Premature ejaculation: a clinical update

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ABSTRACT

- Premature ejaculation (PE) is ejaculation occurring without control, on or shortly after vaginal penetration and before the subject wishes it, causing marked distress or interpersonal difficulties.
- PE is the most common male sexual complaint. Primary (lifelong) PE has a physiological basis.
- Therapy should involve the man and his partner. The primary aims of therapy are for the man to regain a sense of control over his ejaculation time and for him and his partner to feel satisfaction with sexual intercourse.
- The most effective therapies for primary PE are certain selective serotonin reuptake inhibitors, given on a daily basis or "on demand" before sexual activity. Topical anaesthetics have also been shown to be effective.
- The most common cause of secondary PE is declining erectile function. The approach to treating secondary PE is to treat the underlying condition.

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Since the late 1990s, when phosphodiesterase type 5 (PDE5) inhibitors became available for the treatment of erectile dysfunction (ED), men have been more forthcoming in acknowledging and discussing their impotence. However, they are still somewhat reticent about acknowledging the problem of premature ejaculation (PE), despite the fact that it is the most common male sexual complaint and can be managed with a success rate similar to that for ED (about 75%). As with ED, what was originally thought to be a purely psychological disorder is now recognised to have an organic basis.

PE, as defined by the *Diagnostic and statistical manual of mental disorders* (DSM-IV-TR), is ejaculation occurring, without control, on or shortly after penetration and before the person wishes it, causing marked distress or interpersonal difficulty.[1] Although timing of intravaginal ejaculatory latency time (IELT) (ie, time from penetration to ejaculation) is not included in this definition, an IELT of less than 2 minutes, or ejaculation occurring before penetration, has been considered consistent with PE.[2] Recently, the International Society for Sexual Medicine has redefined PE, to include IELT, as:

> . . . ejaculation that always or nearly always occurs before 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.[3]

The core elements for the diagnosis of PE are the time to ejaculation (verified objectively by use of a stopwatch by the man or his partner), the inability to delay ejaculation, and the existence of negative consequences of PE.

True PE may be primary (lifelong), occurring and persisting from the first sexual encounter, or secondary (acquired), occurring after a period of normal control of ejaculatory function. Two further classifications are proposed but not widely accepted: normal variable PE, in which early ejaculation occurs inconsistently and is situational; and premature-like ejaculation, in which there is a subjective perception of PE although the IELT is normal (ie, > 2 minutes).[4]

Reference to the frustration caused by PE can be traced back to the *Kama Sutra*, written between the 1st and 4th centuries CE.[5] It consistently affects about one in three men, although two in three men may be affected at some time in their lives.[6] It is suspected that primary PE has a genetic basis. In one study, 91% of men with primary PE had a first-degree relative with PE.[7] *The Hite report*, which surveyed more than 7000 men in the United States, found that 70% of males responded positively to the question "Do you ever orgasm 'too soon' after penetration?"; 21% reported that they ejaculated within 50–60 seconds of vaginal penetration and 62% ejaculated within 1–5 minutes.[8] Masters and Johnson stated that a man has PE if he ejaculates before his partner achieves orgasm in more than 50% of sexual encounters.[9] But this definition is problematic, as it is couched in terms of the partner's sexual function and/or expectations. A study of 500 couples objectively measuring IELT revealed a highly skewed distribution with a median IELT of 5.4 minutes (range, 0.55–44.1 minutes).[10]

Repeated PE, particularly when the man is criticised, actively or passively, by his partner, may lead to loss of self-esteem, anxiety, ED and reduced libido. It may also lead to sexual difficulties for the partner due to lack of adequate foreplay, and may contribute to anorgasmia. The presence of PE in the man may be revealed when his partner presents with sexual dysfunction.

Neurobiogenesis of ejaculation

The neurobiogenesis of ejaculation is represented in Box 1. Stimulation of the glans penis mucosal sensory receptors (Krause finger corpuscles) is relayed by the pudendal nerve afferent fibres to S4, and then to the hypogastric plexus at the T10–L2 sympathetic ganglia. Sensory information is relayed centrally to the brain, where three ejaculatory centres are situated. Two are in the hypothalamus (the medial preoptic area and the paraventricular nucleus) and one is in the midbrain (the periaqueductal grey).

These centres integrate the peripheral events of seminal emission, ejaculation and orgasm. The efferent dopamine output by these centres is modulated by the nucleus paragigantocellularis. This has an inhibitory influence, from its serotonergic neurones centrally and to the lumbar–sacral motor nuclei, which tonically inhibits ejaculation.[11] Neurotransmitters involved in these centres include noradrenaline, γ-aminobutyric acid, oxytocin, nitric oxide, serotonin and oestrogen.

Ejaculation is triggered by efferent dopamine acting on the D2 receptors of central and spinal efferent fibres, which relay information down to the sympathetic ganglia at T10–L2 and sacral fibres.[12] This stimulates pudendal nerve fibres from the S2–S4 region of the spinal cord, resulting in:

- Smooth muscle contractions of the prostate, seminal vesicles, vas deferens and epididymis. This increases semen volume and fluid content, which is forced into the posterior urethra under the

control of the sympathetic nervous system, producing emission (Stage I).

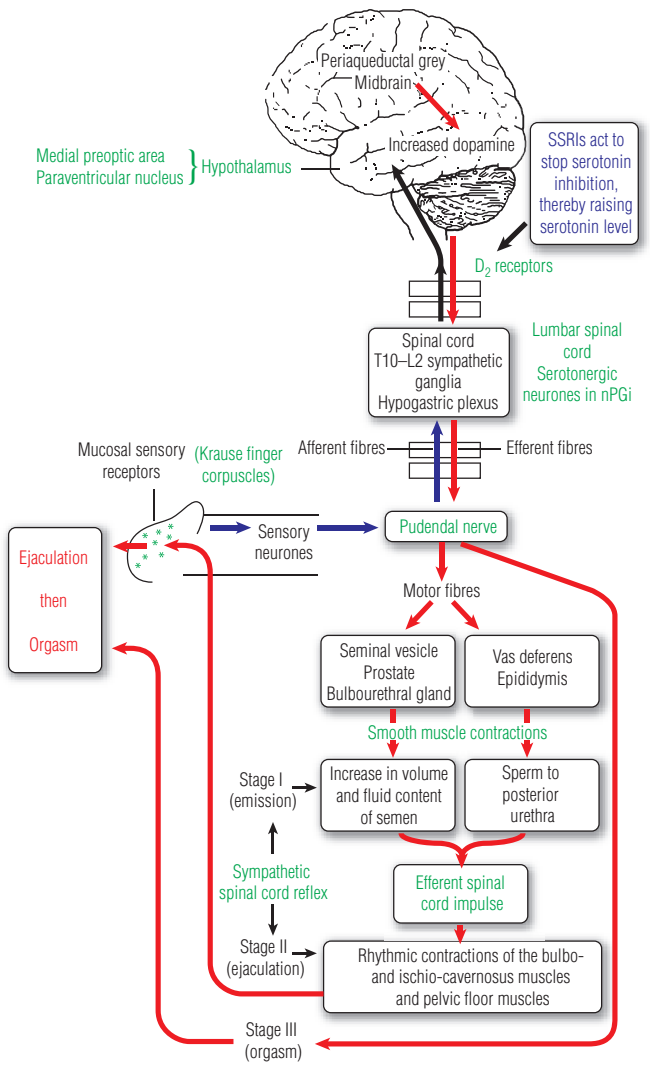
- Rhythmic contractions of the pelvic floor and bulbo- and ischiocavernosus muscles, controlled by parasympathetic nerves, which override sympathetic nerves. This propels seminal fluid out through the urethra, with resultant ejaculation (Stage II).
- Orgasm (Stage III).

Primary PE is thought to be due to hyposensitivity of 5-hydroxytryptamine 2c (5-HT_{2c}) serotonin receptors or hypersensitivity of 5-HT_1 serotonin receptors, causing lowering of the ejaculatory threshold and shortened IELT.[11,13]

Management of the patient

Control over ejaculation and satisfaction with sexual intercourse are the central issues for men with PE.[14] Keep these two outcomes in mind when assessing PE and evaluating treatment for this condition.

1 Neurobiogenesis of ejaculation



nPGi = nucleus paragigantocellularis. ◆

Medical history and medications

PE may be identified when the man or his partner presents with relationship difficulties. In such circumstances, questions about sexual function are natural in history taking. Disclosure of difficulties can be invited, depending on context, by open-ended questions such as "How are things at home?" Often PE is identified when the female partner presents with sexual difficulties.

Ascertain whether the PE is lifelong or acquired. The onset of ED can lead to acquired or compensatory PE. Infrequent sexual activity, cultural and educational background, and novelty of the partner or sexual situation have an influence. Coexistent prostatitis or urethritis should be considered and treated if necessary. A recent study noted greater prevalence of hyperthyroidism in men with PE.[15] With primary PE it is expected that the condition, and therefore the treatment, will be lifelong. For suggested questions to ask a patient presenting with PE, see Box 2.

Physical examination

Practise "the art of medicine" and reassure the patient he is anatomically normal. Check for signs and symptoms of chronic systemic disease, endocrine dysfunction or gynaecomastia. Also check gait, muscle strength, the sacral reflex arc, S2–S4 and general reflexes. It is important to perform a general medical examination as well as a genital examination.

Investigations

Investigations are rarely needed in a younger patient with lifelong PE. In older men with acquired PE, especially if secondary to ED, one should look for relevant risk factors: cardiovascular disease, hypertension, hyperlipidaemia, diabetes, obesity, obstructive sleep

2 Information to elicit from a patient presenting with premature ejaculation (PE)

Date of onset

- Primary (lifelong, from the onset of sexual functioning); or
- Secondary (acquired after a period of normal sexual functioning)

Precipitating factors

- Poor sexual education
- Masturbation guilt
- Religious or cultural inhibitions

How often does PE occur?

- Always/most of the time/sometimes

How often does the patient have sexual relations (eg, once/day to once/year)?

Intravaginal ejaculatory latency time

- Ask the patient or his partner to estimate the time in seconds or minutes (using a stopwatch, if feasible)

What is the effect of the PE on the patient?

- Feeling of control
- Distress or avoidance of sex
- Relationship problems due to PE
- Sexual satisfaction rating
- Quality of life
- Quality of relationship generally

What is the effect of the PE on the partner?

- Raise the same issues as for the previous question ◆

apnoea, Peyronie's disease, lower urinary tract symptoms and hyperthyroidism.

Management plan

Management involves both the patient and his partner. If there is a regular sexual partner, both should be present at a joint consultation. Therapeutic options should suit both partners and be appropriate to their habit in planning and frequency of intercourse. Follow-up at appropriate intervals to judge efficacy, titrate dosage of pharmacological treatments and ascertain side effects is mandatory.

Behavioural techniques

Active treatment of PE probably started over 50 years ago with Semans' "stop-start" technique for prolonging the neuromuscular reflex responsible for ejaculation.[16] The man informs his partner to stop genital stimulation until the subjective sensation of high arousal disappears. Stimulation is reintroduced and the cycle is repeated if necessary. One weakness in Semans' study was the lack of a control group. Further behavioural studies by Wolpe and Lazarus[17] and Masters and Johnson's "squeeze technique"[9] were not able to demonstrate that these behavioural techniques definitely "cured" PE. Such techniques are considered by many to be unhelpful in resolving relationship issues. Generally they are intrusive, mechanical and may fracture a normal love/lust act, relationship and spontaneity.

Measures that reduce penile sensation

Condoms reduce glans penis sensitivity and have been used in the treatment of PE. Topical preparations have also been used to reduce glans penis sensitivity. These include:

- Lignocaine–prilocaine aerosol (topical eutectic mixture for premature ejaculation [TEMPE]) applied 20–30 minutes before sexual intercourse and removed before contact with the partner. Trials of this treatment in the United Kingdom and The Netherlands have shown statistically and clinically significant prolongation of IELT compared with placebo.[18]
- Lignocaine–prilocaine cream (eutectic mixture of local anaesthetic agents [EMLA]) applied thinly to the glans and distal shaft and covered by a condom for 10–20 minutes. If the condom is removed for intercourse, residual cream should be washed off. In a randomised placebo-controlled study of this treatment, IELT improved significantly above baseline.[19]
- Lignocaine spray (Stud 100) applied to the glans in 3–6 sprays, 5–15 minutes before sexual intercourse. Although this treatment has been available for 25 years, there have been no randomised controlled studies of its efficacy.
- Severance Secret (SS) cream. This is available only in Asia and consists of herbal extracts. Efficacy over placebo has been shown in controlled studies.

The most prominent side effect of anaesthetic agents is penile numbness, which may in turn lead to loss of the erection. Adverse effects of SS cream are local symptoms of irritation and burning and delayed ejaculation.[20]

3 Recommended doses of pharmacological agents for premature ejaculation*

Tricyclic antidepressant

Clomipramine

25–50 mg daily
OR
25 mg 4–24 hours before intercourse

Selective serotonin reuptake inhibitors

Paroxetine

10–40 mg daily
OR
20 mg 3–4 hours before intercourse

Sertraline

25–200 mg daily
OR
50 mg 4–8 hours before intercourse

* Careful titration from low starting doses is essential to avoid side effects. Gradual reduction rather than abrupt cessation is advised in patients using daily therapy, especially at high doses, to avoid serotonergic withdrawal effects. ◆

Psychological counselling

It is more common for psychological problems to be secondary to PE rather than the cause. Counselling may be useful in conjunction with other treatments if it is considered to be helpful in improving self-esteem, but is not effective in treating the cause of lifelong PE.

Pharmacological treatments

Certain antidepressants — the tricyclic antidepressant clomipramine and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine and sertraline — have been shown to increase IELT, such that the patient perceives greater control over ejaculation (see Box 3 for recommended doses of pharmacological agents). Other agents, such as nefazodone, citalopram and fluvoxamine, have been found to be ineffective.[21]

Tricyclic antidepressants

Clomipramine administered daily has been shown to have a greater effect on IELT than daily use of the SSRIs fluoxetine or sertraline, but with a greater side effect profile ($P < 0.05$).[22] A double-blind crossover trial of daily clomipramine treatment (25 mg/day or 50 mg/day) in 15 couples found a significant increase in IELT with both dosing schedules. The baseline pretreatment IELT was 81 seconds, increasing to 202 seconds with 25 mg/day and 419 seconds with 50 mg/day clomipramine ($P < 0.01$).[23] Sexual satisfaction increased for both partners, especially at the higher dose, but this was offset by side effects including dry mouth, constipation, feeling "different", nausea, sleep disturbances, fatigue, dizziness and hot flushes.

Selective serotonin reuptake inhibitors

Paroxetine and sertraline have been the preferred SSRIs based on the results of clinical trials.[24,25] SSRIs block serotonin transporters at the synaptic cleft, resulting in increased serotonin within the central nervous system and spinal cord.[2] Serotonin is a potent vasoconstrictor with an inhibitory effect on ejaculation.[13] This is not totally a class effect, as there are differences between SSRIs due to gradual desensitisation of 5-HT receptors on the oxytocin-producing neurones.[26]

However, paroxetine and sertraline have a slow onset of action (5 hours) and long half-lives (1–3 days), making them cumbersome for "on-demand" therapeutic use. Like clomipramine, they need to be taken daily to maintain efficacy in delaying ejaculation. A single-blind placebo-controlled trial using 20 mg paroxetine on-demand 3–4 hours before intercourse showed a significantly delayed IELT compared with placebo. "Priming" by daily dosing with 10 mg paroxetine enhanced this effect.[27] Sertraline given as a 50 mg daily dose has also been shown to significantly increase IELT.[24]

Dapoxetine is the first SSRI developed specifically for PE. It is rapidly absorbed to give peak plasma concentrations within 1–3 hours, has a relatively short half-life of 1.5 hours and a terminal half-life of 18 hours, and can be taken as needed. Studies have confirmed a 50% increase in IELT with 60 mg dapoxetine taken "as needed" compared with placebo.[28]

Side effects of dapoxetine include headache, nausea, diarrhoea and dizziness. The drug has not been approved by the Federal Drug Administration for marketing in the United States. It has been submitted for approval in Europe and is not yet available in Australia.

Note that careful upward titration of SSRIs from low starting doses is recommended to avoid side effects.

Phosphodiesterase inhibitors

It has been proposed that the use of a PDE5 inhibitor (eg, sildenafil) may increase the level of nitric oxide centrally (reducing sympathetic drive) and peripherally (leading to smooth muscle dilatation of the vas deferens and seminal vesicles, opposing sympathetic vasoconstriction), thus prolonging IELT in men with PE. In a randomised placebo-controlled study of men with primary PE without ED, sildenafil did not significantly prolong IELT, but it was associated with a perception of greater control over ejaculation in men receiving active therapy.[29]

Daily versus on-demand therapy

In a questionnaire-based study involving 88 men who had received no prior treatment, 81% identified a preference for taking an oral therapy daily rather than on demand before intercourse.[30] The most frequently reported argument for daily treatment was that this had the least effect on spontaneity of the sexual relationship. McMahon and Touma have demonstrated that daily dosing augments the subsequent response to SSRIs taken on demand.[27] However, anejaculation is more common with daily therapy.

Combination therapy

It is possible that using lower doses of SSRIs and clomipramine in combination may reduce side effects and maintain efficacy,[31] but no controlled clinical trial of this therapy has been reported. Two studies using SSRIs combined with sildenafil to treat PE have reported benefit of the combination over SSRIs alone.[32,33]

Treatment of secondary PE

The approach to treating secondary or acquired PE is to treat the underlying condition. The most common cause of secondary PE is declining erectile function, where rapid ejaculation becomes a compensatory mechanism, either conscious or unconscious, for the inability to maintain the erection. An alternative explanation is that lower levels of nitric oxide and increased sympathetic tone, associated with ageing, both predispose to erectile failure and hasten ejaculation. PDE5 inhibitors may be effective in treating ED but do not prevent detumescence once ejaculation has occurred. By contrast, alprostadil intracavernosal injections prolong an erection beyond the point of ejaculation. However, they are not recommended for treating primary PE without coexistent ED, largely because of the lack of evidence for their use, but also because of the risk of priapism (especially in men without vascular compromise) and the risk of penile fibrosis with long-term use.[4,34,35]

Conclusion

PE is a common problem, and primary (lifelong) PE is thought to have a biological basis. Assessment and management of PE necessarily involves both the patient and his partner. The primary aims of therapy are for the man to regain a sense of control over his ejaculation and for the man and his partner to feel satisfaction with sexual intercourse.

The most effective and well tolerated treatment for PE is pharmacological therapy with certain SSRIs, usually given in small doses on a daily basis. Newer analogues of SSRIs are in development for the treatment of PE.

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Competing interests

Bronwyn Stuckey is on a Pfizer advisory board for female sexual dysfunction.

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