Medical Treatment of Premature Ejaculation

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Introduction

Premature ejaculation (PE) is a common male sexual dysfunction with a prevalence of 30%. It was estimated that 75% of men may experience PE at some point in their sexual lifetime. The inability to control the timing of ejaculation can lead to reduced confidence, increased sexual anxiety and performance anxiety. PE can exert significant distress to both the patient and his partner.

Definition of PE

It is not standardised. Different authorities have their own definitions.

DSM IV TR: Persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it. The condition must also cause marked distress or interpersonal difficulty and cannot exclusively be caused by the direct effects of a substance.

ICD10: For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or during intercourse (if time limit is required, before or within 15 seconds) of the occurrence of ejaculation in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.

International Consultation on Urological Disease: Persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it, over which the sufferer has little or no voluntary control, which causes the sufferer and/or his partner worry or distress.

Physiology of PE

Ejaculation is a spinal reflex under supraspinal control. It is a sequential process composed of emission and expulsion. The emission phase involves the secretion of seminal fluid from the prostate and the seminal vesicles, contraction of the smooth muscles of the seminal tract from the epididymis to the prostate to transport the ejaculate, closure of the bladder neck and the internal urethral sphincter, and the ejection of sperms into the posterior urethra. Expulsion occurs when the semen is forcefully advanced through the urethral meatus by rhythmic contractions of the pelvic floor muscles and the bulbospongious muscles.

The triggers for ejaculation include tactile stimulation of the glans penis and various supraspinal stimuli. The neural control network for ejaculation involves specific spinal, supraspinal and peripheral enural pathways. Regulation of the ejaculatory reflex at the level of the spinal cord requires several neurotransmitters that include 5-hydroxytryptamine (5-HT), dopamine, acetylcholine, adrenaline, neuropeptides, oxytocin, gamma aminobutyric acid (GABA) and nitrous oxide (NO). Their exact role are still yet to be defined but they coordinate the sympathetic, parasympathetic and somatic nervous system.

One of the most investigated neurotransmitter in sexual behaviour is 5-HT. 5-HT neurotransmission is locally regulated by the 5-HT transport re-uptake system. As 5-HT is released, the transport system is activated to remove 5-HT from the synaptic cleft and thus avoiding over-stimulation of the post-synaptic 5-HT receptors. PE might be associated with the presence of lower synaptic levels of 5-HT especially in the ejaculatory modulation region of the CNS.

Assessments of PE include measurements of the Intra-vaginal ejaculation latency time (IELT) and the Patient reported outcomes (PROs). IELT is an objective prospective measurement at-each-coitus using a...
stopwatch handled by the female partner\(^{17}\). PROs assess the subjective components of PE that include control over ejaculation, satisfaction with intercourse, interpersonal distress or difficulty, and the patient’s perception. PROs address both the observable and non-observable aspects of the condition included in the definitions. PROs are typically evaluated by self-completed questionnaires such as the Premature Ejaculation Profile (PEP).

PE can be classified as either a "Life-long" condition (from onset of the first sexual encounter) or "Acquired" condition that develops after an interval of normal sexual function. In life-long PE, there is a potentially biological component due to an inherited hyper/hyposensitivity of central 5-HT receptors. In acquired PE, there is a predominant psychological component that is related to stress or situational factors. It may be associated with erectile dysfunction. The newer third type "Nature variable" PE is rather a normal variation in sexual performance. And lastly, "Premature-like Ejaculatory Dysfunction" is a man who complains of PE despite the fact that his ejaculation time is within the normal range, i.e. 3-6mins or may even be of very long duration.

**Current Treatment Options for PE**

Behavioural, cognitive, and sex therapy are the first line treatment for "Acquired", "Nature variable" and "Premature-like Ejaculatory Dysfunction". An integrated approach, including a combination of psychological/behavioural and pharmacologic treatments, may be most effective because this combined strategy would address both the psychological and physiological dimensions of PE. Behavioural, cognitive, and sex therapy approaches have been used to treat PE. Although these strategies have demonstrated some short-term success, they are associated with substantial relapse\(^1\). Pharmacological therapy can be the first line treatment for "Life-long" PE. However, up to this moment, there are no pharmacological therapies solely indicated and approved for treating PE. Current available pharmaceutical therapies for PE involve the off-label use of serum serotonin reuptake inhibitors (SSRIs), phosphodiesterase type 5 inhibitor (PDE5i) and topical anaesthetics. New agents being designed for on-demand treatment of PE include dapoxetine and tramadol.

**Conventional Agents**

The use of long-acting SSRIs to treat PE is based on the observation that a common side effect of these drugs when used for the treatment of depression is delayed ejaculation. The proposed neurological action following long-term administration of SSRIs is more serotonin release into the synapse, stronger enhancement of serotonin neurotransmission and consequently stronger activation of postsynaptic 5-HT receptors. Clinically observed ejaculation delay can only occur after 1-2 weeks of regular intake. The daily dose of SSRI for treatment of PE is paroxetine (hydrochloride) hemihydrate 20-40mg, clomipramine 10-50mg, sertraline 50-100mg, fluoxetine 20-40mg or citalopram 20-40mg.

However, long-acting SSRIs have been associated with a number of unwanted sexual side effects including lose of libido and erectile dysfunction\(^1\) and abrupt cessation of these agents may lead to the discontinuation syndrome\(^2\). This is characterised by symptoms such as tremor, shock-like sensation when turning the head, dizziness, nausea or vomiting, fatigue, and headache\(^16\). Therefore, patients taking an SSRI should be advised not to stop taking the medication abruptly. Further, SSRIs should not be prescribed to men aged <18 or men known to have a depressive disorder, particularly when associated with suicidal thoughts. Although daily use of an SSRI for PE treatment is efficacious and safe, its clinical use is still limited by an absence of approval for this indication by the US Food & Drugs Agency (FDA).

**Newly Developed Agents**

**Dapoxetine** is a new "designed-for-purpose" agent, currently in development for the treatment of PE, and which may address the shortcomings of existing pharmacological therapy. It has been approved for use on PE in Sweden, Finland, Portugal, Austria and Korea. 24 phase I trials, 2 phase II trials and 5 phase III trials have been conducted worldwide.

**Mechanism of Action**

Dapoxetine is a new short-acting SSRI in development for the on-demand treatment of PE. It is believed to delay the timing of ejaculation via modulation of the expulsion reflex at a supraspinal level\(^6,9\).

**Pharmacology**

Dapoxetine, or (+)-(S)-N,N-dimethyl-(a)-(2-[1-naphthalenyloxy]ethyl)-benzenemethanamine hydrochloride, is a water-soluble white powder with a molecular weight of 341.88, a pKa of 8.6, and an absolute bioavailability of 42%.

Following oral administration of a single dose, peak plasma concentrations were reached with dapoxetine 30 and 60 mg, respectively, at 1.01 and 1.27 hours postdose. This abrupt rise in plasma concentrations has been shown to prolong intravaginal ejaculatory latency time (IELT) in the absence of 5-HT1a receptor desensitisation, which is an important factor in the ejaculation-delaying effects produced by other long-acting SSRIs.

**Dosage and Administration**

Following a single dose, mean (standard deviation) IELT increased from 0.9 minute at baseline to 2.05 (3.02)
and 2.41 (3.82) minutes with dapoxetine 30 and 60 mg, respectively (vs 1.38 [1.84] minutes with placebo; P ≤ 0.0006 for both). Although dapoxetine is intended to be taken 1 to 3 hours prior to anticipated intercourse, significant increases in mean IELT have also been seen with doses taken 0.5 to 1 hour, 3 to 4 hours, and more than 4 hours before sexual activity. Elimination of dapoxetine is rapid and biphasic, with initial half-lives of 1.31 and 1.42 hours following oral administration of dapoxetine 30 and 60 mg, respectively; plasma levels typically fall to less than 4% to 5% of peak concentrations 24 hours after dosing. Unlike long-acting SSRIs, the pharmacokinetics of dapoxetine is not affected by multiple dosing. After 6 days of daily treatment, plasma concentrations decreased to less than 7% of peak levels within 24 hours of taking the last dose. Daily dosing of dapoxetine resulted in only modest accumulation.

**Drug Interactions**

The pharmacokinetics of dapoxetine 60 mg was found to be similar among young (ages 18-45 years) and elderly (age >65 years) men. The consumption of a high-fat meal demonstrated only a modest effect on the pharmacokinetics of dapoxetine. Following a high-fat meal, peak plasma concentrations decreased by 11% and time to peak concentration was delayed, whereas elimination kinetics was not affected. Consumption of alcohol before taking dapoxetine did not appear to impair the pharmacokinetics of dapoxetine. Co-administration of dapoxetine may alter the effects of ethanol on some cognitive and subjective measures, such as dizziness, drowsiness, slow reflexes, and impaired judgement. Similarly, dapoxetine has no clinically important pharmacokinetic interactions with PDE5is, including tadalafil or sildenafil. The co-administration of dapoxetine and tamsulosin was not found to alter the pharmacokinetics of either drug or the orthostatic profile of tamsulosin.

**Adverse Effects**

Nausea (15.3%), dizziness (10.2%), headache (8.1%) and diarrhea (6.1%) are top reported adverse effects19. They were mild to moderate in severity and occurred within the first 4 weeks of treatment.

**Tramadol**

Tramadol is a central acting analgesic agent that combines u-opioid receptor activation and reuptake inhibition of serotonin and noradrenaline. On-demand use of tramadol 50mg (taken 2 hours prior to coitus) was associated with a clinically relevant ejaculation delay in a double-blind, placebo-controlled study on men with PE18. The most common adverse effects were nausea (15.6%), vomiting (6.2%) and dizziness (6.2%). However, further long-term follow up studies are needed to evaluate the risk of opioid addiction with this drug.

**Conclusion**

Long-acting daily SSRIs have been very effective and are still the best treatment option for life-long PE. Significant adverse effects from daily SSRIs treatment can contribute to poor drug compliance. Topical agents are simple treatment options but they have never gained popularity among men with life-long premature ejaculation. Newer short-acting on-demand agents like dapoxetine have been developed to treat PE as the main indication and have shown in multiple phase III trials to prolong IELT and improve PROs. However, there is no randomised, double-blind, placebo-controlled trial directly comparing the potency of this short-acting on-demand agent and long-acting daily SSRIs. Long-term follow up studies are also required to evaluate the safety use of opioid analgesic agents for PE.

**References**