In the works: pharmacological treatment for premature ejaculation

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The ideal treatment for premature ejaculation – the most common male sexual dysfunction – would be an approved, discreet and on-demand therapy that is effective from the first dose and has no side-effects. The author takes a look at what is available.

Premature ejaculation (PE) has been defined by the wise men and women of the International Society for Sexual Medicine (ISSM) as 'a male sexual dysfunction characterised 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'.[1]

Premature ejaculation is a more common problem than erectile dysfunction (ED), although the prevalence data depend on the definition used. In a study in the USA of men aged 18–59 years, around 30 per cent of men reported that they 'climaxed too early' compared to 10 per cent of men who reported that they 'had trouble achieving or maintaining an erection'. This article gives a flavour of the differing pharmacological options for treating PE.

'ON-DEMAND' VERSUS DAILY PHARMACOTHERAPY

Given that PE is not a life-threatening condition and that most men are unlikely to be having sex on a daily basis (indeed, it may be a relatively infrequent event), the ideal treatment for PE has often been described as one that can be taken or administered 'on-demand'. It is interesting, however, to note that surveys of the prescribing patterns of urologists indicate that similar proportions of urologists are prescribing on-demand dosing as daily dosing.[2]

AETIOLOGY OF PE AND DRUG TARGETS

In contrast to ED, no organic disease has been firmly associated with PE, except perhaps some evidence that prostatitis, hyperthyroidism and penile hypersensitivity may play a role in the aetiology of PE in some men,[3] with a possible familial genetic overlay.[4] Many different pathways are involved (Figure 1)[3] and the relative importance of these is incompletely understood. A particular focus has been on serotonin (5-hydroxytryptamine, 5-HT), which appears to be a key mediator in the neurophysiology of ejaculation, with at least three 5-HT receptor subtypes (5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C}) so far implicated. The final common path, however, is undoubtedly the afferent-efferent reflex, which can be influenced like any other by local anaesthetics.

ASSESSMENT OF CLINICAL BENEFIT

Drug companies tend to present data in many different ways, which can make

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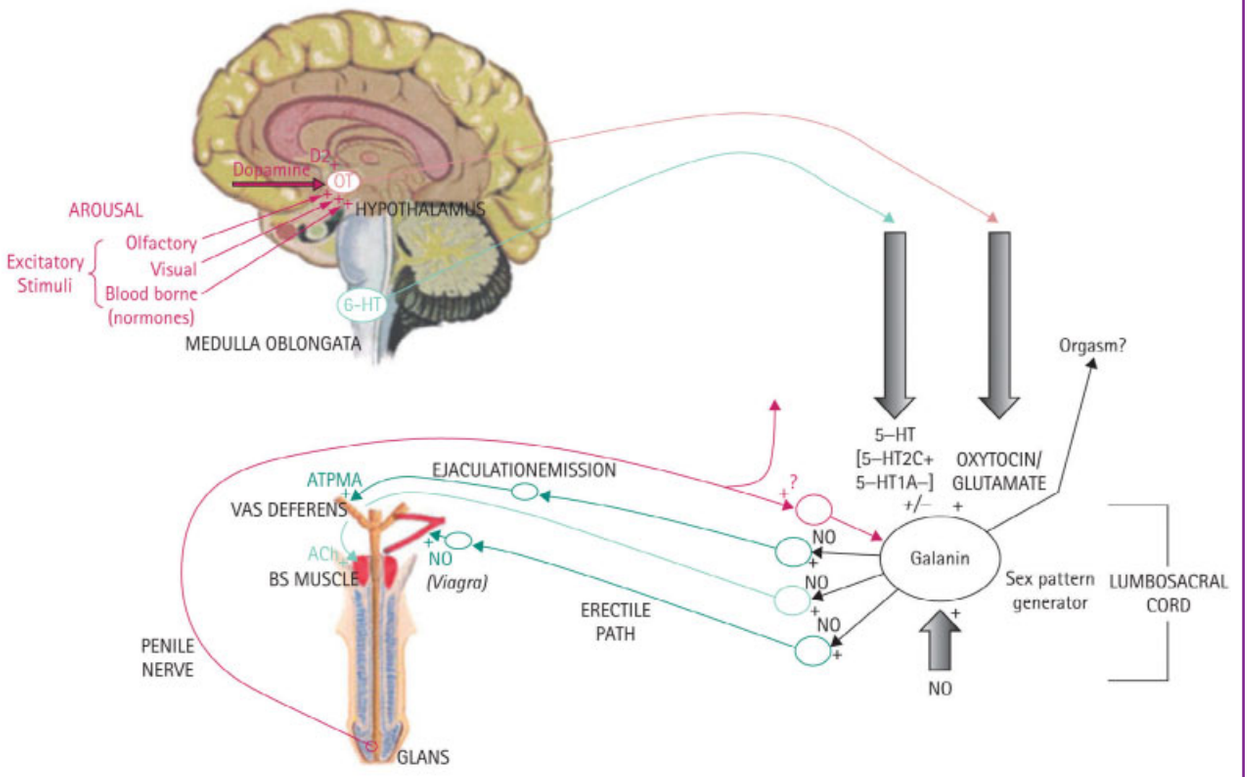

OT, oxytocin; 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; NO, nitric oxide; BS, bulbospongiosus muscle.

Figure 1. Pathways involved in ejaculation[3]

interpretation and drug–drug comparison problematic. A more reliable index of drug performance can be an analysis of what the regulatory authorities require for marketing authorisation.

The efficacy of therapy in clinical trials is generally based on a change in intravaginal ejaculatory latency time (IELT), which is assessed by stopwatch measurement, sometimes coupled with a patient-reported outcome, such as the index of PE. The latter is used to capture 'bother' or 'distress', which may not be directly related to ejaculation time. One potentially useful benchmark in evaluating clinical data is that the ISSM uses a cut-off point in their PE definition of 'within about one minute'. It would appear that the regulatory authorities require to see at least a doubling of time as the index of an effective drug.

As PE is generally not life-threatening, the regulators are insistent on wide therapeutic ratios, *ie* potential drugs have to be squeaky clean.

It is not anticipated that the endpoints used in clinical trials will have any real diagnostic value in the work-up of patients with PE.

ORAL THERAPIES

Traditionally, as in most therapeutic areas, patients with PE prefer oral medication to other routes.

Tricyclic antidepressants

Clomipramine is a tricyclic antidepressant that inhibits the uptake of noradrenaline and 5-HT by adrenergic and 5-HT neurons. Daily dosing with 25mg or 50mg clomipramine can significantly increase IELT compared with placebo,[5] and several studies using 'on-demand' dosing with clomipramine have shown some degree of benefit.

To circumvent some of the issues relating to the use of an antidepressant in non-depressed patients and the limitations of clomipramine, other formulations of the drug have been evaluated. One such example is VR776 (Vectura Group plc, Chippenham, UK), a novel proprietary formulation of clomipramine delivered by oral inhalation via Vectura's dry powder inhaler (Aspirair). Although having some effect, VR776 has a high level of respiratory side-effects, which suggest that the drug may not reach the market.

Selective serotonin reuptake inhibitors

The use of selective serotonin reuptake inhibitors (SSRIs) in PE, like many

good drug discoveries, started with clinical observation rather than rational drug design. Delayed ejaculation is a common side-effect of the SSRI class of antidepressant drugs (such as paroxetine, fluoxetine, sertraline and citalopram) when used to treat depressed patients, and this serendipitous discovery has led to the use of SSRIs as a treatment for PE.

SSRIs inhibit the reuptake of 5-HT into the presynaptic cell as a result of blockade of 5-HT transporters, increasing levels of 5-HT within the synaptic cleft. The use of SSRIs in the treatment of PE has been the subject of a number of comprehensive reviews and a meta-analysis,[6] with the general conclusion that, with daily treatment, all the SSRIs produced an increase in IELT.

In spite of a lack of regulatory authority approval, the off-label use of SSRIs in the management of PE is currently endorsed by the American Urological Association guidelines as well as the Second International Consultation on Sexual Dysfunctions.

Although daily SSRIs are highly effective in the treatment of PE, there are accompanying nuisance side-effects (such as dry mouth, headaches and dizziness) and the risk of more serious consequences (including psychiatric and neurological as well as the potential for drug interactions and problems related to SSRI withdrawal and the potential for suicidal ideation). These may be important considerations when SSRIs are used outside our normal comfort zone in the treatment of depression, *ie* for the management of PE.

The use of continuous versus on-demand administration of SSRIs for managing PE has recently been reviewed by Giuliano and Hellstrom,[7] with the conclusion that studies using conventional SSRI antidepressants with as-needed dosing to date have not been rigorous.

To get round the actual or perceived issues of long-term use of 'off-label' SSRIs, short-active agents are being developed to optimise on-demand benefit. Dapoxetine (Johnson & Johnson, Mountain View, California, USA) is a short-acting SSRI in development for the on-demand treatment of PE.[8] On-demand administration of dapoxetine three hours before intercourse resulted in an up to four-fold increase in IELT. Dapoxetine was also relatively well tolerated compared to longer-acting SSRIs, although nausea, diarrhoea, headache and dizziness were commonly reported adverse events. In spite of these promising findings, the Food and Drug Administration issued a non-approvable letter for dapoxetine in 2005, although a European marketing authorisation has been obtained.

Several other novel short-acting SSRIs have reached preclinical and early clinical development. These include UK-390,957 (Pfizer Inc., New York, USA) and BMS-505130 (Bristol-Myers Squibb, New York, USA). However, Pfizer has withdrawn UK-390,957 from further clinical studies, and there appears to be no further news of BMS-505130, possibly as a result of problems with low oral bioavailability. Similarly, VI-0134, an oral 5-HT_4 agonist developed by Vivus Inc. (Mountain View, California, USA) for on-demand use in PE also appears to have been abandoned.

5-HT_{1A} receptor antagonists

The time taken to desensitise 5-HT_{1A} receptors is thought to be the reason for the delay of several weeks in the clinical improvement of depression with SSRIs. 5-HT_{1A} antagonists have therefore been investigated as potential treatments for PE on the basis that they could mimic the desensitisation of the receptor and speed up the onset of action of the SSRI, thereby inducing strong immediate ejaculatory delay. Two 5-HT_{1A} antagonists, WAY-100635 and robalzotan (NAD-299), have been used in animal models of ejaculation and both drugs delayed ejaculation acutely when administered together with an SSRI. Neither was effective when used alone.

Opioid receptor agonists

Tramadol, a centrally acting agonist of μ-opioid receptors, is a narcotic analgesic indicated for the management of moderate to severe pain. Its mode of action in PE is not completely understood; however, in animal models it binds to opioid receptors and is suggested to inhibit noradrenaline and serotonin reuptake.

Tramadol 25 or 50mg has been shown to be effective in prolonging IELT when used on-demand (one to two hours before anticipated intercourse) in patients with PE, although interestingly, a recent study showed that daily treatment with one 100mg sustained-release tablet for four weeks was no better at prolonging IELT than placebo.[9]

Phosphodiesterase-5 inhibitors

On-demand oral phosphodiesterase-5 (PDE-5) inhibitors are a popular and effective treatment for ED, but there is no pharmacological rationale for their use in the treatment of PE. A review of 14 clinical trials of PDE-5 inhibitors in the treatment of PE concluded that there is no convincing evidence to support their role in the treatment of men with lifelong PE and normal erectile function.[10] However, there is limited evidence to support a potential role for PDE-5 inhibitors alone or combined with daily or on-demand SSRIs in the treatment of acquired PE in men with comorbid ED.

Other potential drug targets for oral therapy

As ejaculation is a sympathetic spinal cord reflex (see Figure 1), sympatholytic agents such as alpha-1 adrenoreceptor antagonists could theoretically be used in the treatment of PE, and there has been some success in ejaculatory delay with daily use of alfuzosin and terazosin. Plasma oxytocin levels rise during tumescence and are significantly higher at the point of ejaculation than at baseline. Systemic administration of oxytocin has been shown to shorten the ejaculatory latency time and

the post-ejaculation recovery interval in rats, and a recent study elucidated the site of action of oxytocin receptors involved in the sexual response and ejaculation. Theoretically, oxytocin receptor antagonists could be used to prolong IELT, although to date there has been no report on their efficacy in the treatment of PE.

TOPICAL THERAPIES

Treatments that can be used 'as needed', with the potential to avoid systemic toxicity, are a logical area for further development. Topical treatments can be messy to use and the time to onset of action can mean that spontaneity is compromised. Important differentiating factors in patient acceptability are whether or not ejaculatory delay can be achieved without adversely affecting the sensation of ejaculation for the man and without transfer of the desensitising agent to the partner. Progress on this approach has been reviewed by Morales *et al.*[11]

Anaesthetic creams and sprays

The treatment options are creams or sprays commonly used for topical anaesthesia of the skin and mucosa before minor skin procedures (*eg* lidocaine-prilocaine cream). These have been used off-label as a topical treatment for PE when applied to the penis and covered with a condom before intercourse. The optimum application time for lidocaine-prilocaine is considered to be 20 minutes before intercourse. Patients using the cream have reported a 5.6-fold increase in IELT to 6.7±2.5 minutes and improved sexual satisfaction, although loss of sensation (hypoaesthesia) and penile irritation were reported by around 17 per cent of men.[12]

A topical agent that has been designed specifically for the treatment of PE (Topical Eutectic-like Mixture for Premature Ejaculation, TEMPE/PSD502; Plethora Solutions plc, London, UK; Shionogi Pharma Inc., New Jersey, USA) appears to be in the latest stage of development. PSD502 is a proprietary metered-dose aerosol that delivers a eutectic mixture of 7.5mg lidocaine and 2.5mg prilocaine (dissolved in a non-chlorofluorocarbon propellant) per actuation.[13]

This method of delivery enables a concentrated film of local anaesthetics in their base form (uncharged) to be deposited onto the glans penis. As only the base forms of local anaesthetics are able to penetrate skin or mucosa, the onset of action of the spray is more rapid than that seen with cream formulations (which contain a mixture of base and ionised forms of local anaesthetics; Figure 2).

Results from phase 2/3 placebo-controlled studies have shown a four- to six-fold increase in geometric IELT (from baseline in the lidocaine-prilocaine spray group compared with placebo),[13,14] with only 3–5 per cent of men reporting hypoaesthesia. In theory, as the eutectic mixture of lidocaine and prilocaine is absorbed by the poorly keratinised skin of the glans penis and is less likely to penetrate fully keratinised skin on the shaft of the penis, sensation is more likely to be retained.

Other transdermal delivery systems

While the use of a eutectic mixture is one way of maximising skin/mucosa penetration, products containing other transdermal delivery systems are also in development. Promising results were presented by NexMed Inc. (East Windsor, New Jersey, USA) for their topical cream (NM100061) containing the local anaesthetic dyclonine with alprostadil, a prostaglandin with vasodilatory effects together with NexMed's patented permeation enhancer known as NexACT. However, the product no longer appears in NexMed's list of pipeline products.

Futura Medical (Guildford, UK) is (according to the company website) developing a non-prescription topical product (PET500) utilising their proprietary skin delivery technology DermaSys and containing a 'well characterised mild topical anaesthetic compound', targeting men who suffer only situational or occasional PE.

Natural products

Among the range of 'herbal' creams claiming to delay ejaculation, SS-Cream

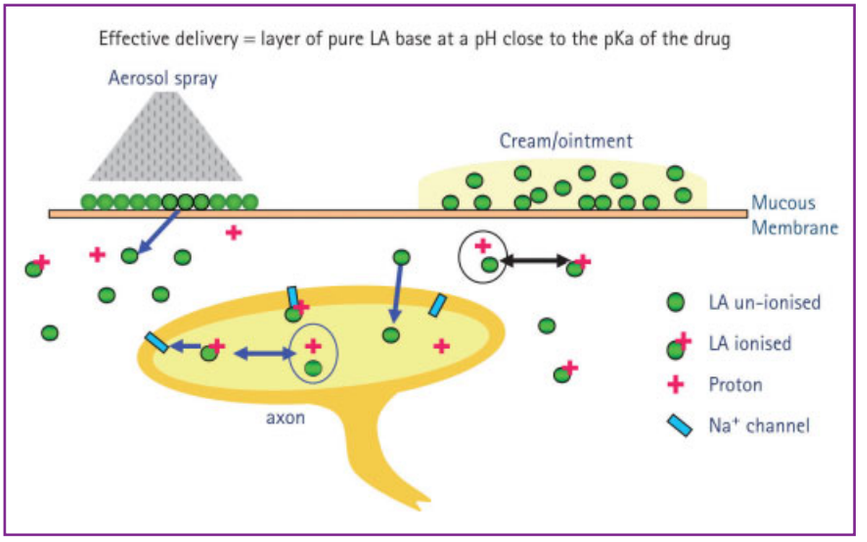

Figure 2. Mode of action of topical local anaesthetics (LA).[11] Aerosol sprays contain purely base (uncharged) forms of local anaesthetics, while creams contain a mixture of base and ionised forms. Only the uncharged base forms are able to penetrate skin or mucous membranes. Local anaesthetics produce localised reversible inhibition of nerve conduction by reducing the permeability of the neuronal membranes to sodium ions, the movement of which is necessary for the transmission of nerve impulses

(Severance Secret-Cream; Cheil Jedan Corporation, Korea) appears to be the only one that has been subject to clinical trials. It is made from extracts of natural products, some of which have local anaesthetic and vasodilatory properties and is applied to the glans penis one hour before intercourse and washed off immediately before coitus. In spite of promising results in clinical trials, where it significantly prolonged ejaculatory latency in 89 per cent of patients, SS-cream is unacceptable to some patients as a result of its unpleasant odour and colour, and it is unlikely to gain approval outside of Korea.

BEHAVIOURAL TECHNIQUES AND PSYCHOLOGICAL THERAPY

Ironically, based not so much on evidence-based support but history, behavioural techniques and psychological therapy are the only approved therapies in the USA. There is nothing new about the use of psychological therapy in the treatment of PE; indeed, variations of the stop-squeeze and stop-pause technique, as introduced by Masters and Johnson and Kaplan, respectively, have been in use for decades. It has been argued that a combination treatment integrating pharmaceuticals and sex therapy would provide an optimised approach to treatment, although the question of which psychotherapies are most effectively combined with pharmacotherapy remains unanswered.

SUMMARY AND CONCLUSIONS

In the absence of a 'cure' for PE, one must look towards long-term pharmacological treatment either with or without behavioural or psychological therapy. For those who do not engage in sexual activity on a daily basis, the ideal pharmacotherapy for PE would be an approved, discreet and on-demand therapy that is effective from the first dose, has proven efficacy, a low incidence of side-effects and with no unwanted effects on the partner. Within the past decade, a number of novel pharmacological therapies were emerging for the treatment of this problem, but the demise of dapoxetine in the USA and poor sales in the EU may have curbed the enthusiasm of the pharmaceutical industry.

Apart from dapoxetine (in the EU), as all therapies for PE are used 'off-label' and demand appears to be growing, there is an unmet need for an effective, licensed treatment. With the recent publication of the ISSM definition of PE and the development of validated PE diagnostic tools, the scene is now set for wider regulatory approval of more products for the treatment of PE.

Any of the novel oral agents described above may have a difficult hurdle to cross to gain regulatory approval in terms of the risk–benefit ratio, particularly the combination therapies, for which there are additional issues to consider such as cost and drug interactions. As a minimum, regulatory authorities will want to see long-term safety data, such as suicidal ideation risk and addiction potential. Topical agents, used 'off-label', are effective and have a more favourable risk–benefit profile, but may have deficits because of ease of application and spontaneity. These may have been largely overcome in PSD502, the novel topical spray formulation of lidocaine-prilocaine, which shows promise as an on-demand therapy with proven efficacy and a low incidence of systemic side-effects.

KEY POINTS

- **There is now a consensus definition for premature ejaculation**
- **Premature ejaculation is the most common male sexual dysfunction**
- **Penile hypersensitivity and genetics may be important**
- **Regulatory authorities are insistent on an excellent therapeutic ratio in what they sometimes see as a 'lifestyle' disorder**
- **There is no good evidence that 'off-label' selective serotonin reuptake inhibitors are effective 'on-demand'. However, their chronic 'off-label' use represents the mainstay of current therapy**
- **Dapoxetine, although approved, does not appear to be widely used; cost could be an issue**
- **The evidence supporting the use of phosphodiesterase-5 inhibitors in the treatment of premature ejaculation is somewhat limited**
- **Available topical treatments have limitations in terms of patient acceptability; there is no approved topical agent but there is some degree of 'off-label' use of desensitising creams**
- **PSD502, if approved, may have an optimal clinical profile in terms of therapeutic ratio and patient acceptance**

Declaration of interests
Michael Wyllie is a Board Member of Plethora Solutions.

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