ethyl]-benzenemethanamine) hydrochloride is a water-soluble, white to off-white powder with a molecular weight of 341.88 Da. Dapoxetine has a pKa value of 8.6 and is mainly charged at physiological pH. These features allow for its rapid distribution in the body. Pharmacological research shows dapoxetine to be a potent inhibitor of serotonin transporters.[78] Although its pharmacological activity is similar to that of clomipramine and that of conventional SSRIs, chemical features of the structure of dapoxetine and its pharmacokinetic profile differentiate it from other SSRIs.[79]

Dapoxetine has a unique pharmacokinetic profile that allows a relatively rapid achievement of high serum concentrations (time to maximum serum concentration: 1.29 h)[79] and rapid elimination (half-life: 1.49 h) after oral dosing, which might contribute to its utility as an on-demand therapy for PE.[79] In two 12-week placebo-controlled trials in the United States enrolling 2614 moderate or severe PE patients, on-demand administration of 30 or 60 mg dapoxetine significantly improved outcomes compared with a placebo. The IELT was significantly ($P<0.001$) increased, up to 3.6-fold over baseline versus 1.9-fold for placebo. Patient-reported perception of control over ejaculation and satisfaction with sexual intercourse was also significantly better than both baseline values and placebo.[80] The most common adverse events with 30 and 60 mg dapoxetine in these 12-week trials in the United States were nausea (8.7% and 20.1%, respectively versus 1.9% with placebo), diarrhoea (3.9% and 6.8%, respectively versus 1.4% with placebo), headache (5.9% and 6.8%, respectively versus 4.0% with placebo) and dizziness (3.0% and 6.2%, respectively versus 0.8% with placebo), and 5% of all subjects discontinued because of adverse events.[80]

Another well-designed, randomized, double-blind, multicentre, placebo-controlled, phase 3, randomized clinical trial was published in 2009.[81] It involved 618 men with PE separated into dapoxetine 30 mg, dapoxetine 60 mg and placebo groups. In this trial, IELT and the other outcomes assessed improved significantly more with dapoxetine than with placebo ($P<0.001$ for all). The adverse effects were similar to those previously reported. Results from a 9-month, open-label extension study that assessed dapoxetine 60 mg revealed the most common adverse events to be nausea (15.4%), dizziness (5.1%) and headache (4.6%), and 6.7% of subjects withdrew due to adverse events, including nausea (1.6%), dizziness (1%), diarrhoea (0.8%), headache (0.6%) and insomnia (0.5%).[82] In addition, dapoxetine has been already approved for the treatment of PE in seven European countries: Austria, Finland, Germany, Italy, Portugal, Spain and Sweden.[5]

Other SSRIs with a short half-life. In addition to dapoxetine, which is produced by Alza/Johnson & Johnson, Pfizer Inc. and Bristol-Myers Squibb have similar patent agents under development.[76] The Bristol-Myers Squibb drug, BMS-505130, is a powerful and selective SSRI with a short half-life and a slight advantage in the treatment of PE because its concentration in plasma declines rapidly after dosing.[83] Although specific data on these candidate drugs are not available by now, the Pfizer drug (UK 390957; Pfizer Inc., New York, USA) has been described as a rapid-acting serotonin modulator as well as a short-acting SSRI.[84]

Novel topical agents

Prilocaine–Lidocaine spray. The topical eutectic mixture for PE (Plethora Solutions Holdings PLC, London, UK) is a metered-dose spray of lidocaine and prilocaine under development. Its metered-dose aerosol-delivery system is specifically designed for use in treating PE. The system delivers a 7.5-mg lidocaine base plus a 2.5-mg prilocaine base per actuation.[85] The first open-label pilot study involved 11 cases in which the IELT was recorded by stopwatch. Using the spray 15 min before intercourse, the average IELT increased from 1.40 to 11.35 min ($P=0.008$). In addition, eight of 11 patients and seven of 11 partners reported their sexual satisfaction after the spray as 'better' or 'much better', respectively.[75] In a phase II placebo-controlled trial recently published,[86] 54 patients using topical eutectic mixture for PE prolonged their IELT from a mean baseline of 1.0 to 4.9 min. Only three cases (12%) experienced hypoaesthesia (numbness in the penis) and four experienced ED; none interrupted treatment as a result. Topical eutectic mixture for PE was also well tolerated by the female partners.

Dyclonine/alprostadil cream. Dyclonine is a local anaesthetic most commonly used in dentistry. It is under development as a topical agent (NexMed Inc., San Diego, CA, USA) for treatment of PE as a cream formulation in combination with alprostadil and prostaglandin E1. A pilot study (in summary form) involved 30 patients who applied the cream 5–20 min before intercourse.[87] There was a significant synergistic effect observed with the cream containing 0.5% dyclonine/0.4% alprostadil compared with creams containing 1% dyclonine alone or 0.4% alprostadil alone ($P<0.05$). The mean IELTs after dosing were 2.34 and 4.08 min in the placebo and dyclonine/alprostadil combination groups, respectively ($P<0.05$). Adverse events were reported by 17.5% of men. The most frequently reported adverse events were application site-related, such as penile burning, genital pain and genital swelling. The problems were mainly solved in 2 h.

Therapeutical combination

5-HT$_{1A}$ receptor antagonist and an SSRI. For those patients with severe PE, some researchers have suggested that on-demand SSRIs for PE should be able to induce at least a five- to sixfold IELT delay within 1–2 h. While at present such persistent strong-acting, on-demand SSRIs are not available, some data provided from animal studies have indicated that, in principle, such a potent acute ejaculation delay induced by SSRIs should be achievable if treatment is combined with a 5-HT$_{1A}$ receptor antagonist.

Desensitisation of receptors due to chronic SSRI exposure can be imitated in acute treatment by blocking 5-HT$_{1A}$ autoreceptors through co-administration of a 5-HT$_{1A}$ receptor antagonist and an SSRI. In an *in vivo* microdialysis study, when a selective 5-HT$_{1A}$ receptor antagonist WAY-100635 was combined with citalopram, WAY-100635 was able to increase extracellular 5-HT concentrations.[88] Williamson *et al.*[89] tried another 5-HT$_{1A}$ receptor antagonist, robalzotan, in combination with fluoxetine and citalopram in male mice. Neither fluoxetine nor citalopram affected ejaculation latency at day 1. However, at day 11, fluoxetine was shown to significantly increase ejaculation time, whereas citalopram had no such effect. Interestingly, both acute and chronic co-administration of fluoxetine or citalopram and robalzotan significantly delayed ejaculation time.[89] de Jong *et al.*[90] administered citalopram, WAY-100635, and citalopram and WAY-100635 together to male rats. In this study, WAY-100635 alone had no effect on ejaculation latency. Chronic treatment with citalopram alone diminished ejaculation frequency. However, both acute and chronic co-administration of citalopram and WAY-100635 delayed ejaculation time immediately. The results of these studies may lead to the conclusion that 5-HT$_{1A}$ receptor blockers do not change ejaculatory latency alone, but do so during SSRI treatment. However, human studies are needed to provide more evidence of effectiveness and safety in men.

Behavioural and physiological therapy. To increase the success of PE treatment, a new perspective is to combine behavioural and physiological therapy. PE is a multidimensional condition, and it most likely reflects a physiological response in combination with intraphysical and interpersonal problems. Perelman[13] suggests that doctors and sex therapists working together might significantly improve initial and long-term treatment response rates for PE by combining the two disciplines. Growing evidence indicates that combination therapy using the new drug and psychological therapy has become a new treatment choice for PE.

Oxytocin

Immunohistochemical studies have revealed that local synthesis of oxytocin and its synthesis-associated protein, neurophysin I, occurs in the epithelial cells of the epididymis.[91] Therefore, as an alternative to the SSRI approach, the use of oxytocin as a potential therapeutic agent in the treatment of PE is under investigation.[76]

Surgical treatment

To decrease penile sensitivity, some have reported the selective resection of branches of the dorsal nerves of penis for treatment of lifelong PE.[92] Although this treatment seems to be effective, such an invasive therapy still lacks animal studies on safety and efficacy. Furthermore, indication of such a therapy, surgical technique, adverse event and long-term efficacy and safety still require further assessment in large-sample, prospective, randomized controlled trials. Thus surgical treatment could not be recommended as a therapeutic method on PE by now.

Animal model

Researching the aetiology of PE and developing a treatment agent for PE are challenging due to the difficulty in setting up a standard animal model of PE. Most of our current animal studies use rats or rabbits with normal sexual behaviour.[93] In other words, the restriction on the development of animal models of PE is one of the primary factors limiting the development of PE therapy. Olivier *et al.*[94] and Pattij *et al.*[95,96] reported an animal model of PE that could be used to study delayed ejaculation. In this model, a large number of male Wistar rats were observed over 4–6 weeks using sexual behavioural tests. Fast and slow ejaculatory rats were distinguished based on the number of ejaculations during 30-min tests, each presenting almost 10% at both ends of the Gaussian distribution. However, a standard guideline with a more convenient way to set up PE animal models still needs to be developed.

SUMMARY

Research in PE therapy is currently experiencing an upsurge. Although all current pharmaceutical treatments are 'off-label', some novel oral agents and established methods of drug administration now provide important relief for PE patients. Research interest in PE therapy is probably due to the high incidence of PE and the increased needs of men afflicted with this condition. However, the lack of a widely accepted definition and assessment tools is still a major hindrance to PE research. Furthermore, the aetiology is still not unified. Moreover, in our opinion, the most important priorities that need to be addressed in the research of PE are the lack of a standard animal model and adequately powered aetiological studies enrolling both PE patients and unafflicted control males. There remains a long way to go in terms of future research.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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