Medical therapy for premature ejaculation

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***Abstract*:** Premature ejaculation (PE) is a common male sexual dysfunction. Advances in PE research have been hampered owing to a nonstandardized definition of PE, until the definition by the International Society of Sexual Medicine (ISSM) in 2009. Once the diagnosis of PE is established through a thorough history, a variety of medical therapies is available, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), centrally acting opiates, phosphodiesterase 5 inhibitors and topical desensitizing creams. Most of these treatments increase the intravaginal ejaculation latency time (IELT) and patient satisfaction scores, with the most convincing evidence for SSRIs and topical creams. Daily SSRIs such as paroxetine, although efficacious, do have a substantial and prolonged side effect profile. Dapoxetine, which is a on-demand SSRI, is the only licensed drug for the treatment of PE, increasing IELT by a factor of 2.5 to 3 with limited and tolerable side effects. In the near future, the topical aerosol PSD502 is due to be licensed for the treatment of PE, increasing IELT by up to a factor of 6 but having minimal local and negligible systemic side effects.

***Keywords*:** male sexual dysfunction, medical therapy, medical treatment, premature ejaculation

Introduction

Premature ejaculation (PE) can be a debilitating male sexual impairment. A range of studies have suggested a prevalence of 4–39% [Laumann *et al.* 1999; Grenier and Byers, 1995; Spector and Carey, 1990; Nathan, 1986; Reading and West, 1984]. This wide range can be partly attributed to variations in the way that PE is defined, but may also reflect differences between populations and differences in the degree of bother. Furthermore, because of the intimate nature of the problem, PE tends to be under-reported by patients who do not typically seek medical help [Grenier and Byers, 1995].

Definition of premature ejaculation

Over the years, PE has been defined in various ways. Some consider it controversial that PE is even considered to be a sexual dysfunction at all, since all male upper mammalian species, including primates ejaculate almost immediately on penetration of the vagina [Wainberg, 1984].

However, initial definitions of PE revolved around ejaculation which regularly occurs at or around initial vaginal penetration [Marmor, 1976]. A quantitative element was subsequently added to the definition. For instance, the arbitrary time of 1 minute from vaginal penetration to ejaculation was suggested by some [Marmor, 1976] while others defined the condition in terms of the number of penile thrusts (at least 15) inside the vagina before ejaculation [Colpi *et al.* 1986]. Other authors added a more subjective element to the definition by defining PE as ejaculation that happens prior to when the male desires it [Hastings, 1963] or ejaculations which are satisfactory to the female partner in less than 50% of sexual intercourses [Masters and Johnson, 1970]. A consensus on a standardized definition for PE was clearly needed.

Several attempts have been made over the years by a number of major societies (WHO, APA, EAU, AUA, ISSM) dealing with male sexual dysfunction to reach a consensus on the definition of PE. Table 1 illustrates the various definitions of PE.

All of the above definitions acknowledge one or more of the three core components to PE:

- a short ejaculatory latency;
- a lack of control over ejaculation;
- a lack of sexual satisfaction.

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Table 1. Early definitions of premature ejaculation.

Organization	Definition
The World Health Organisation (WHO) (International Classification of Diseases-ICD, 1994) [WHO, 1994]	An inability to delay ejaculation sufficiently to enjoy lovemaking, which manifests as either of the following: • occurrence of ejaculation before or very soon after the beginning of intercourse (within 15 seconds of the beginning of intercourse) • occurrence of ejaculation in the absence of sufficient erection to make intercourse possible Exclusion criteria: PE is not the result of prolonged absence from sexual activity.
The American Psychiatric Association (APA) (The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), 2000) [APA, 2000]	• Persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it. The disturbance causes marked distress or interpersonal difficulty. Exclusion: PE is not due exclusively to the direct effects of a substance (e.g. withdrawal from opioids) and factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.
The European Association of Urology (EAU) (Guidelines on Disorders of Ejaculation, 2001) [Colpi *et al.* 2001]	• The inability to control ejaculation for a sufficient length of time before vaginal penetration. Exclusion: Impairment of fertility does not happen when intravaginal ejaculation occurs.
The American Association of Urology (AUA) (Guidelines on the pharmacologic management of premature ejaculation, 2004) [Montague *et al.* 2004]	• Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.

PE, premature ejaculation.

In 2009, the International Society of Sexual Medicine (ISSM) [Althof *et al.* 2009] produced its guidelines of the diagnosis and management of PE. It postulated an evidence-based definition of PE and defined PE as a male sexual dysfunction characterized by:

- ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration;
- inability to delay ejaculation on all or nearly all vaginal penetrations;
- negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual encounters.

This definition is regarded as the most robust to date owing to its evidence-based nature and has largely replaced the previous definitions as the standard definition of PE.

However, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) due to be published in May 2013 [APA, 2013] may offer an alternative take on the definition of PE. The impact of this new definition on the diagnosis and management of PE is awaited. In the interim, the definition advocated by the authors is the ISSM's definition of PE.

Diagnosis and classification

PE can be divided into two distinct entities: acquired and lifelong PE [Godpodinoff, 1989]. Lifelong PE is a condition which has existed since the onset of sexual activity and is not reliant on either the conditions or the environment under which sexual activity is taking place. Acquired PE develops in an individual who has previously had normal ejaculatory control and can develop gradually or suddenly.

The cause of PE is usually not apparent. Some have characterized these cases as being psychogenic in origin, while others have postulated 'biogenic' causes [Sadeghi-Nejad and Watson, 2008]. This fundamental controversy about whether PE is behavioural or biomedical has been reflected in the two differing approaches to therapy (i.e. behavioural or psychotherapy *versus* pharmacological therapy). Those proposing a

psychogenic basis in the absence of a definitive physical cause suggest that PE may be associated with situations such as:

- anxiety;
- novelty of partner or situation;
- low frequency of sexual activity.

Biogenic PE is linked to an identifiable organic cause and the following conditions have been identified as possible causes:

- substance abuse (e.g. alcohol);
- endocrinopathy (e.g. hyperthyroidism);
- chronic prostatitis;
- opiate withdrawal.

Once the condition is treated, the expectation is for PE to cease.

Those who have proposed biogenic theories for the development of PE have suggested that one of the following may be the pathophysiological mechanism:

- penile hypersensitivity;
- hyperexcitable ejaculatory reflex;
- hyperarousability;
- genetic predisposition;
- 5-hydroxy tryptamine (5-HT)-receptor dysfunction.

Waldinger and Schweitzer introduced the concept of PE as a syndrome, with patients experiencing a continuum of symptoms [Waldinger and Schweitzer, 2006]. The four main interweaving sets of symptoms are:

- short IELT, with control;
- short IELT, no control;
- normal IELT, no control;
- normal IELT, with control.

This spectrum of symptoms can therefore include a category called 'natural variable PE' whereby the episodes of PE are not consistent and can be situational. This group falls under the umbrella 'short IELT and no control'. This may represent a variation of natural ejaculatory function. Another category that stems from this syndrome is the 'Premature-like ejaculatory function' whereby the patients perceive that they are experiencing PE while the IELTs fall in the normal range. This falls under the umbrella 'normal IELT and no control'.

Classification of PE is still evolving as different classification models offer different clinical and research benefits [Cahangirov *et al.* 2011; Chan *et al.* 2011; Clément *et al.* 2009; Waldinger and Olivier, 2005; Pattij *et al.* 1995].

Clinical assessment

Clinical history plays an important part in the diagnosis of PE since it is by definition a self-reported diagnosis. However, clinical assessment can be challenging owing to the nature of the problem. Patients may be embarrassed and shy when relating details of their sexual experiences and exact details are not forthcoming. It may then be useful to involve the partner in the consultation.

To elicit a diagnosis of PE, the three main components of PE (timing, control and satisfaction) should be specifically addressed. Once a diagnosis of PE is established, other related avenues that should be explored are:

- the nature of the PE (lifelong or acquired);
- the presence or absence of any associated erectile dysfunction (ED);
- the impact of the PE on the relationship with his partner;
- the impact of the PE on quality of life;
- previous treatment (including over the counter medication) and response to that treatment.

Examination of the patient involves a general examination as well as a more focused examination of the genitalia outlining the scrotal contents and the penis in detail. A digital rectal examination to palpate the prostate gland is also recommended. Questionnaires such as the Index of Premature Ejaculation [Yuan *et al.* 2004] and the Premature Ejaculation Diagnostic Tool [Symonds *et al.* 2007] also have a role is evaluating PE. It must be noted that the routine use of questionnaires is not very useful, as they have a tendency to confuse the picture, especially when ED occurs concurrently. ED specific questionnaires such as the IIEF and its shorter version, IIEF-5, have been shown to further complicate the issue, especially in ED and PE trials [Ramanathan *et al.* 2007].

Laboratory and other physiological tests are rarely indicated. History and examination are sufficient to reach a diagnosis.

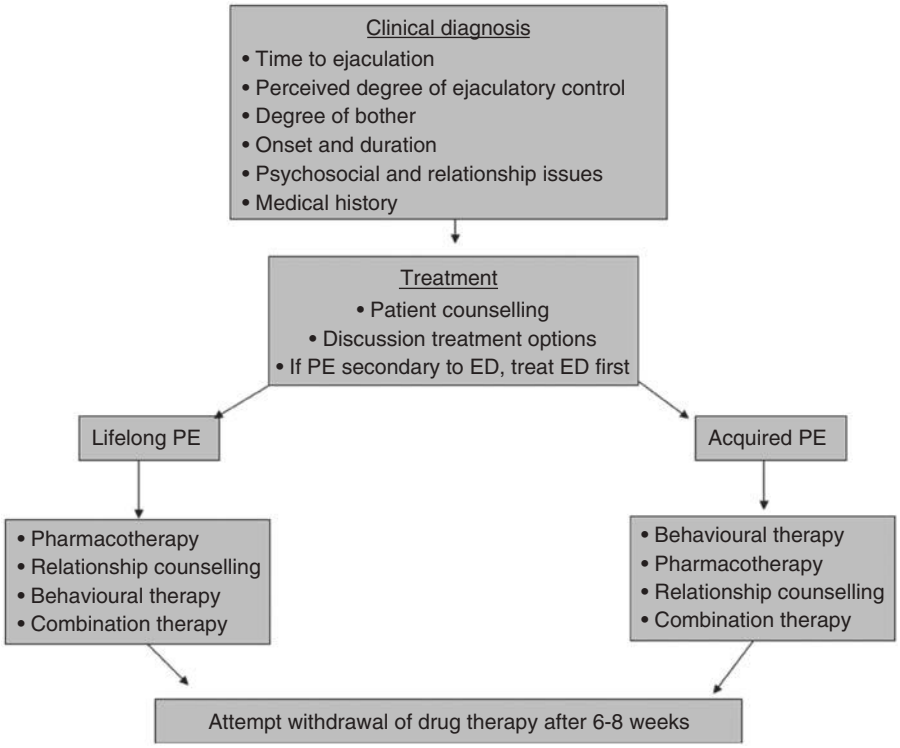

Figure 1. Management of premature ejaculation. PE, premature ejaculation; ED, erectile dysfunction.

Treatment

Treatment of PE can be a real challenge for the clinician (Figure 1). This is primarily because the pathophysiology of PE is so poorly understood. Over the years multiple treatment modalities have been tried, often with initial promise. However, there are few studies on long-term efficacy and durability for most of the currently available treatment options. This article aims to provide an overview of the different treatment options available together with an assessment of the supporting evidence.

Nonmedical therapy

Psychological and behavioural therapy historically have a significant role in the management of PE.

Behavioural therapy. The 'stop–start' strategy (stopping coitus *in situ* and restarting after a delay) and its evolution to the 'squeeze' technique (the physical application of pressure at the base of the head of the penis) have been reported since the 1950s [Semans, 1956]. However, while short-term benefits have been reported (symptomatic benefit in 45–65%), the long-term results of treatment have not been conclusive (after 3 years of follow up, 75% of men showed no lasting improvement) [Hawton *et al.* 1986]. One strategy, particularly for younger men suffering from PE, is precoitus masturbation which partially desensitizes the penis and leads to a delay in ejaculation [Sadeghi-Nejad and Watson, 2008].

Psychotherapy. Psychotherapy involves educating both the male patient and the female partner. This can happen in the context of marriage/relationship counselling as well as psychosexual therapy [Hatzimouratidis *et al.* 2010]. Again short-term results have been promising although long-term benefits are unproven.

Medical therapy

The quest to develop an effective tablet to aid and ultimately cure PE has been ongoing for many decades [Schapiro, 1943]. A number of drugs have shown some promise in treating PE with varying degrees of success. At the present time, only one drug (dapoxetine) is licensed (in some countries only) for the treatment of PE. However, the other drugs described below can also be used, as long as the patient is fully

aware that they are not licensed for the treatment of PE.

Historical agents

Alpha-adrenergic blocking agent (Phenoxybenzamine, alfusozin, terazosin) and monoamine oxidase inhibitor (Isocarboxazid, Phenelzine). Together with monoamine oxidase (MAO) inhibitors, alpha-blockers were the first oral medication used for the treatment of PE. However, the side effects associated with the nonselective alpha-blockers limited their use. These agents are not used for PE anymore [Beretta *et al.* 1986; Shilon *et al.* 1984; Aycock, 1949]. More selective alpha-blockers such as terazosin have shown some promise in treating PE in patients suffering from concurrent lower urinary tract symptoms [Başar *et al.* 2005].

More recent agents

A range of drugs are currently used by clinicians for the management of PE including antidepressants, local anaesthetic agents and phosphodiesterase type 5 inhibitors.

Whether the medication is used regularly or on demand is an important consideration for patients when choosing the most appropriate drug for the treatment of their PE. An on-demand drug offers the flexibility of using the medication just prior to sexual intercourse, thereby reducing the risks of side effects associated with the drug for the rest of the time. Data so far suggest that generally speaking the benefit of on-demand dosing is inferior to the benefits seen with regular dosing. On the other hand, daily dosage allows for a more spontaneous sexual experience. Set against this, regular dosing results in greater exposure to the drug and may be associated with more pronounced side effects. Waldinger and colleagues showed that the majority of men (81%) preferred a daily regimen as opposed to an on-demand regimen [Waldinger *et al.* 2007]. Moreover, the stigma associated with the daily use of an antidepressant (i.e. selective serotonin reuptake inhibitors [SSRI]) may be a complicating factor in the compliance of patients to the treatment.

Tricyclic antidepressants (clomipramine). There is evidence that continuous and on-demand dosing of clomipramine increases the IELT in patients suffering from PE [Strassberg *et al.* 1999; Kim and Seo, 1998; Segraves *et al.* 1993], with reports of improved sexual satisfaction both from patients and partners [Althof *et al.* 1995]. The use of clomipramine is limited by its associated side effects, mainly fatigue, dizziness, dry mouth and hypotension. During continuous dosing, the adverse event profile of clomipramine in men with PE was reported to be significantly worse than with SSRI treatment [Kim and Seo, 1998].

SSRIs unlicensed (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). Serotonergic agents have been shown to be effective in the management of PE. The mechanism probably revolves around activation of the 5-HT_{2C} receptor which leads to a delay of ejaculation [Lue and Broderick, 2007; Waldinger *et al.* 1998]. The effect of SSRIs on the delay of ejaculation was first noted by Patterson when treating men with depression [Patterson, 1993]. Since then, studies have shown that the effect of SSRIs to delay ejaculation can be seen within days of the start of treatment with a plateauing of the effect within 4 weeks. In the variously reported studies the IELT is increased between twofold and eightfold with the use of SSRI.

The use of fluoxetine to treat PE was first described in 1994 by Forster [Forster, 1994] and Waldinger and colleagues conducted the first randomized, controlled trial to evaluate the use of paroxetine in treating PE [Waldinger *et al.* 1994]. Further work by the same research group demonstrated efficacy of a number of SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline) in the treatment of PE, although with varying efficacy and side-effect profiles [Waldinger *et al.* 1998]. Fluoxetine, sertraline and paroxetine increased IELT significantly whereas there was no statistical difference with fluvoxamine.

Kim and Seo demonstrated that treatment with sertraline was nearly as effective and had a lower incidence of side effects than clomipramine [Kim and Seo, 1998]. Further studies (prospective studies and randomized controlled trials) have confirmed the efficacy of sertraline in the management of PE [Balbay *et al.* 1998; Biri *et al.* 1998; Mendels, 1995]. Duloxetine [Athanasios *et al.* 2007] and Escitalopram [Safarinejad, 2007] have also been shown to be effective in treating PE. The efficacy and side-effects associated with SSRIs are described later (see Table 5).

Adverse effects with SSRIs are usually minor and include fatigue, yawning, mild nausea, loose stools and perspiration. They usually present at the beginning of the treatment and they tend to disappear within 2–3 weeks. There have been reports of decreased libido, mild ED and increased suicide risks with the use of SSRIs, especially long-term paroxetine [McMahon *et al.* 2004; Kim and Seo, 1998; Waldinger *et al.* 1998]. Therefore, it is important that patients are adequately counselled about the risks involved with the use of these drugs. Once patients have been started on SSRI treatment, it is essential to perform follow-up assessments to not only evaluate the efficacy of the drug but also to identify any side effects, especially regarding associated sexual dysfunction and suicide risks.

Licensed SSRI (dapoxetine). Dapoxetine is the only licensed drug in the treatment of PE. It has been approved for treatment for the treatment of PE in New Zealand, Sweden, Austria, Finland, Germany, Spain, Italy and Portugal. National approvals and licenses in five other European countries are expected to follow. Dapoxetine is not approved for marketing in the United States.

Dapoxetine is a drug specifically developed for the on-demand treatment of PE. It has been extensively evaluated in five randomized, placebo-controlled phase III clinical trials involving more than 6000 men with PE. This is the largest and most comprehensive clinical trial programme to date for a drug therapy to treat PE. It is a short-acting SSRI designed to be taken only when needed and is taken 1–3 hours before sexual intercourse is anticipated.

There is evidence of its efficacy, its relatively mundane side effect profile and its validity as an on-demand medication [Feige *et al.* 2011; Hoy and Scott, 2010; Kaufman *et al.* 2009; McMahon *et al.* 2009; Giuliano *et al.* 2007]. However, the durability of the effects of dapoxetine has not yet been demonstrated in prospective, randomized trials since long-term follow up is not yet available [Safarinejad and Hosseini, 2006].

Table 2 summarizes the double-blind, randomized, placebo-controlled parallel trials to date looking at the use of dapoxetine for the treatment of PE [McMahon *et al.* 2011; Buvat *et al.* 2009; Kaufman *et al.* 2009; Patrick *et al.* 2009; Pryor *et al.* 2006]. A total of 6081 patients were randomized.

Table 2. Treatment of premature ejaculation with dapoxetine (phase III clinical trials).

Study population (number, *N*)	Fold Increase in IELT	Most commonly reported side effects
1162 randomized 618 completed	30 mg PRN: 3.5 60 mg PRN: 3.8	Nausea Dizziness Diarrhoea Headache
1067 randomized 858 completed	30 mg PRN: 3.5 60 mg PRN: 3.8	Nausea Dizziness Somnolence Headache Vomiting Diarrhoea Nasopharyngitis
2614 randomized 1958 completed	30 mg PRN: 3.0 60 mg PRN: 3.4	Nausea Headache Dizziness Diarrhoea
Patient Reported Outcome 1238 randomized 811 completed	60 mg PRN Statistically significant improvement in: • Personal distress related to ejaculation • Interpersonal difficulty related to ejaculation • Perceived control over ejaculation • Satisfaction with sexual intercourse	Nausea Dizziness Headache Diarrhoea Insomnia

IELT, intravaginal ejaculation latency time; PRN, *pro re nata*.

Desensitizing agents (SS Cream, benzocaine, prilocaine, lidocaine). The use of a local anaesthetic to desensitize the penis prior to coitus has been described since the middle part of the last century [Damrau, 1963]. A number of these products are available as 'over-the-counter' medications and can be readily purchased online. They predominantly come in the form of creams although topical sprays are also available.

Xin and colleagues published data demonstrating that patients suffering from PE had an increased vibratory threshold on the glans penis when it was smeared with desensitizing cream (SS-Cream – herbal cream). Moreover, the effect was dose related [Xin *et al.* 2000]. Thereafter, the same research group performed a randomized controlled trial demonstrating an increase in IELT by eightfold when using the cream [Choi *et al.* 2000].

The efficacy of prilocaine–lidocaine cream (EMLA cream) and aerosol sprays have been demonstrated in prospective cohort studies [Dinsmore *et al.* 2007; Henry and Morales, 2003; Berkovitch *et al.* 1995] and in randomized, controlled trials [Carson and Wyllie, 2010; Busato and Galindo, 2004]. The optimum time of application of the EMLA cream has been shown to be 20 minutes prior to intercourse and the optimum concentration 5% [Atikeler *et al.* 2002]. However, topical cream can be messy to apply and requires the use of a condom to minimize the effect of the cream upon vaginal sensation.

With this in mind there has been a move to the use of aerosols which can be more discreet and patient friendly [Dinsmore *et al.* 2007]. An aerosol delivered combination of lidocaine–prilocaine spray for use in PE, labelled PSD 502 has been tested in two early stage clinical trials and two phase III study [Carson and Wyllie, 2010; Dinsmore and Wyllie, 2009; Dinsmore *et al.* 2007; Henry and Morales, 2003]. The spray forms a clear, slightly oily, odourless solution that remains adherent to the application site, with no condom required. It is easily wiped off, if necessary, before penetration and the anaesthetic penetrates the glans within 5 minutes although it is not capable of penetrating intact keratinised skin and will therefore not anaesthetize the shaft of the penis or the hands. Table 3 shows the efficacy and side effect profiles of PSD 502 in the phase III trials.

Desensitizing creams and sprays can cause side effects including hypoanaesthesia of the penile shaft and numbing of the vaginal vault of the partner, unless a condom is used [Lue and Broderick, 2007]. Irritating local and systemic effects have also been reported, although they are rare [Busato and Galindo, 2004; Atikeler *et al.* 2002].

PDE5 inhibitors (sildenafil, vardenafil, tadalafil). The role of PDE5 inhibitors (PDE5-I) in the management of PE is controversial. Although a prospective study showed an increase of IELT of a factor of 5.7 in patients using sildenafil for the treatment of PE [Wang *et al.* 2007], there still is minimal evidence to propose the use

Table 3. Treatment of PE with PSD 502 (randomized controlled trials).

Study population (number, *N*)	Efficacy	Side effects
300 randomized 290 completed	Fold increase in IELT: 6.3 Statistically significant improvement in: • Distress • Control • Satisfaction • Interpersonal difficulty	Patient ED Burning sensation Partner Vulvovaginal burning
256 randomized 249 completed	Fold increase in IELT: 4.1 Statistically significant improvement in: • Ejaculatory • Sexual satisfaction control • Distress	Patient ED Hypoanaesthesia Headache Partner Vulvovaginal burning

IELT, intravaginal ejaculation latency time; PE, premature ejaculation; ED, erectile dysfunction.

Table 4. Randomized, controlled trials of PDE5-I.

Study population	Efficacy for treatment of PE	Side effects
42 randomized 40 completed *Drug: vardenafil*	Fold increase in IELT (vardenafil): 7.3 Fold increase in IELT (placebo): 1.3 Statistically significant increase in: • control • satisfication • distress	Headache Dyspepsia Flushing
157 randomized 144 completed *Drug: sildenafil*	Fold increase in IELT (sildenafil): 2.6 Fold increase in IELT (placebo): 1.6 Moderate increase in patient satisfaction	Headache Flushing Dyspepsia Abnormal vision Rhinitis

IELT, intravaginal ejaculation latency time; PE, premature ejaculation.

of PDE5-I in treating PE. Table 4 gives a summary of the randomized, controlled trials for PDE5-I.

Epidemiological studies have shown that a third of men with ED suffer from PE [Corona *et al.* 2004]. This association between PE and ED may be explained by the fact that when a man suffers from ED, he makes a compensatory effort to achieve ejaculation before the loss of the erection, leading to PE. A possible carry on effect from this is when the man suffering from ED tries to overstimulate himself to achieve a rigid erection, whereby this overstimulation leads to PE [Jannini *et al.* 2005]. Therefore, by treating the ED with PDE5 inhibitors, the corresponding associated PE improves. However, evidence that this mechanism is actually occurring is not forthcoming as yet. There are just two randomized controlled trials evaluating a PDE5-I in the management of PE [Aversa *et al.* 2009; McMahon *et al.* 2005].

Although the evidences does not strongly support the use of PDE5-I in primary PE, it may have a role in treating PE in patients intolerant to dapoxetine, especially if the PE is associated with ED.

Centrally acting opioid analgesic (tramadol). Safarinejad and Hosseini have published a randomized, controlled trial on the use of tramadol HCL to treat PE [Safarinejad and Hosseini, 2006]. Various research groups have shown tramadol to have some efficacy in treating PE [Alghobary *et al.* 2010], especially as an on-demand medication, although the mechanism is poorly understood [Alghobary *et al.* 2010; Salem *et al.* 2008; Safarinejad and Hosseini, 2006]. However, there is evidence that some cases of secondary PE are seen in men who are withdrawing from opiate addiction. There may therefore be a relation between central opioid receptors and ejaculatory control.

Table 5 gives a summary of the medication currently being used for the treatment of PE.

Future possibilities

Additional research is required to eventually develop a product which is acceptable to the patient by being effective all of the time with minimal side effects and that is easy and discreet to use without compromising spontaneity during sexual intercourse. Some of the possibilities are as follows:

- 9-hydroxycanthin-6-one (9-HC-6-one), a β-carboline alkaloid isolated from *Eurycoma longifolia. In vitro,* it has been noted that 9-HC-6-one attenuated PE-induced contraction by blocking calcium channels [Chiou and Wu, 2011].
- It has been noted that decreased levels of magnesium may give rise to vasoconstriction from an increased thromboxane level, increased endothelial intracellular Ca2+, and decreased nitric oxide. This mechanism has been attributed to PE [Mohammadreza *et al.* 2009].

However, there is a long way to go before these products can be marketed. Moreover, reproducible *in vitro* and *in vivo* studies are required and

Table 5. Efficacy and side effects of drugs used in the management of PE.

Drug	Dose	Usage	Side effects	Relative increase in IELT
Clomipramine	12.5–50 mg	PRN Daily dose	Fatigue Nausea Dizziness Dry mouth Hypotension	4
Unlicensed SSRI		Daily dose	Fatigue	
• Escitalopram	20–40 mg		Nausea	2
• Fluoxetine	20–40 mg		Diarrhoea	5
• Fluvoxamine	25–50 mg		Yawning	1.5
• Paroxetine	10–40 mg		Diaphoresis	8
• Sertraline	50–200 mg		ED Decreased libido	5
Dapoxetine (licensed SSRI)	30–60 mg	PRN	Nausea Diarrhoea Headache Dizziness	2.5–3.0
Desensitizing agents				
• EMLA	Smear		Messy	4–8
• SS Cream	Smear	PRN	Numbing of the vagina	
• TEMPE (PSD502)	Spray		Skin irritation ED	
PDE5-I				
• Vardenafil	10 mg		PRN	Headache Flushing Nausea 3
Tramadol	50 mg	PRN	Dizziness Drowsiness Nausea Constipation	3.6–7.0

IELT, intravaginal ejaculation latency time; PE, premature ejaculation; ED, erectile dysfunction; SSRI, selective serotonin reuptake inhibitor; PRN, *pro re nata*.

the formulation of a standardized definition of PE is possibly the first building block towards standardization of PE research.

Conclusion

PE is a common condition affecting around one in five men. It can be a cause of significant personal distress which may in turn affect the relationship of the man with his partner. While many men with PE do not seek medical attention, when they do, SSRIs, desensitizing creams and to a lesser extent PDE5-I have been used in the treatment. All of these medications are sold off-label for the treatment of PE except for the recently licensed dapoxetine (Priligy™) which provides an effective, on-demand treatment regimen with relatively minimal side effects. PSD 502 is currently in the development phase and with the conclusion of phase III trials, may soon be licensed as a topical aerosolised spray for the treatment of PE.

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