6

# Premature Ejaculation Re-Visited: Definition and Contemporary Management Approaches

Tariq F. Al-Shaiji
*University Health Network, University of Toronto*
*Canada*

## 1. Introduction

Interest in the definition and management of premature ejaculation (PE) has been increasing significantly among all healthcare professionals and its clinical perceptions continue to evolve in recent years. Accumulating evidence suggests that it is considered to be the most common male sexual disorder (Metz & Pryor, 2000). Obtaining a universally accepted definition for PE has been problematic. Nevertheless, all definitions to date have repeatedly included two basic components which are the inability to control or delay ejaculation, and the resultant distress to one or both partners. Based on these components, the currently accepted definitions have been reported by a number of authorities which are authority-based rather than evidence-based (Table 1). In addition, PE can be divided into primary, that begins when the patient becomes sexually active, and secondary, which by definition is acquired later in life (Godpodinoff, 1989). Further subdivisions include global PE presenting in all circumstances, versus situational PE which occurs only with certain partners and situations (Donatucci, 2006). Intravaginal ejaculatory latency time (IELT) refers to the time between vaginal penetration and ejaculation, usually measured with a stopwatch or simply estimated in retrospect (Payne & Sadovsky, 2007). There has been no widely accepted standard for 'normal' IELT. In 2005, Patrick et al. found on a large community-based population of men and their partners that the median IELT, recorded using a partner-held stopwatch, was 7.3 min for men without PE, whereas men with PE had a median IELT of 1.8 min (Patrick et al., 2005). A multinational population survey of IELT by Waldinger et al. showed that 90% of 110 men with self-reported lifelong PE had an IELT of less than 60 seconds (Waldinger et al., 2005). IELT of less than 2 minutes is generally accepted as defining PE (Waldinger et al, 1998). A small percentage of men will ejaculate even before penetration. Others have advocated not to define the disorder with a specific time duration and instead suggested that a diagnosis is made when the man ejaculates too early for female partner satisfaction in greater than one-half of encounters (Masters & Johnson, 1970).

**World Health Organization (WHO), 1994** (Lue & Broderick, 2007)**:**

Inability to delay ejaculation sufficiently to enjoy lovemaking manifests as either of the following: occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse);

| |
|---|
| 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. |
| **American Psychiatric Association, the diagnostic and statistical manual of mental disorders-fourth edition (DSM-IV), 2000** (American Psychiatric Association, 2000)**:**<br>A. Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.<br>B. The disturbance causes marked distress or interpersonal difficulty.<br>C. The premature ejaculation is not due exclusively to the direct effects of a substance (eg, withdrawal from opioids).<br>Specify type:<br>Lifelong vs acquired<br>Specify type:<br>Generalized vs situational |
| **European Urology Association (EUA), 2001**(Colpi et al., 2001)**:**<br>The inability to control ejaculation for a "sufficient" length of time before vaginal penetration. It does not involve any impairment of fertility, when intravaginal ejaculation occurs. |
| **Second International Consultation on Sexual Dysfunctions (ICSD), 2003** (World Health Organization [WHO], 2004)**:**<br>Ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress and over which the sufferer has little or no voluntary control. |
| **American Urological Association (AUA), 2004** (Montague et al., 2004)**:**<br>Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners. |
| **International Society for Sexual Medicine (ISSM), 2007** (International Society for Sexual Medicine [ISSM], 2007)**:**<br>A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the 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. |

Table 1. Definitions of PE

## 2. Epidemiology

PE is considered as a culture-dependent symptom which is self-identified, self-reported, and self rated with respect to severity, a fact that has influenced the reported prevalence in the literature. Laumann et al. performed analysis of the National Health and Social Life Survey (NHSLS) which was a probability-based household survey in 1992 that included 1,410 men aged 18 to 59 years (Laumann et al., 1999b). The authors found that approximately 30% of surveyed men reported what they described as "climaxing too soon." Interestingly, the analysis showed that the likelihood of PE was not affected by age, marital status, or race/ethnicity. Similarly, analysis the Global Study of Sexual Attitudes and Behaviours (GSSAB), an international survey of various aspects of sex and relationships among adults aged 40-80 y, was carried out to estimate the prevalence and correlates of sexual problems in 13,618 men from 29 countries representing seven geographic regions (Laumann et al., 2005). The majority of the prevalence rates reported in these seven regions were very similar to the one reported by the NHSLS, with four of the seven regions reporting prevalence rates from 27.4 to 30.5%. One exception was the Middle East region, in which the rate was 12.4%, however lack of sampling standardization from country to country could have led to such a result. In a more recent data by Porst et al. (Porst et al., 2007), the PE Prevalence and Attitudes (PEPA) internet-based survey of 12,133 men aged 18–70 in Germany, Italy, and the United States reported a prevalence of 22.7%. PE prevalence as reported by female partners has also been examined. In a preliminary report of a survey undertaken on 129 women presenting to a community practice, 23.2% of women reported that their partner had PE (defined as ejaculating before she desired at least half of the time they had sex) (Rosenberg et al., 2006).

Some have argued that despite the relatively high reported prevalence rates of PE, men do not frequently offer it as a medical complaint, raising the distinct possibility that the problem may be more prevalent than currently estimated(Grenier & Byers, 1995; Spector & Carey, 1990). In addition, most physicians do not inquire about the condition which support the above argument (Payne & Sadovsky, 2007). Underreporting of PE can be attributable to a number of patient or physician related factors (Table 2).

| Patient factors | Physician factors |
|---|---|
| • Embarrassment/Stigma<br>• Loss of self-esteem<br>• Belief that the condition is psychological<br>• Belief that the condition is transient<br>• Perception of no medical treatment exists<br>• Lack of routine screening | • Lack of knowledge with the condition<br>• Lack of comfort discussing sexual issues<br>• Lack of expertise<br>• Consideration of PE as quality of life (QoL) not medical issue<br>• Low prioritization of the condition by the medical system<br>• Time constraints<br>• Lack of training/motivation<br>• lack of effective treatment options |

Table 2. Factors affecting PE reporting (McMahon, 2005; Moreira et al., 2005; Payne & Sadovsky, 2007; Shabsigh, 2006; Symonds et al., 2003)

## 3. Risk factors

PE by its nature is dependent on subjective description as reported by patients or their partners. The condition has significant heterogeneity with regards to classification and etiology. Several investigators have attempted to pin point specific risk factors or risk association pertaining to PE. Some of these factors show persistent association or co-existence whereas others show modest or conflicting one calling for further well designed studies to determine the impact of these factors on PE. Suggested risk factors for PE are shown in Table 3.

- Erectile dysfunction (ED) (Corona et al., 2004; Laumann et al., 1999b)
- Hypoactive sexual desire (Rowland et al., 2010)
- Low libido (Payne & Sadovsky, 2007)
- Youth (Carson & Gunn, 2006)
- Limited sexual experience (American Psychiatric Association, 2000)
- Low frequency of sexual intercourse (Grenier & Byers, 2001; Laumann et al., 2005)
- Longer period of sexual abstinence (Jannini & Lenzi, 2005)
- Poor overall health and/or a simultaneous urological condition (Carson & Gunn, 2006; Screponi et al., 2001)
- Type II diabetes mellitus, especially with poor metabolic control (El-Sakka, 2003)
- Emotional disturbances and stress (Laumann et al., 1994; Laumann et al., 1999b)
- Generalized clinical anxiety (Dunn et al., 1999)
- Anxiety over sexual encounters (Dunn et al., 1998)
- Familial/genetic predisposition (Waldinger et al., 1997)
- Previous traumatic sexual experiences (Laumann et al., 1999b)
  - Any same sex activity ever
  - Partner had an abortion ever
  - Sexually touched before puberty
  - Sexually harassed ever
- Ethnic group (hispanic/black > white) (Carson & Gunn, 2006; Laumann et al., 1999b)
- Low education status (Laumann et al., 2005)
- Financial problems (Nicolosi et al., 2004)
- Hidden female partner arousal difficulties (Levine, 1975)
- Substance abuse (Payne & Sadovsky, 2007)

Table 3. PE risk factors

## 4. Physiology of ejaculation and pathophysiology of PE

The normal male sexual response results from a complex integrated neurophysiologic pathway with four components: excitement, plateau, ejaculation and orgasm followed by resolution (McMahon & Samali, 1999). Normal antegrade ejaculation involves the processes of emission and expulsion of semen, which are coordinated by a network of afferent and efferent neural pathways (Coolen et al., 2004; Waldinger, 2002). Three distinct physiological phases of the ejaculatory process have been described including emission, ejaculation, and orgasm. During emission, the smooth muscles in the prostate, seminal vesicles, and vas deferens undergo rhythmic contractions that result in seminal fluid being deposited into the

posterior urethra. At the same time, the bladder neck contracts to prevent retrograde flow of seminal fluid into the bladder (Bohlen et al., 2000). The ejaculation phase involves relaxation of the external urinary sphincter and pulsatile contractions of the bulbocavernosus and pelvic floor muscles. Ejaculatory inevitability occurs in response to distention of the posterior urethra. Orgasm, which is the centrally experienced conclusion of sexual excitation, may or may not follow the ejaculatory phase (Donatucci, 2006).

In case of PE, there appears to be a blunting of the normal curve of ejaculatory response, characterized by a steep excitement phase with a shortened plateau phase followed by ejaculation/orgasm and a rapid resolution phase (Payne & Sadovsky, 2007). Historically, attempts to explain the etiology of PE have included a diverse range of psychological and biological factors. Psychological factors include anxiety, an unpleasant introductory or early sexual experience, infrequent sexual intercourse, poor ejaculatory control techniques, and evolutionary as well as psychodynamic factors (Sadeghi-Nejad & Watson, 2008). On the other hand, biological factors include penile hypersensitivity, hyperexcitable ejaculatory reflex, hyperarousability, endocrinopathy, genetic predisposition, and 5 hydroxytryptamine (5-HT)-receptor dysfunction (Donatucci, 2006). Increasing interest is focused on neurobiological explanations, such as hyposensitivity of 5-hydroxytryptamine 2C (5-HT2c) receptors or hypersensitivity of 5-HT1a receptors (Diaz & Close, 2010). It has been suggested that the ejaculatory threshold for men with low 5-HT levels and/or 5-HT 2C receptor hyposensitivity may be genetically 'set' at a lower point, resulting in a more rapid ejaculation (Abdel-Hamid et al., 2009). On the contrary, men with a very high set point may experience delayed or absent ejaculation despite prolonged sexual stimulation and despite achieving a full erection (Abdel-Hamid et al., 2009). Injection of a selective serotonin reuptake inhibitor (SSRI) into rat hypothalamus has been shown to delay ejaculation, whereas administration of a selective serotonin receptor agonist has been shown to cause PE in the rat (Ahlenius et al., 1981). This idea is supported in humans by the successful use of SSRIs, which increase 5-HT levels, in patients with PE (Diaz & Close, 2010). It has been postulated that men with PE have a hyperexcitable ejaculatory reflex that prevents them from controlling ejaculation (Donatucci, 2006).

## 5. Evaluation

It is universally accepted that a validated instrument to diagnose PE does not exist as yet. In its absence, when men present with PE, a thorough sexual history is of paramount importance to the evaluation. In 2004, the American Urological Association (AUA) Guideline on the Pharmacologic Management of Premature Ejaculation recommends that the diagnosis of PE be based solely upon information gathered through the taking of a sexual history (Montague et al., 2004). Nevertheless, discussion about one's private sexual life is usually not easy for anybody and even more difficult for a person who feels stigmatized for having a sexual-related problem. This embarrassment, especially in case of a male patient interacting with a female healthcare provider, is likely to prevent an open and a frank discussion about sexual problems. The evaluation of the problem should be grounded in recognition that the patient is placing great trust in his physician to treat his problem with respect and sensitivity. A skilled interviewer can help the patient clearly describe his true concerns. This should be carried out in a manner that avoids invasion of privacy, embarrassment, stigmatizing, and guilt. Patients are usually relieved when the

healthcare provider acts on subtle cues that give permission for the patient to discuss the issue. Active listening and a compassionate acceptance of the patient are key components to melt the ice and of allow the patient to discuss a sensitive issue such as PE. Including the partner in the discussion is often helpful, but this should be at the patient's discretion. If the patient does not offer it as a complaint, it is useful to perform the sexual history in the context of the review of symptoms, often during discussion of urinary tract symptoms or with the behavioural/relationship questions that are appropriate in the social history.

Four key factors need to be considered when making the diagnosis of PE, three of which are subjective, in essence that they are self-reported, and one factor is objective. The former include poor control over ejaculation, dissatisfaction with intercourse by the patient or partner, and perceived distress about the condition by the patient or partner. Indeed not all of these factors need to be present to identify PE (Diaz & Close, 2010). The latter is decreased IELT. IELT has been assessed by patient and partner recall, and by stopwatch evaluation. There appears to be considerable overlap in times between PE and non-PE groups, suggesting that, until better normative values are available, the diagnosis cannot be made on an individual's IELT alone. Waldinger suggested that in daily clinical practice, diagnosis PE is not difficult, and thus, evaluation with questionnaires or the use of a stopwatch is not required (Waldinger, 2007). Nevertheless, the importance of history taking cannot be overlooked and the above factors should be enquired about.

Establishing an accurate sexual and psychosocial history is critical in identifying the etiology of PE and establishing an effective treatment regimen. There are several key areas that should be addressed when taking the history of a patient with possible PE and these areas has summarized by the AUA Guideline on the Pharmacologic Management of PE (Table 4).

- Frequency and duration of PE
- Proportion of sexual attempts with PE
- Relationship to specific partners
- Frequency and nature of sexual activity
- Aggravating or alleviating factors
- Impact of PE on sexual activity
- Effect on relationships and QoL
- Relationship to drug use/abuse
- Other considerations
  - Lifelong vs. acquired
  - Situational vs. universal/global
  - Because of psychological or combined psychological/biological factors
  - Any links to ED?

AUA: American Urological Association; PE: premature ejaculation; QoL: quality of life; ED: erectile dysfunction.

Table 4. AUA Guideline: sexual history for PE (Montague et al., 2004)

Examples of direct questions that clinicians can ask initially to assist in the process of diagnosing PE have been suggested by Laumann et al. (Laumann et al., 2005):

1. How well are you enjoying your sex life?

2. Do you ejaculate too soon or earlier than desired? If so, can you estimate the amount of time before you ejaculate?
3. Do you feel you have control over the timing of your ejaculation?
4. Does ejaculating early bother/distress you and/ or your partner?

Since a full sexual history may be difficult to incorporate into the timeframe of a typical office visit, the development of brief screening tools to assist in diagnosis and minimize patient and provider embarrassment is warranted (Althof, 2006). Questionnaires in development include the 36-item Premature Ejaculation Questionnaire, the 10-item Index of Premature Ejaculation (IPE), the 10-item Chinese IPE, and the 2-part question used by Rowland et al. (Althof, 2004, 2006; Rowland et al., 2004).

A comprehensive urological and medical history is equally important in evaluating PE patients because of the established relationship between some medical conditions, such as diabetes and other neuropathies, with ejaculatory dysfunction (El-Sakka, 2003). A medical history should include thorough information regarding current medications that might influence sexual functioning (Perelman et al., 2004). Physical examination should include a complete general examination and a genital examination. The examiner should look for signs of underlying chronic disease, endocrine dysfunction, and neurological impairment. Infection in the urethra, prostate, or epididymis should also be ruled out. There is no laboratory test currently available to assist clinicians with the diagnosis of PE. In fact, Laboratory evaluation is rarely necessary in men with lifelong PE, unless there are complicating factors or concerning physical examination findings (Laumann et al., 2005). The physician should always bear in mind that a mixture of decreased libido and ejaculatory problems, or a mixture of ED and PE, is possible. Acquired PE, especially if secondary to ED, may need additional laboratory work, specifically focused on relevant risk factors such as vascular disease, obesity, diabetes, and depression (Palmer & Stuckey, 2008).

## 6. Treatment

The ultimate aim of PE treatment is to increase the overall sexual satisfaction and relationship satisfaction. The goal is to increase ejaculatory latency. It should be emphasized that PE is not a life-threatening condition and that the primary target outcome for PE treatment is patient and partner satisfaction. In general, treatment options include psychological, behavioral, and attempts to alter the sensory input or retard the ejaculatory reflex through pharmacologic means. It is important to review all available treatment options with the patient and preferably with his partner. The risks, benefits and success of each strategy should be delineated clearly. Each treatment modality can be used individually or in combination with others. Therapeutic options should suit both partners and be appropriate to their habit in planning and frequency of their sexual activities. Arranging follow-up at appropriate intervals to judge treatment efficacy and progress is needed.

### 6.1 Patient self-help measures

Some patients may attempt self-help measures before seeking medical attention. Self-help approaches are usually gained through personal experience, bibliotherapy (books), or online research. The effectiveness of such remedies is not known and rarely long-lasting. Some of

the common measures include using distracting thoughts as well as engaging in short foreplay, gentle thrusting, interrupting thrusting and withdrawing for a few moments (Hartmann et al., 2005; Riley & Segraves, 2006). In other instance, young men with a short refractory period can often experience a second and more controlled ejaculation during a subsequent episode of lovemaking (McMahon, 2005). Some men masturbate before sexual intercourse to desensitize the penis and delay subsequent ejaculations. Other remedies include taking alcohol, using thick condoms or multiple condoms, and applying an over-the-counter purchased anaesthetic preparation to the penis (Riley & Segraves, 2006). Many of these tactics, although creative, curtail the pleasures of lovemaking and are unsuccessful for delaying ejaculatory latency (Althof, 2006).

### 6.2 Psychological treatment

PE exerts a significant psychological burden on men and their partners (Rowland et al., 2001). These men tend to have mental preoccupation with their condition, show general negative affect associated with sexual situations, more intense feelings of embarrassment/guilt, worry/tension and fear of failure (Hartmann et al., 2005). Psychosexual therapy is best used to help the patient cope with the stress and relationship problems that develop secondary to sexual dysfunction (Palmer & Stuckey, 2008). It promotes open discussion between sexual partners, education about the condition, and expression of physical and emotional concerns (Althof, 2006). Counselling may be useful in conjunction with other treatments if it is considered to be helpful in improving self-esteem, but is rarely effective in treating the cause of lifelong PE. It is more likely to be successful in patients with acquired PE, especially those with situational PE.

Cognitive strategies that are relevant to treatment include the man's increased attention to his somatic sensations so he might better monitor his level of physical arousal, and the use of sensate focus, which in turn permit enjoyment of physical sensations without necessarily generating sexual arousal (Carey, 1998). In another word, the treating physician should teach his PE patient to recognize the signs of increased sexual arousal and then teaching him how to keep his level of sexual excitement below the level of intensity that elicits the ejaculatory reflex. Preliminary studies indicate that this approach is superior to a waiting list control (de Carufel & Trudel, 2006). These techniques also deemphasize the focus on intercourse and orgasm within the sexual relationship and can help to decrease the man's performance anxiety, which, because it presumably operates through sympathetic pathways, may serve to prime the ejaculatory response prematurely (Rowland & Rose, 2008).

### 6.3 Behavioral techniques

Behavioural techniques were once the mainstay of treatment of PE. The cornerstones of behavioral treatment are the 'stop-start' manoeuvre and its modification, the 'squeeze technique'. Both methods are based on the theory that PE occurs because the man fails to pay sufficient attention to pre-orgasmic levels of sexual tension (Masters & Johnson, 1970; Semans, 1956). In addition, the procedures may act to attenuate stimulus–response connections by gradually exposing the patient to progressively more intense and more prolonged stimulation but maintaining the intensity and duration of the stimulus just below the threshold for triggering the response (Guthrie, 1952).

In 1956, Semans described one of the earliest behavioral interventions, namely the "stop –start technique" (Semans, 1956). This method involves the partner stimulating the man's penis until he has the sensation of almost climaxing, at which time stimulation is ceased until this feeling abates. This cycle is repeated until the ejaculation can be controlled voluntarily. Eventually, the length of time before each stop gets gradually longer. Once the couple feels comfortable with vaginal penetration, they may be instructed to engage in "quiet vagina," in which the female partner temporarily stops moving during intercourse when the man indicates that he is approaching ejaculation, resuming once he says that he has regained control (Payne & Sadovsky, 2007). A similar technique was proposed by sex therapists Masters and Johnson in 1970 (Masters & Johnson, 1970). Their technique differed from the previous in that the partner squeezes the frenulum of the penis after cessation of the stimulus, resulting in a partial loss of erection. The female partner resumes sexual stimulation after at least 30 seconds have passed. However, many practitioners and patients report that this technique is unpractical.

Unfortunately most men do not show any lasting improvement using either of these techniques (De Amicis et al., 1985). Hawton et al. reported that 75% of men with PE who initially responded to behavioral therapy showed no long lasting improvement after 3 years of follow-up (Hawton et al., 1986). The ICSD noted that psychological and/or behavioral therapies, have been at least moderately successful in alleviating PE for some men (Sharlip, 2006). Based on their Guidelines, these approaches have no adverse effects, are specific to the problem, and encourage open communication between men and their partners. However, they lack immediacy and can require a substantial investment of time and money. Generally, the best results have been seen in men who are motivated, are hopeful, and are in a stable monogamous relationship with a cooperative partner (Althof, 2005). The popularity of these practices is declining because of their lack of reproducible success and their intrusiveness in normal sexual activity.

Other behavioral measures that have been described including encouraging couples to carry out attempts with the partner superior or lateral positions, as these typically provide men with a greater sense of ejaculatory control (Rowland & Rose, 2008). Other suggestions include moving the pelvis in a circular motion, slowing down during intercourse, breathing deeply, and practicing shallower penile penetration (Rowland & Cooper, 2005).

### 6.4 Pharmacologic interventions

#### 6.4.1 Locally acting topical therapy

The oldest form of therapy for PE is the use of local anesthetic agents as described by Schapiro in 1943 (Schapiro, 1943). Topical anesthetics are available in cream, ointment, spray formulations and the rational for their application is based on the theory that men with PE are hypersensitive to penile stimulation. Some of these formulations have been shown to improve IELT compared with baseline (Busato & Galindo, 2004; Dinsmore et al., 2007). The advantages of topical therapies are that they can be applied as needed and systemic side effects are likely to be minimal. However, there are several drawbacks that make them a less than ideal therapeutic option. They are associated with inconvenience of use, messiness and interference with spontaneity (as the agents have to be applied and wiped off at specific times before sexual contact). Like all topical medications, there is always a risk of local burning, irritation, or allergic reaction. Significant penile hypoesthesia may occur which in

turn can lead to excessive loss of pleasurable sensation and in some instances prevent the patient from achieving an orgasm (McMahon & Samali, 1999). Some reports indicated that the use of local anesthetics can induce mild erectile dysfunction and lowering of sexual arousal (Slob et al., 2000). One of the most feared drawbacks is the potential for transvaginal absorption of the agents used, which could induce vaginal numbness and even female anorgasmia (Morales et al., 2007). However, this can be prevented with condom use. As a general rule, reliable controlled studies have been lacking in this area.

### 6.4.2 Lidocaine–prilocaine cream

The eutectic mixture of local anesthetic (EMLA™; AstraZeneca, London, UK) is a local anesthetic cream that contains 2.5% of both lidocaine and prilocaine for topical application. This mixture has a 16ºC melting point and thus can be formulated into preparations without the use of a non-aqueous solvent (Gurkan et al., 2008). The cream is applied thinly to the glans penis and distal shaft and covered by a condom for 20-30 minutes. If the condom is removed for intercourse, residual cream should be washed off. The high water content of this mixture enables it to penetrate the intact skin of the penis (Atikeleret al., 2002). The AUA 2004 guideline document described the lidocaine–prilocaine cream to be effective in treating PE when applied 20–30 min before intercourse (Montague et al., 2004). Nevertheless, trials using this topically in men with PE are scant. Busato and Galindo performed a double-blind, randomized, placebo-controlled study to determine the efficacy of EMLA cream in treating PE (Busato & Galindo, 2004). The study included 42 men divided in two groups; group A used a lidocaine-prilocaine solution and group B used an inert cream. There was a significant increase in the mean IELT, from 1.49 to 8.45 min ($P < 0.001$) in group A but not in group B following 2 months use. Although 42 patients were initially recruited, only 29 completed the study; however, none of the drop-outs were due to adverse effects. Adverse events were reported in five (17%) patients in the treatment group. In another study, Atikeler et al. randomized 40 patients into four groups, each comprising 10 patients to assess the efficacy and optimum usage of EMLA cream in managing PE (Atikeler et al., 2002). Patients in group 1 applied lidocaine-prilocaine cream 5% for 20 min, the patients in group 2 applied it for 30 min, and the patients in group 3 applied the cream for 45 min before sexual contact, with all patients covering the penis with a condom. Patients in the fourth group applied a base cream to act as placebo. In the placebo group, there was no change in their pre-ejaculation period. In group 1, the pre-ejaculation period increased to 6.71 +/- 2.54 min without any adverse effects. In group 2, the pre-ejaculation period increased in four patients up to 8.70 +/- 1.70 min, however six patients in this group and all patients in group 3 had erection loss because of numbness.

### 6.4.3 Lidocaine–prilocaine spray (PSD502)

Topical eutectic mixture for premature ejaculation (TEMPE Plethora Solutions PLC, London, UK) is a formulation of lignocaine and prilocaine in a metered dose aerosol-delivery system. Each spray delivers 7.5 mg of lidocaine and 2.5 mg of prilocaine. It is designed to optimize tissue penetration such that the onset of effect is more rapid than with the cream formulations and a condom is not required (Gurkan et al., 2008). The spray does not penetrate keratinized epithelium, and so only anesthetizes the glans; however there still appears to be some risk of hypoesthesia associated with its use (Dinsmore et al., 2007). It has an oily texture that enhances

adherence to the penile surface and is easily washed off with water (Henry et al., 2008). TEMPE has been examined in a pilot study (N = 14) , a placebo-controlled phase II study (N = 55) (48), and in two large, placebo-controlled phase III trials, all of which have shown statistically and clinically significant prolongation of IELT compared with placebo (Carson & Wyllie, 2010; Dinsmore et al., 2007; Dinsmore & Wyllie, 2009; Henry & Morales, 2003).

#### 6.4.4 Lignocaine spray

The active ingredient within this spray is the local anesthetic lignocaine (9.6%). It is marketed as Stud 100 or Premjact and applied to the glans penis in 3-6 sprays, 5-15 minutes before sexual intercourse. In theory, this agent works in the same way as other topical anesthetic agents. Although it has been available for more than 25 years and can often be bought over the counter without a prescription, there has been a paucity of data from clinical trials to support its use in the management of PE.

#### 6.4.5 Dyclonine/alprostadil cream

A preparation which combines dyclonine, a local anesthetic usually used in the field of dentistry, with the vasodilator alprostadil has been described in the management of PE by one pilot study published as an abstract (Gittleman et al., 2005). The cream is applied to the tip of the penis in the region of the meatus 5–20 min before intercourse. The study claims some positive results, however the data is limited and further studies are needed before any conclusion can be drawn.

#### 6.4.6 Severance-secret (SS) cream

SS-cream (Cheil Jedan Corporation, Seoul, Korea), developed at the Yong-Dong Severance Hospital in Korea, is made with extracts from nine herbal products including Korean ginseng, bufonoid venom and cinnamon. Some of these products have local anaesthetic as well as vasoactive properties (Morales et al., 2007). It is thought to also act through desensitization , although its exact mechanism is unclear. The cream is applied topically to the glans penis 1 hour prior to intercourse and washed off immediately before coitus begins. It is marked with its unpleasant smell and colour, which makes it unacceptable to many patients. It is available for use only in Korea in which all studies conducted on its efficacy were published there by the same group. Within these clinical trials, SS cream resulted in significant increases in IELT and satisfaction with sexual intercourse in comparison with placebo (Choi et al., 1999, 2000). Because of its unpleasant odour, the original SS-cream was unlikely to be of interest outside of South Korea (Powell & Wyllie, 2009). To compensate for the unpleasant smell and color, a reformulation was designed by the producers that contain only couple of the main ingredients present in the original cream. However, only animal data is available for this new formulation that claims higher efficacy than the original formulation (Tian et al., 2004).

### 6.5 Systemic therapy

#### 6.5.1 Phosphodiesterase Type 5 (PDE5) Inhibitors

It has been estimated that at least 30% of PE men have concomitant ED (Laumann et al.,1999a). Whether the man with ED ejaculates early during intercourse before his erection

fails, or whether the man with PE develops secondary ED due to anxiety regarding his PE is unknown. An alternative view held by other investigators suggests that PE and ED share a vicious circle, in which the level of excitation is instinctively reduced by a man with PE trying to control his ejaculation (thus leading to ED), and on the other hand, a man suffering from ED will try to increase his excitation to achieve an erection, thus leading to a rapid ejaculation (Jannini et al., 2005). Whatever the cause of PE co-existing with ED, the ssuccessful use of PDE-5 inhibitors in this subgroup of patients has raised the question of whether PDE-5 inhibitors can be efficacious in the treatment of primary PE. It has been proposed that the use of a PDE5 inhibitor 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 leading to prolongation of IELT in men with PE (Palmer & Stuckey, 2008). Despite this theory, it is deemed unlikely that PDE-5 inhibitors have a significant role in the treatment of primary PE. This argument is supported by McMahon et al. who reviewed all reports on the use PDE-5 inhibitors for PE that were published between 2001 and 2006 (McMahon et al., 2006). The authors analysed 14 studies that reported on sildenafil, vardenafil and tadalafil. They concluded that PDE-5 inhibitors were not effective in the management of men with lifelong PE and normal erectile function. However, Sadeghi-Nejad and Watson suggested that PDE-5 inhibitors may exert a secondary beneficial effect for patients with PE since they (i) allow for a sustained penile erection, even after ejaculation; (ii) facilitate a second coitus after the initial ejaculation, which is likely to be less prone to PE; and/or (iii) help the patient to overcome performance anxiety, that often exacerbates PE (Sadeghi-Nejad & Watson, 2008).

### 6.5.2 α1-adrenoceptor antagonist

Ejaculation is peripherally controlled by the sympathetic nervous system, and therefore blocking the sympathetic system by α1-blockers may theoretically delay ejaculation. This hypothesis has been supported by a rat model demonstrating a decreased vasal and seminal vesicle pressure in response to hypogastric nerve stimulation (S.W. Kim et al., 2004). Clinically, terazosin and alfuzosin have been investigated in men with PE. Cavallini showed that both terazosin 5 mg/d and alfuzosin 6 mg/d proved effective in approximately 50% of the cases in a placebo-controlled study in 91 men with PE (Cavallini, 1995). Similarly but more recently, Basar et al. demonstrated that daily use of terazosin 5 to 10 mg showed a clinically significant improvement during a short-term follow up in another placebo-controlled study in 90 men with PE and urinary tract symptoms without chronic prostatitis and benign prostatic hyperplasia (Basar et al., 2005). It should be pointed out that the methodology of both studies has been rather weak making their validity under question and calling for additional well-designed controlled studies. Despite these limitations, α-blockers use in the PE patient with concomitant lower urinary track symptoms may be of benefit (Basar et al., 2005).

### 6.5.3 Tramadol

Tramadol is a centrally acting synthetic on-demand analgesic that has been on the market for a number of years. It has two distinct mechanisms of action: it exerts an effect on the ∝–opioid receptor, but also inhibits noradrenaline and serotonin reuptake (Frink et al., 1996). It is available in generic form in most countries and has been used in an on-demand

fashion (off-label and empirically) to treat PE. The exact mechanism by which it delays ejaculation is not well understood, however it is thought to be related to its action on the ∝–opioid receptor, which may reduce sensitivity, in addition to the inhibition of serotonin reuptake, which may delay ejaculation (Linton & Wylie, 2010). It has a short half-life and acceptable safety profile. Since its is rapidly absorbed and eliminated, it makes it desirable for an as needed dosing regimen (Eradiri et al., 2006).

Salem et al. conducted a single-blind, placebo-controlled, crossover, stopwatch monitored two-period study on 60 patients with lifelong PE utilizing 25 mg of tramadol (Salem et al., 2008). The treatment group experienced a 6.3 fold increase in IELT compared to a 1.7 fold increase in the placebo group. Patients uniformly reported satisfaction with their resulting control over ejaculation. Mild side effects were reported in eight patients (13.3%), consisting of mild dyspepsia and somnolence. In another study, Safarinejad and Hosseini performed a double-blind, placebo-controlled, fixed-dose, randomized study to evaluate the efficacy and safety of tramadol (Safarinejad & Hosseini, 2006). They randomly assigned 64 potent men with PE to receive 50 mg tramadol or placebo and showed an increase in IELT from 19 seconds to over 4 minutes in the tramadol arm. The most common adverse events were nausea (15.6%), vomiting (6.2%), and dizziness (6.2%), but they were reported to be mild. A large phase III trials is in progress in Europe and other trials are anticipated (Hellstrom, 2011). Although tramadol is reported to have a decreased risk of dependence compared to traditional opioids, its use as an on-demand treatment for PE is still limited by the potential risk of addiction (Cossmann et al.,1997). In community settings, dependence does occur, albeit minimal (McDiarmid et al., 2005).

### 6.5.4 Clomipramine

Clomipramine is a tricyclic antidepressant used in the treatment of obsessive compulsive disorders. It inhibits the reuptake of noradrenaline and 5-HT by adrenergic and 5-HT neurones (Gur et al., 1999). In 1973, Eaton published his novel report on the efficacy of clomipramine to manage PE marking the beginning of a new era in the approach to treating this condition and several subsequent publications have confirmed its effectiveness (Eaton, 1973). It has been studied both as a daily dose and as an on-demand medication.

On-demand use of 20 to 40 mg clomipramine can effectively delay ejaculation if taken 3 to 5 hours prior to intercourse (Haensel et al., 1996; Segraves et al., 1993). Waldinger et al. showed a 4-fold increase in the IELT with on demand 25 mg of clomipramine (Waldinger et al., 2004a). The on demand dosing appears to be associated with high incidence of side effects with nausea being the most common, which is experienced on the day of sexual intercourse and the day after (Waldinger et al., 2004a). Rowland et al. indicated that patients with initial ejaculatory latencies over 60 seconds, self-reported sexual satisfaction of 5 or higher (on a seven-point scale) and ejaculation frequency of twice or more per week were more likely to benefit from on-demand 25 mg clomipramine therapy (Rowland et al., 2004). In the 1970s to the 1990s, various studies demonstrated clomipramine efficacy in delaying ejaculation in daily rather low dosages of 10 to 30 mg (Assalian, 1988). For instance, in a randomized, placebo-controlled crossover trial in 36 men with PE, Kim an Seo were able to show that continuous dosing with clomipramine significantly lengthened the IELT compared with placebo ( $P < 0.01$), as measured by stopwatch assessment (S. C. Kim & Seo, 1998). In addition, a meta-analysis evaluating the systemic treatments for PE by Waldinger

et al found clomipramine to be efficacious, particularly continuous dosing (Waldinger et al., 2004b). The results also showed it to be comparable to the commonly used selective serotonin re-uptake inhibitors (SSRIs) in its effects. Small studies showed that after daily treatment with clomipramine, men with PE reported improved relationship and emotional satisfaction, men and their partners reported increased sexual satisfaction, and the partners reported an increased ability to achieve coital orgasm (Althof et al., 1995). Rowland et al. examined the role of daily treatment with clomipramine in 4 men with PE when the as required regimen was ineffective (Rowland et al., 2001). They recommended a two-tiered approach, initially using a single dose of up to 25 mg, taken from 4 to 24 hours prior to intercourse. If on-demand treatment proved unsatisfactory, a daily, long-term dose of 10–30 mg was instated. The study concluded that men with PE who do not respond to clomipramine 'as required' are probably not insensitive to pharmacological treatment, but may simply require higher doses or a different regimen. All four subjects improved when taking daily clomipramine at varying doses.

Use of clomipramine in men with PE might be limited by its associated adverse events. Common side effects include dry mouth, fatigue, nausea, and dizziness (Haensel et al., 1996). Although these side effects may abate over time, stopping the medication is also associated with a loss of efficacy (Althof et al., 1995). The study by Kim and Seo showed that on continuous dosing, the adverse event profile of clomipramine was found to be significantly worse than with SSRI treatment (S. C. Kim & Seo, 1998). Furthermore, Waldinger et al. reported that the use of an on-demand regimen to reduce exposure to clomipramine did not eliminate potentially annoying nonsexual side-effects, including sleepiness, yawning and nausea, which were significantly worse on the day of dosing and the subsequent day with clomipramine than with SSRI therapy (Waldinger et al., 2004a). Other possible side effects involved with the usage of clomipramine include an increased risk of suicide, especially when initiated in men under the age of 24 (U S Food and Drug Administration [FDA], 2007) and an adverse effect on sperm function when used at higher doses (75 mg for more than 3 months) (Maier & Koinig, 1994). It may impede both sperm motility and vasal/epididymal contractility by blocking calcium channel mechanisms (Mousavizadeh et al., 2002). This potential consequence of long-term, high dose usage should be kept in mind when choosing PE therapy for men who may be contemplating fatherhood in the future (Sadeghi-Nejad & Watson, 2008).

### 6.5.5 Selective serotonin reuptake inhibitors

Although none of the selective serotonin reuptake inhibitors (SSRIs) are approved by regulatory bodies for the management of PE, their common "side effect" of delaying ejaculation in 30%–50% of otherwise healthy depressed patients has made them the preferred "off-label" treatment option for PE (Balon, 2006). Indicated primarily in the treatment of depression, SSRIs can increase the level of serotonin in the brain, inhibiting the ejaculatory reflex centre, and can prolong IELT for several minutes (Hellstrom, 2006). The extent of this delay varies widely depending upon the type, dose, and frequency of SSRI administration and the genetically determined ejaculatory threshold set point (Sadeghi-Nejad & Watson, 2008). The effect of this class of medication is not restricted to PE patients since its use by otherwise healthy subjects can also significantly delay ejaculation (Wang et al., 2007). Dosing levels of SSRIs are generally lower for PE than for depression, and various

dosing regimens have been tested (including continuous, daily or situational). Indeed, this is the most common class of medications used to treat PE nowadays.

Currently four SSRIs are commonly in use in the treatment of PE including fluoxetine, paroxetine, sertraline and citalopram. Paroxetine has been found to have substantially greater efficacy, increasing IELT approximately 8.8-fold above the baseline, followed by sertraline and fluoxetine (Waldinger et al., 2003, 2004). Among the SSRIs, fluvoxamine and venlafaxine have been shown to be ineffective (Kilic et al., 2005; Waldinger et al., 2002). Daily treatment with paroxetine 10–40 mg, sertraline 50–200 mg, fluoxetine 20–40 mg, and citalopram 20–40 mg is usually effective in delaying ejaculation (Rowland et al., 2010). The desired ejaculation delay usually occurs within 5–10 days of starting treatment, however the full therapeutic effect may require 2–3 weeks of treatment and is usually sustained during long-term use (McMahon, 2002). The first publication about the delaying effect of paroxetine was published in 1994 and since then multiple placebo-controlled randomized studies have confirmed the effectiveness of each of the aforementioned SSRIs in treating PE (Biri et al., 1998; Gurkan et al., 2008; Kara et al., 1996; S. C. Kim & Seo, 1998; Waldinger et al., 1998). The argument for daily dosing comes from the fact that the pharmacokinetic profile of conventional antidepressants should be optimized for the treatment of depression which requires their continuous presence in the bloodstream to achieve the maximum effect (Althof, 2006b). Side effects are usually minor, starting in the first week after intake and gradually disappearing within 2–3 weeks of starting the course of treatment which include fatigue, yawning, mild nausea, loose stools and perspiration (McMahon, 2005). Diminished libido and mild erectile dysfunction are reported infrequently (Waldinger, 2007), especially in the absence of concomitant depression (Montejo et al., 2001). Rare side effects that have been reported include bleeding (Halperin & Reber, 2007), weight gain related type II diabetes mellitus (Raeder et al., 2006), bone mineral density loss with prolonged treatment (Haney et al., 2007), and priapism (Dent et al., 2002), however, these events were reported in patients suffering from depression. The use of SSRIs, especially in young depressed patients, is reported to increase impulsive actions and suicide Rate (Cohen, 2007). There is also the potential for the development of a serious drug interaction that can lead to 'serotoninergic syndrome' which manifests as headache, nausea, sweating and dizziness in mild cases, and in hyperthermia, rigidity and delirium in severe cases (Sharlip, 2006). Symptoms can occur following abrupt cessation or reduction of SSRI therapy beginbeginning from 24 to 72 hours after discontinuance and may last more than a week (Linton & Wylie, 2010). This is thought to be more prevalent with the SSRIs that have shorter half lives (Hellstrom, 2009). Based on this, it is generally recommended that SSRIs should not be stopped suddenly but reduced over several weeks (Sadeghi-Nejad & Watson, 2008). Several physicians may consider the reported side effects hard to 'justify' for the treatment of PE, in which the primary outcome is patient satisfaction. However, the AUA has suggested that the level of side effects is acceptable for the benefit derived in the patient with PE, and the type and rate of occurrence of these effects also appears to be acceptable to most patients (Montague et al., 2004).

The side effect profile of the SSRIs taken on a chronic daily basis has led to the suggestion that an "on demand" SSRI may be useful for PE. This is supported by the fact that men may be reluctant to receive an antidepressant to treat a condition other than depression and use it chronically, having known that sexual activity does not generally occur on a daily basis (Althof, 2006b). On-demand administration of paroxetine, sertraline, and fluoxetine 4–6 hours before intercourse is modestly efficacious and well tolerated but is associated with

substantially less ejaculatory delay than daily treatment (S. W. Kim & Paick, 1999; McMahon & Touma, 1999; M. D. Waldinger et al., 2004a). McMahon and Touma performed a comparison of 20 mg paroxetine PRN 3 to 4 hours prior to intercourse vs 20 mg paroxetine daily for 4 weeks, followed by PRN paroxetine in those who responded to daily paroxetine (McMahon & Touma, 1999). The authors showed that the schedule of daily dosing followed by PRN dosing was significantly superior to the PRN only schedule. However, sexual side effects were observed in the daily paroxetine group and the initial benefits that they experienced were not sustained with time in men with primary PE (11 of 16 failures). In the PRN only group 15 of 19 men with primary PE failed to respond. Publications focusing on on-demand use of SSRIs for PE continue to be limited and the data available is difficult to compare as it is heterogeneous in terms of medications used, study design and outcome reporting. Paroxetine appears to be the most effective medication again (Gurkan et al., 2008).

Dapoxetine is the first compound specifically developed for the treatment of PE. It is a novel fast-acting SSRI that exerts its effects through the inhibition of the serotonin reuptake transporter (Hellstrom, 2009). Because of its short acting property, it probably better suited as an "on-demand" treatment for PE. In fact, it has received regulatory approval as an on-demand treatment for PE in several parts of the world (McMahon et al., 2010). In contrast to conventional SSRIs, maximum plasma concentrations are achieved 1.01 h after a 30-mg oral dose, initial half-life is 1.42 h and 24 h after administration, plasma concentrations decrease to less than 5% of peak levels (Dresser et al., 2006). Pryor et al. published an integrated analysis of two double-blind, randomised controlled trials to determine the efficacy and tolerability of dapoxetine in the treatment of PE (Pryor et al., 2006). Men with moderate-to-severe premature ejaculation took placebo (n=870), 30 mg dapoxetine (874), or 60 mg dapoxetine (870) on-demand (as needed, 1-3 h before anticipated sexual activity). The primary endpoint was IELT measured by stopwatch. At the completion of the study, 672, 676, and 610 patients completed in the placebo, 30 mg dapoxetine, and 60 mg dapoxetine groups, respectively. Dapoxetine significantly prolonged IELT ($p<0.0001$, all doses vs placebo). Mean IELT at baseline was 0.90 minute, 0.92 minute, and 0.91 minute, and at study endpoint (week 12 or final visit) was 1.75 (2.21) minutes for placebo, 2.78 (3.48) minutes for 30 mg dapoxetine, and 3.32 (3.68) minutes for 60 mg dapoxetine. Both dapoxetine doses were effective on the first dose. Common adverse events (30 mg and 60 mg dapoxetine, respectively) were nausea (8.7%, 20.1%), diarrhoea (3.9%, 6.8%), headache (5.9%, 6.8%), and dizziness (3.0%, 6.2%). More recently, Buvat et al. published results from phase III trial from 22 countries, evaluating dapoxetine 30 mg and 60 mg versus placebo (Buvat et al., 2009). The trial showed that IELT was significantly increased with dapoxetine. At the end of 24 weeks the IELT had increased from 0.9 minutes to 1.9 minutes, 3.1 minutes, 3.5 minutes with placebo, dapoxetine 30 mg and 60 mg. All patients reported outcome measures were significantly improved with dapoxetine versus placebo. The drug was submitted for FDA approval in 2004, however in October 2005, the company developing the drug received a "not approvable" letter from the FDA ("Dapoxetine: LY 210448," 2005; Press release, 2005).The questions raised by the FDA letter were not disclosed, however dapoxetine's developer mentioned that it plans to address the questions and continue the drug's global development program (Press release, 2005).

### 6.6 Combination therapy

While the choice of PE treatment is essentially between behavioural and pharmacological approaches, physicians should recognize that combination treatment is an option,

especially for patients with severe PE or those refractory to mono-therapy. In a study by Atan et al., oral fluoxetine 20 mg/day, when reinforced by the topical application of lidocaine ointment, showed a "cure" or an improvement in 83.3% of men with PE, compared with 72% of those treated with fluoxetine alone (given as 20 mg/day then increased to 40 mg/day) (Atan et al., 2000). Chen et al. examined the efficacy of sildenafil as adjuvant therapy to paroxetine in alleviating PE (Chen et al., 2003). They found that sildenafil combined with paroxetine was effective in 97% of patients, compared to an improvement for only 47% using paroxetine alone. In addition, the best results obtained in this study were observed when sildenafil was combined with SSRIs as well as implementing behavioral counseling. In another study, Salonia et al. have shown in a prospective open-label study that paroxetine combined with sildenafil provided significantly better results in terms of ejaculatory latency time and intercourse satisfaction versus paroxetine alone in potent patients with PE, albeit with a mild increase in drug related side effects (Salonia et al., 2002). Perelman and Althof independently described combination therapy as a "concurrent or stepwise integration of psychological and medical interventions"(Althof, 2006a; Perelman, 2006). Patients with severe PE need more than pharmacotherapy to overcome obstacles to effective sexual activity and require targeted psychoeducational interventions termed "coaching" (S. Althof, 2006a). Steggall et al. speculated that a combination approach may offer both an improvement in ejaculatory delay, but also facilitate engagement with behavioural therapies (Steggall et al., 2008). In a small-scale study, the authors randomised participants with PE either to paroxetine 20 mg daily or to a lidocaine-based spray (Premjact) for 2 months followed immediately by a standardized behavioral therapy programme for a further 2 months. Of the 60 men who consented to participate in this trial, 44 completed the pharmacologic phase and 22 completed both phases of the program. It was found that both paroxetine and premjact Spray provided a statistically significant delay in ejaculation (as measured by stopwatch); which was partially maintained during the behavioral program. However, the improvement induced by medications could only be continued through sex therapy in those men reporting acquired PE; the men with lifelong PE returned to baseline. It was concluded that for acquired PE, combination therapy may offer advantages through an initial stabilizing effect on the couple with subsequent increased acceptance of and adherence to behavioral therapy. There is growing evidence that combination therapy using new pharmaceuticals and psychotherapy will become the treatment of choice (Perelman, 2006).

### 6.7 Emerging and experimental treatment options for PE

It has been demonstrated that desensitisation of the 5-HT 1A receptor during chronic administration of SSRIs [e.g., combination of robalzotan (NAD-299) with fluoxetine and citalopram (Williamson et al., 2003) and combination of WAY-100635 with citalopram (de Jong et al., 2005) and paroxetine (Looney et al., 2005) induces prolonged delay in ejaculation in the rat. However, when used alone they had no effect on ejaculation. Although this novel pharmacological combination is promising, further clinical research is warranted to evaluate the efficacy and potential adverse effects of this combination. A new avenue being explored in the pharmacological treatment of PE is the use of oxytocin compounds as potential therapeutic agents (Giuliano, 2007), based on immunohistochemical studies that have demonstrated local synthesis of oxytocin and its synthesis-associated protein, neurophysin I,

in the epithelial cells of the epididymis (Filippi et al., 2005). Dietary deficiencies, such as low magnesium intake, may prove to play a limited role as well (Aloosh et al., 2006). Although its role in the management of ED is well established, the use of vasoactive intracavernosal injection (ICI) pharmacotherapy for the treatment of PE is not supported by a large body of peer-reviewed literature, and is not commonly used in clinical practice. ICI has been used as a strategy in certain cases to allow men with PE to maintain their erections and continue satisfactory sexual intercourse despite rapid ejaculation (Fein, 1990).

Non-pharmacological approaches are also being explored. Optale et al. showed that immersive virtual reality can speed up the therapeutic psychodynamic process, wherein the patient wears a helmet with miniature television screen and earphones to discuss and summarize his thoughts (Optale et al., 2004). Wise and Watson suggested a novel device based on the penile hypersensitivity hypothesis (Jan Wise & Watson, 2000). This experimental device is a "desensitizing band" which, when worn during masturbation, does not constrict blood flow and helps the PE sufferer gain control over ejaculation. Unfortunately, the device is hardly available for patient use for economic reasons of viability of sales (Linton & Wylie, 2010). Basal et al. described the application of pulsed radio frequency neuromodulation to treat PE by the desensitization of the dorsal penile nerves (Basal et al., 2010). This was a small pilot study consisting of 15 patients and showed a significant increase in the IELT compared to baseline. After the procedure, there were no reported problems with pain, penile hypoesthesia, or ED. Nevertheless, sham-controlled studies with larger numbers of patients are needed. Recently, Sunay et al. performed a randomized, placebo-controlled trial to determine if acupuncture is an effective measure to manage PE (Sunay et al., 2011). Ninety PE patients were randomly assigned into paroxetine 20mg/day, acupuncture or sham-acupuncture (placebo) which was treated twice a week for 4 weeks. The acupuncture points were selected and performed by an experienced acupuncturist according to the publication World Health Organization Standard Acupuncture Point Locations in the Western Pacific Region. Significant differences were found between IELTs of the paroxetine and placebo groups ($p=0.001$) and the acupuncture and placebo groups ($p=0.001$) after treatment. Increases of IELTs with paroxetine, acupuncture, and placebo acupuncture were 82.7, 65.7, and 33.1 , respectively. The study is criticized for obvious lack of follow up.

Some authors have reported the use of surgically induced penile hypoanesthesia as a mean to manage PE. A surgical approach consisting of a dorsal neurectomy with or without glandular augmentation using hyaluronic acid gel has been reported (J.J. Kim et al., 2004). Although there are reported positive results with significantly increased IELT, the two groups that underwent dorsal neurectomy or dorsal neurectomy and glandular augmentation, both had significant side effects, including penile numbness, paresthesia and pain. The group that underwent hyaluronic acid augmentation alone reported no adverse side effects. Five years study on the glans augmentation arm of the trial and the hyaluronic acid implants were well maintained, showing long-term efficacy (Kwak et al., 2008). The role of surgery in the management of PE remains unclear, and thus further trials are needed before its role can be established.

### 6.8 Treatment recommendation

Since the frequency of sexual intercourse is very variable, and spontaneity in sexual intercourse is usually an important factor, an ideal drug for treating PE would be a discrete

and 'on-demand' therapy with a predictable therapeutic effect within a few minutes of administration so that it could be taken once sexual foreplay has commenced (Riley & Segraves, 2006). It should have a low incidence of side-effects and have no unwanted effects on the partner (Hellstrom, 2006). Unfortunately, such drug is not currently available. In addition, no drug exists yet that was able to obtain FDA approval as specific treatment for PE. Until such a day is seen, the off-label application of different pharmacotherapy continues to be practiced.

Based on the above mentioned limitations, several authorities have attempted to produce guidelines and algorithms on the management of PE. These guidelines include but are not limited to those published by the American Urological Association (AUA) (Montague et al., 2004), the European Association for Urology (EAU) (Colpi et al., 2004) and the International Consultation on Sexual Dysfunctions (ICSD) (McMahon et al., 2004). These guidelines share common directions and similarities. For example, in terms of treatment modalities, the AUA committee suggested that although oral antidepressants and topical anaesthetic agents are not approved by the FDA for PE, they have been shown to delay ejaculation in men with PE and have a low side effect profile when used at the lower doses commonly used for the treatment of PE (Montague et al., 2004). The commonly used agents in the management of PE as published by the AUA guidelines are shown in Table 5. Additionally, it was suggested that medication could be used to restore confidence together with behavioral treatment, where available, to help men learn to overcome PE on their own (Althof, 2006b; Perelman, 2006). This strategy has become an important part of many of the currently published algorithms (Figure 1).

| Drug | Dosage |
|---|---|
| **Topical** | |
| Lidocaine/prilocaine cream | Lidocaine 2.5%/prilocaine 2.5%, 20–30 minutes before intercourse |
| **Oral (Selective serotonin reuptake inhibitors)** | |
| **Daily** | |
| Sertaline | 25–200 mg/day |
| Fluoxetine | 5–20 mg/day |
| Paroxetine | 10, 20, 40 mg/day |
| **On-demand** | |
| Sertaline | 50mg, 4–8 hours before intercourse |
| Paroxetine | 20 mg, 3–4 hours before intercourse |
| **Oral (Tricyclic)** | |
| **Daily** | |
| Clomipramine | 25–50 mg/day |
| **On-demand** | |
| Clomipramine | 25 mg, 4–24 hours before intercourse |

Table 5. Pharmacological options for the management of PE (Montague et al., 2004)

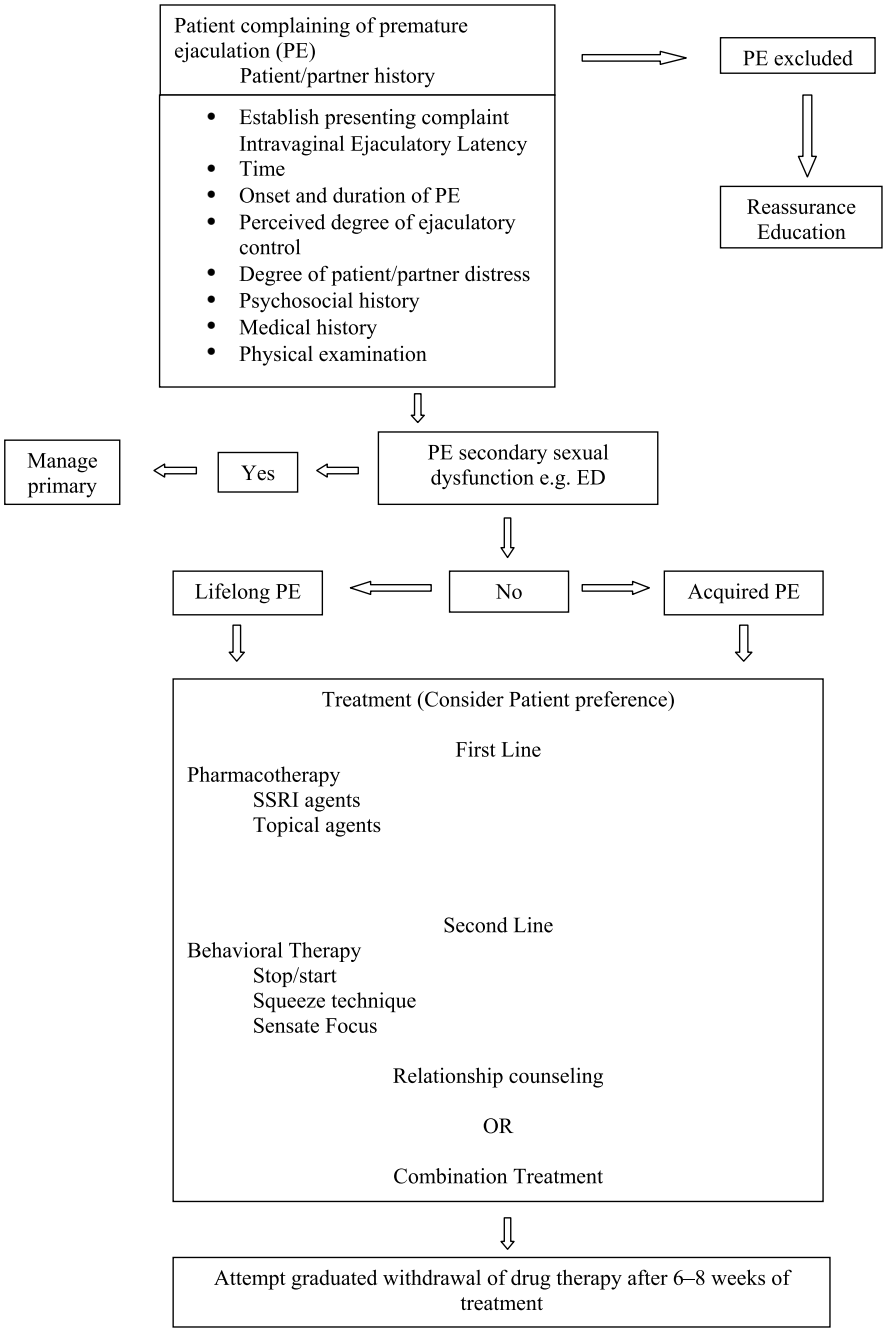



Fig. 1. Algorithm for the management of premature ejaculation (McMahon, 2005; Morales et al., 2007; Rowland et al., 2010).

## 7. Concluding message

PE is one of the most common male sexual disorders that can have a significant impact on the quality of life of couples. It is a complex disease process that requires clear definition to facilitate research and treatment. It remains substantially under-diagnosed and under-treated, since it is not very well understood by healthcare providers. It is a self reported disorder and one in which the diagnosis is mainly based on history. A sexual history should include all three aspects of PE, namely short IELT, lack of control and distress for both partners. Among the many neurotransmitter systems involved in ejaculatory modulation, central 5-HT has been implicated as a key mediator of ejaculatory control and thus a therapeutic target. Both behavioral and pharmacological options are available to manage PE. Behavioral techniques and psychotherapy can be cumbersome and expensive, with limited long-term efficacy, and therefore are used to complement pharmacotherapy. Currently available pharmaceutical therapy involves the off-label use of SSRIs, Clomipramine, tramadol, PDE-5 inhibitors, as well as topical anaesthetics, each of which have shown varying degrees of efficacy and tolerability. These pharmacotherapies are far from ideal. Their clinical utility is limited by several factors, including a high incidence of adverse events. Each treatment option should be discussed with the PE patient including dosing, the anticipated success rate and possible side effects such that the patient participates in the decision making. Therapy should be tailored for each patient as one treatment does not fit all, as well as preference varies between men. Therapy for PE will continue to develop as the understanding of ejaculation expands and current agents in development may eventually come closer to an ideal and specific therapy for PE.

## 8. References

Abdel-Hamid, I. A., Jannini, E. A., & Andersson, K. E. (2009). Premature ejaculation: focus on therapeutic targets. *Expert Opin Ther Targets, 13*(2), 175-193.

Ahlenius, S., Larsson, K., Svensson, L., Hjorth, S., Carlsson, A., Lindberg, P., Wikstrom, H., Sanchez, D., Arvidsson, L. E., Hacksell, U., & Nilsson, J. L. (1981). Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. *Pharmacol Biochem Behav, 15*(5), 785-792.

Aloosh, M., Hassani, M., & Nikoobakht, M. (2006). Seminal plasma magnesium and premature ejaculation: a case-control study. *BJU Int, 98*(2), 402-404.

Althof, S. (2006). The psychology of premature ejaculation: therapies and consequences. *J Sex Med, 3 Suppl 4*, 324-331.

Althof, S. E. (2004). Assessment of rapid ejaculation: review of new and existing measures. *Curr Sexual Health Rep, 1*, 61.

Althof, S. E. (2005). Psychological treatment strategies for rapid ejaculation: rationale, practical aspects, and outcome. *World J Urol, 23*(2), 89-92.

Althof, S. E. (2006). Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. *J Urol, 175*(3 Pt 1), 842-848.

Althof, S. E., Levine, S. B., Corty, E. W., Risen, C. B., Stern, E. B., & Kurit, D. M. (1995). A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry, 56*(9), 402-407.

American Psychiatric Association. (2000). *The Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: American Psychiatric Association.

Assalian, P. (1988). Clomipramine in the treatment of premature ejaculation. *J Sex Res, 24*, 213-215.

Atan, A., Basar, M. M., & Aydoganli, L. (2000). Comparison of the efficacy of fluoxetine alone vs. fluoxetine plus local lidocaine ointment in the treatment of premature ejaculation. *Arch Esp Urol, 53*(9), 856-858.

Atikeler, M. K., Gecit, I., & Senol, F. A. (2002). Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia, 34*(6), 356-359.

Balon, R. (2006). SSRI-associated sexual dysfunction. *Am J Psychiatry, 163*(9), 1504-1509; quiz 1664.

Basal, S., Goktas, S., Ergin, A., Yildirim, I., Atim, A., Tahmaz, L., & Dayanc, M. (2010). A novel treatment modality in patients with premature ejaculation resistant to conventional methods: the neuromodulation of dorsal penile nerves by pulsed radiofrequency. *J Androl, 31*(2), 126-130.

Basar, M. M., Yilmaz, E., Ferhat, M., Basar, H., & Batislam, E. (2005). Terazosin in the treatment of premature ejaculation: a short-term follow-up. *Int Urol Nephrol, 37*(4), 773-777.

Biri, H., Isen, K., Sinik, Z., Onaran, M., Kupeli, B., & Bozkirli, I. (1998). Sertraline in the treatment of premature ejaculation: a double-blind placebo controlled study. *Int Urol Nephrol, 30*(5), 611-615.

Bohlen, D., Hugonnet, C. L., Mills, R. D., Weise, E. S., & Schmid, H. P. (2000). Five meters of H(2)O: the pressure at the urinary bladder neck during human ejaculation. *Prostate, 44*(4), 339-341.

Busato, W., & Galindo, C. C. (2004). Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int, 93*(7), 1018-1021.

Buvat, J., Tesfaye, F., Rothman, M., Rivas, D. A., & Giuliano, F. (2009). Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. *Eur Urol, 55*(4), 957-967.

Carey, M. P. (1998). Cognitive behavioral treatment of sexual dysfunction. In V. E. Caballo (Ed.), *International Handbook of Cognitive and Behavioural Treatments for Psychological Disorders* (pp. 251-280). Kidlington, Oxford: Pergamon.

Carson, C., & Gunn, K. (2006). Premature ejaculation: definition and prevalence. *Int J Impot Res, 18 Suppl 1*, S5-13.

Carson, C., & Wyllie, M. (2010). Improved ejaculatory latency, control and sexual satisfaction when PSD502 is applied topically in men with premature ejaculation: results of a phase III, double-blind, placebo-controlled study. *J Sex Med, 7*(9), 3179-3189.

Cavallini, G. (1995). Alpha-1 blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. *Eur Urol, 28*(2), 126-130.

Chen, J., Mabjeesh, N. J., Matzkin, H., & Greenstein, A. (2003). Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. *Urology, 61*(1), 197-200.

Choi, H. K., Jung, G. W., Moon, K. H., Xin, Z. C., Choi, Y. D., Lee, W. H., Rha, K. H., Choi, Y. J., & Kim, D. K. (2000). Clinical study of SS-cream in patients with lifelong premature ejaculation. *Urology, 55*(2), 257-261.

Choi, H. K., Xin, Z. C., Choi, Y. D., Lee, W. H., Mah, S. Y., & Kim, D. K. (1999). Safety and efficacy study with various doses of SS-cream in patients with premature ejaculation in a double-blind, randomized, placebo controlled clinical study. *Int J Impot Res, 11*(5), 261-264.

Cohen, D. (2007). Should the use of selective serotonin reuptake inhibitors in child and adolescent depression be banned? *Psychother Psychosom, 76*, 5-14.

Colpi, G., Weidner, W., Jungwirth, A., Pomerol, J., Papp, G., Hargreave, T., & Dohle, G. (2004). EAU guidelines on ejaculatory dysfunction. *Eur Urol, 46*(5), 555-558.

Colpi, G. M., Hargreave, T. B., Papp, G. K., Pomerol, J. M., & Weidner, W. (2001). *Guidelines on Disorders of Ejaculation*. Retrieved July 17, 2011, from http://www.uroweb.org/files/uploaded_files/guidelines/ejaculationdisor.pdf

Coolen, L. M., Allard, J., Truitt, W. A., & McKenna, K. E. (2004). Central regulation of ejaculation. *Physiol Behav, 83*(2), 203-215.

Corona, G., Petrone, L., Mannucci, E., Jannini, E. A., Mansani, R., Magini, A., Giommi, R., Forti, G., & Maggi, M. (2004). Psycho-biological correlates of rapid ejaculation in patients attending an andrologic unit for sexual dysfunctions. *Eur Urol, 46*(5), 615-622.

Cossmann, M., Kohnen, C., Langford, R., & McCartney, C. (1997). [Tolerance and safety of tramadol use. Results of international studies and data from drug surveillance]. *Drugs, 53 Suppl 2*, 50-62.

Dapoxetine: LY 210448. (2005). *Drugs R D, 6*(5), 307-311.

De Amicis, L. A., Goldberg, D. C., LoPiccolo, J., Friedman, J., & Davies, L. (1985). Clinical follow-up of couples treated for sexual dysfunction. *Arch Sex Behav, 14*(6), 467-489.

de Carufel, F., & Trudel, G. (2006). Effects of a new functional-sexological treatment for premature ejaculation. *J Sex Marital Ther, 32*(2), 97-114.

de Jong, T. R., Pattij, T., Veening, J. G., Dederen, P. J., Waldinger, M. D., Cools, A. R., & Olivier, B. (2005). Citalopram combined with WAY 100635 inhibits ejaculation and ejaculation-related Fos immunoreactivity. *Eur J Pharmacol, 509*(1), 49-59.

Dent, L. A., Brown, W. C., & Murney, J. D. (2002). Citalopram-induced priapism. *Pharmacotherapy, 22*(4), 538-541.

Diaz, V. A., Jr., & Close, J. D. (2010). Male sexual dysfunction. *Prim Care, 37*(3), 473-489, vii-viii.

Dinsmore, W. W., Hackett, G., Goldmeier, D., Waldinger, M., Dean, J., Wright, P., Callander, M., Wylie, K., Novak, C., Keywood, C., Heath, P., & Wyllie, M. (2007). Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. *BJU Int, 99*(2), 369-375.

Dinsmore, W. W., & Wyllie, M. G. (2009). PSD502 improves ejaculatory latency, control and sexual satisfaction when applied topically 5 min before intercourse in men with premature ejaculation: results of a phase III, multicentre, double-blind, placebo-controlled study. *BJU Int, 103*(7), 940-949.

Donatucci, C. F. (2006). Etiology of ejaculation and pathophysiology of premature ejaculation. *J Sex Med, 3 Suppl 4*, 303-308.

Dresser, M. J., Kang, D., Staehr, P., Gidwani, S., Guo, C., Mulhall, J. P., & Modi, N. B. (2006). Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: Impact of age and effects of a high-fat meal. *J Clin Pharmacol, 46*(9), 1023-1029.

Dunn, K. M., Croft, P. R., & Hackett, G. I. (1998). Sexual problems: a study of the prevalence and need for health care in the general population. *Fam Pract, 15*(6), 519-524.

Dunn, K. M., Croft, P. R., & Hackett, G. I. (1999). Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. *J Epidemiol Community Health, 53*(3), 144-148.

Eaton, H. (1973). Clomipramine in the treatment of premature ejaculation. *J Int Med Res, 1*, 432.

El-Sakka, A. I. (2003). Premature ejaculation in non-insulin-dependent diabetic patients. *Int J Androl, 26*(6), 329-334.

Eradiri, O., Sista, S., Lai, J. C.-K., Danyluk, A., & Brett, V. (2006). Bioavailability of extendedrelease and immediate-release formulations of tramadol HCI. *J Clin Pharmacol, 46*, 1091.

FDA. (2007). *FDA proposes new warnings about suicidal thinking, behavior in young adults who take antidepressant medications*. Retrieved July 17, 2011, from http://69.20.19.211/bbs/topics/NEWS/2007/ NEW01624.html

Fein, R. L. (1990). Intracavernous medication for treatment of premature ejaculation. *Urology, 35*(4), 301-303.

Filippi, S., Morelli, A., Vignozzi, L., Vannelli, G. B., Marini, M., Ferruzzi, P., Mancina, R., Crescioli, C., Mondaini, N., Forti, G., Ledda, F., & Maggi, M. (2005). Oxytocin mediates the estrogen-dependent contractile activity of endothelin-1 in human and rabbit epididymis. *Endocrinology, 146*(8), 3506-3517.

Frink, M. C., Hennies, H. H., Englberger, W., Haurand, M., & Wilffert, B. (1996). Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittelforschung, 46*(11), 1029-1036.

Gittleman, M. C., Mo, J., & Lu, M. (2005, December 4-7). *Synergistic effect of meatal application of dyclonine/alprostadil cream for the treatment of early ejaculation (EE) in a double-blind and crossover study.* Paper presented at the the 8th Congress of the European Society for Sexual Medicine, Copenhagen, Denmark.

Giuliano, F. (2007). Interview with Dr Francois Giuliano (by Christine McKillop). New avenues in the pharmacological treatment of premature ejaculation. *Eur Urol, 52*(4), 1254-1257.

Godpodinoff, M. L. (1989). Premature ejaculation: clinical subgroups and etiology. *J Sex Marital Ther, 15*(2), 130-134.

Grenier, G., & Byers, E. S. (1995). Rapid ejaculation: a review of conceptual, etiological, and treatment issues. *Arch Sex Behav, 24*(4), 447-472.

Grenier, G., & Byers, E. S. (2001). Operationalizing premature or rapid ejaculation. *J Sex Res, 38*, 169-178.

Gur, E., Lerer, B., & Newman, M. E. (1999). Chronic clomipramine and triiodothyronine increase serotonin levels in rat frontal cortex in vivo: relationship to serotonin autoreceptor activity. *J Pharmacol Exp Ther, 288*(1), 81-87.

Gurkan, L., Oommen, M., & Hellstrom, W. J. (2008). Premature ejaculation: current and future treatments. *Asian J Androl, 10*(1), 102-109.

Guthrie, E. (1952). *The Psychology of Learning*. New York: Harper.

Haensel, S. M., Rowland, D. L., & Kallan, K. T. (1996). Clomipramine and sexual function in men with premature ejaculation and controls. *J Urol, 156*(4), 1310-1315.

Halperin, D., & Reber, G. (2007). Influence of antidepressants on hemostasis. *Dialogues Clin Neurosci, 9*(1), 47-59.

Haney, E. M., Chan, B. K., Diem, S. J., Ensrud, K. E., Cauley, J. A., Barrett-Connor, E., Orwoll, E., & Bliziotes, M. M. (2007). Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. *Arch Intern Med, 167*(12), 1246-1251.

Hartmann, U., Schedlowski, M., & Kruger, T. H. (2005). Cognitive and partner-related factors in rapid ejaculation: differences between dysfunctional and functional men. *World J Urol, 23*(2), 93-101.

Hawton, K., Catalan, J., Martin, P., & Fagg, J. (1986). Long-term outcome of sex therapy. *Behav Res Ther, 24*(6), 665-675.

Hellstrom, W. J. (2006). Current and future pharmacotherapies of premature ejaculation. *J Sex Med, 3 Suppl 4*, 332-341.

Hellstrom, W. J. (2009). Emerging treatments for premature ejaculation: focus on dapoxetine. *Neuropsychiatr Dis Treat, 5*, 37-46.

Hellstrom, W. J. (2011). Update on treatments for premature ejaculation. *Int J Clin Pract, 65*(1), 16-26.

Henry, R., & Morales, A. (2003). Topical lidocaine-prilocaine spray for the treatment of premature ejaculation: a proof of concept study. *Int J Impot Res, 15*(4), 277-281.

Henry, R., Morales, A., & Wyllie, M. G. (2008). TEMPE: Topical Eutectic-Like Mixture for Premature Ejaculation. *Expert Opin Drug Deliv, 5*(2), 251-261.

International Society for Sexual Medicine. (2007). *ISSM definition of premature ejaculation*. Retrieved July 17, 2007, from http://www.issm.info/

Jan Wise, M. E., & Watson, J. P. (2000). A new treatment for premature ejaculation: case series for a desensitizing band. *Sex and Relation Ther, 15*, 345-350.

Jannini, E. A., & Lenzi, A. (2005). Epidemiology of premature ejaculation. *Curr Opin Urol, 15*(6), 399-403.

Jannini, E. A., Lombardo, F., & Lenzi, A. (2005). Correlation between ejaculatory and erectile dysfunction. *Int J Androl, 28 Suppl 2*, 40-45.

Kara, H., Aydin, S., Yucel, M., Agargun, M. Y., Odabas, O., & Yilmaz, Y. (1996). The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind placebo controlled study. *J Urol, 156*(5), 1631-1632.

Kilic, S., Ergin, H., & Baydinc, Y. C. (2005). Venlafaxine extended release for the treatment of patients with premature ejaculation: a pilot, single-blind, placebo-controlled, fixed-dose crossover study on short-term administration of an antidepressant drug. *Int J Androl, 28*(1), 47-52.

Kim, J. J., Kwak, T. I., Jeon, B. G., Cheon, J., & Moon, D. G. (2004). Effects of glans penis augmentation using hyaluronic acid gel for premature ejaculation. *Int J Impot Res, 16*(6), 547-551.

Kim, S. C., & Seo, K. K. (1998). Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol, 159*(2), 425-427.

Kim, S. W., Lee, S. H., & Paick, J. S. (2004). In vivo rat model to measure hypogastric nerve stimulation-induced seminal vesicle and vasal pressure responses simultaneously. *Int J Impot Res, 16*(5), 427-432.

Kim, S. W., & Paick, J. S. (1999). Short-term analysis of the effects of as needed use of sertraline at 5 PM for the treatment of premature ejaculation. *Urology, 54*(3), 544-547.

Kwak, T. I., Jin, M. H., Kim, J. J., & Moon, D. G. (2008). Long-term effects of glans penis augmentation using injectable hyaluronic acid gel for premature ejaculation. *Int J Impot Res, 20*(4), 425-428.

Laumann, E. O., Gagnon, J. H., Michael, R. T., & Michaels, S. (1994). The Social Organization of Sexuality. *University of Chicago Press*.

Laumann, E. O., Nicolosi, A., Glasser, D. B., Paik, A., Gingell, C., Moreira, E., & Wang, T. (2005). Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res, 17*(1), 39-57.

Laumann, E. O., Paik, A., & Rosen, R. C. (1999a). The epidemiology of erectile dysfunction: results from the National Health and Social Life Survey. *Int J Impot Res, 11 Suppl 1*, S60-64.

Laumann, E. O., Paik, A., & Rosen, R. C. (1999b). Sexual dysfunction in the United States: prevalence and predictors. *Jama, 281*(6), 537-544.

Levine, S. B. (1975). Premature ejaculation: some thoughts about its pathogenesis. *J Sex Marital Ther, 1*(4), 326-334.

Linton, K. D., & Wylie, K. R. (2010). Recent advances in the treatment of premature ejaculation. *Drug Des Devel Ther, 4*, 1-6.

Looney, C., Thor, K. B., Ricca, D., & Marson, L. (2005). Differential effects of simultaneous or sequential administration of paroxetine and WAY-100,635 on ejaculatory behavior. *Pharmacol Biochem Behav, 82*(3), 427-433.

Lue, T., & Broderick, G. (2007). Evaluation and nonsurgical management of erectile dysfunction and premature ejaculation. In P. C. Walsh, A. B. Retik, E. D. Vaughan, A. J. Wein, L. R. Kavoussi, A. C. Novick, A. W. Partin & C. A. Peters (Eds.), *Campbell-Walsh urology* (9th ed., pp. 750-787). Philadelphia, PA: Saunders-Elsevier.

Maier, U., & Koinig, G. (1994). Andrological findings in young patients under long-term antidepressive therapy with clomipramine. *Psychopharmacology (Berl), 116*(3), 357-359.

Masters, W., & Johnson, V. (1970). *Premature ejaculation: Human sexual inadequacy*. Boston: Little Brown & Co.

McDiarmid, T., Mackler, L., & Schneider, D. M. (2005). Clinical inquiries. What is the addiction risk associated with tramadol? *J Fam Pract, 54*(1), 72-73.

McMahon, C. (2005). Premature ejaculation: past, present, and future perspectives. *J Sex Med, 2 Suppl 2*, 94-95.

McMahon, C., Kim, S. W., Park, N. C., Chang, C. P., Rivas, D., Tesfaye, F., Rothman, M., & Aquilina, J. (2010). Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. *J Sex Med, 7*(1 Pt 1), 256-268.

McMahon, C. G. (2002). Long term results of treatment of premature ejaculation with selective serotonin re-uptake inhibitors. *Int J Imp Res, 14*, 19.

McMahon, C. G. (2005). The etiology and management of premature ejaculation. *Nat Clin Pract Urol, 2*(9), 426-433.

McMahon, C. G., Abdo, C., Incrocci, L., Perelman, M., Rowland, D., Waldinger, M., & Xin, Z. C. (2004). Disorders of orgasm and ejaculation in men. *J Sex Med, 1*(1), 58-65.

McMahon, C. G., McMahon, C. N., Leow, L. J., & Winestock, C. G. (2006). Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. *BJU Int, 98*(2), 259-272.

McMahon, C. G., & Samali, R. (1999). Pharmacological treatment of premature ejaculation. *Curr Opin Urol, 9*(6), 553-561.

McMahon, C. G., & Touma, K. (1999). Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol, 161*(6), 1826-1830.

Metz, M. E., & Pryor, J. L. (2000). Premature ejaculation: a psychophysiological approach for assessment and management. *J Sex Marital Ther, 26*(4), 293-320.

Montague, D. K., Jarow, J., Broderick, G. A., Dmochowski, R. R., Heaton, J. P., Lue, T. F., Nehra, A., & Sharlip, I. D. (2004). AUA guideline on the pharmacologic management of premature ejaculation. *J Urol, 172*(1), 290-294.

Montejo, A. L., Llorca, G., Izquierdo, J. A., & Rico-Villademoros, F. (2001). Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J Clin Psychiatry, 62 Suppl 3*, 10-21.

Morales, A., Barada, J., & Wyllie, M. G. (2007). A review of the current status of topical treatments for premature ejaculation. *BJU Int, 100*(3), 493-501.

Moreira, E. D., Jr., Brock, G., Glasser, D. B., Nicolosi, A., Laumann, E. O., Paik, A., Wang, T., & Gingell, C. (2005). Help-seeking behaviour for sexual problems: the global study of sexual attitudes and behaviors. *Int J Clin Pract, 59*(1), 6-16.

Mousavizadeh, K., Ghafourifar, P., & Sadeghi-Nejad, H. (2002). Calcium channel blocking activity of thioridazine, clomipramine and fluoxetine in isolated rat vas deferens: a relative potency measurement study. *J Urol, 168*(6), 2716-2719.

Nicolosi, A., Laumann, E. O., Glasser, D. B., Moreira, E. D., Jr., Paik, A., & Gingell, C. (2004). Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. *Urology, 64*(5), 991-997.

Optale, G., Pastore, M., Marin, S., Bordin, D., Nasta, A., & Pianon, C. (2004). Male sexual dysfunctions: immersive virtual reality and multimedia therapy. *Stud Health Technol Inform, 99*, 165-178.

Palmer, N. R., & Stuckey, B. G. (2008). Premature ejaculation: a clinical update. *Med J Aust, 188*(11), 662-666.

Patrick, D. L., Althof, S. E., Pryor, J. L., Rosen, R., Rowland, D. L., Ho, K. F., McNulty, P., Rothman, M., & Jamieson, C. (2005). Premature ejaculation: an observational study of men and their partners. *J Sex Med, 2*(3), 358-367.

Payne, R. E., & Sadovsky, R. (2007). Identifying and treating premature ejaculation: importance of the sexual history. *Cleve Clin J Med, 74 Suppl 3*, S47-53.

Perelman, M., McMahon, C., & Barada, J. (2004). Evaluation and treatment of the ejaculatory disorders. In T. F. Lue (Ed.), *Atlas of male sexual dysfunction* (pp. 127-157). Philadelphia, PA: Current Medicine, Inc.

Perelman, M. A. (2006). A new combination treatment for premature ejaculation: a sex therapist's perspective. *J Sex Med, 3*(6), 1004-1012.

Porst, H., Montorsi, F., Rosen, R. C., Gaynor, L., Grupe, S., & Alexander, J. (2007). The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *Eur Urol, 51*(3), 816-823; discussion 824.

Powell, J. A., & Wyllie, M. G. (2009). 'Up and coming' treatments for premature ejaculation: progress towards an approved therapy. *Int J Impot Res, 21*(2), 107-115.

Press release. (2005). ALZA Corporation receives letter from FDA on dapoxetine application. *Alza Corporation Press*.

Pryor, J. L., Althof, S. E., Steidle, C., Rosen, R. C., Hellstrom, W. J., Shabsigh, R., Miloslavsky, M., & Kell, S. (2006). Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet, 368*(9539), 929-937.

Raeder, M. B., Bjelland, I., Emil Vollset, S., & Steen, V. M. (2006). Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study. *J Clin Psychiatry, 67*(12), 1974-1982.

Riley, A., & Segraves, R. T. (2006). Treatment of premature ejaculation. *Int J Clin Pract, 60*(6), 694-697.

Rosenberg, M. T., Sailor, N., Tallman, C. T., & Ohl, D. A. (2006, May 20-25). *Premature ejaculation as reported by female partners: prevalence and sexual satisfaction survey results from a community practice*. Paper presented at the American Urological Association Annual Meeting, Atlanta, GA.

Rowland, D., McMahon, C. G., Abdo, C., Chen, J., Jannini, E., Waldinger, M. D., & Ahn, T. Y. (2010). Disorders of orgasm and ejaculation in men. *J Sex Med, 7*(4 Pt 2), 1668-1686.

Rowland, D., Perelman, M., Althof, S., Barada, J., McCullough, A., Bull, S., Jamieson, C., & Ho, K. F. (2004). Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. *J Sex Med, 1*(2), 225-232.

Rowland, D. L., & Cooper, S. E. (2005). Behavioral and psychological models in ejaculatory function research. In J. P. Mulhall (Ed.), *Current Sexual Health Reports* (Vol. 2, pp. 29-34). Philadelphia, PA: Current Science Inc.

Rowland, D. L., Cooper, S. E., & Schneider, M. (2001). Defining premature ejaculation for experimental and clinical investigations. *Arch Sex Behav, 30*(3), 235-253.

Rowland, D. L., De Gouveia Brazao, C. A., & Koos Slob, A. (2001). Effective daily treatment with clomipramine in men with premature ejaculation when 25 mg (as required) is ineffective. *BJU Int, 87*(4), 357-360.

Rowland, D. L., & Rose, P. (2008). Understanding & treating premature ejaculation. *Nurse Pract, 33*(10), 21-27.

Rowland, D. L., Tai, W. L., Brummett, K., & Slob, A. K. (2004). Predicting responsiveness to the treatment of rapid ejaculation with 25 mg clomipramine as needed. *Int J Impot Res, 16*(4), 354-357.

Sadeghi-Nejad, H., & Watson, R. (2008). Premature ejaculation: current medical treatment and new directions (CME). *J Sex Med, 5*(5), 1037-1050; quiz 1051-1032.

Safarinejad, M. R., & Hosseini, S. Y. (2006). Safety and efficacy of tramadol in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. *J Clin Psychopharmacol, 26*(1), 27-31.

Salem, E. A., Wilson, S. K., Bissada, N. K., Delk, J. R., Hellstrom, W. J., & Cleves, M. A. (2008). Tramadol HCL has promise in on-demand use to treat premature ejaculation. *J Sex Med, 5*(1), 188-193.

Salonia, A., Maga, T., Colombo, R., Scattoni, V., Briganti, A., Cestari, A., Guazzoni, G., Rigatti, P., & Montorsi, F. (2002). A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. *J Urol, 168*(6), 2486-2489.

Schapiro, B. (1943). Premature ejaculation: a review of 1130 cases. *J Urol, 3*, 374-379.

Screponi, E., Carosa, E., Di Stasi, S. M., Pepe, M., Carruba, G., & Jannini, E. A. (2001). Prevalence of chronic prostatitis in men with premature ejaculation. *Urology, 58*(2), 198-202.

Segraves, R. T., Saran, A., Segraves, K., & Maguire, E. (1993). Clomipramine versus placebo in the treatment of premature ejaculation: a pilot study. *J Sex Marital Ther, 19*(3), 198-200.

Semans, J. H. (1956). Premature ejaculation: a new approach. *South Med J, 49*(4), 353-358.

Shabsigh, R. (2006). Diagnosing premature ejaculation: a review. *J Sex Med, 3 Suppl 4*, 318-323.

Sharlip, I. D. (2006). Guidelines for the diagnosis and management of premature ejaculation. *J Sex Med, 3 Suppl 4*, 309-317.

Slob, A., Van Berke, A., & Van der Werff ten Bosch, J. (2000). Premature ejaculation treated by local penile anaesthesia in an uncontrolled clinical replication study. *J Sex Res, 37*, 244-247.

Spector, I. P., & Carey, M. P. (1990). Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. *Arch Sex Behav, 19*(4), 389-408.

Steggall, M. J., Fowler, C. G., & Pryce, A. (2008). Combination Therapy for Premature Ejaculation: Results of a Small-Scale Study. *Sex Rel Ther, 23*, 365-376.

Sunay, D., Sunay, M., Aydogmus, Y., Bagbanci, S., Arslan, H., Karabulut, A., & Emir, L. (2011). Acupuncture versus paroxetine for the treatment of premature ejaculation: a randomized, placebo-controlled clinical trial. *Eur Urol, 59*(5), 765-771.

Symonds, T., Roblin, D., Hart, K., & Althof, S. (2003). How does premature ejaculation impact a man s life? *J Sex Marital Ther, 29*(5), 361-370.

Tian, L., Xin, Z. C., Xin, H., Fu, J., Yuan, Y. M., Liu, W. J., & Yang, C. (2004). Effect of renewed SS-cream on spinal somatosensory evoked potential in rabbits. *Asian J Androl, 6*(1), 15-18.

Waldinger, M. D. (2002). The neurobiological approach to premature ejaculation. *J Urol, 168*(6), 2359-2367.

Waldinger, M. D. (2003). Towards evidence-based drug treatment research on premature ejaculation: a critical evaluation of methodology. *Int J Impot Res, 15*(5), 309-313.

Waldinger, M. D. (2007). Premature ejaculation: definition and drug treatment. *Drugs, 67*(4), 547-568.

Waldinger, M. D., Berendsen, H. H., Blok, B. F., Olivier, B., & Holstege, G. (1998). Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res, 92*(2), 111-118.

Waldinger, M. D., Hengeveld, M. W., Zwinderman, A. H., & Olivier, B. (1998). Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled

study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol, 18*(4), 274-281.

Waldinger, M. D., Quinn, P., Dilleen, M., Mundayat, R., Schweitzer, D. H., & Boolell, M. (2005). A multinational population survey of intravaginal ejaculation latency time. *J Sex Med, 2*(4), 492-497.

Waldinger, M. D., Rietschel, M., Nothen, M. M., Hengsveld, M. W., & Olivier, B. (1997). Familial occurrence of primary premature ejaculation. *Psychiatr Genet, 8*, 37-40.

Waldinger, M. D., van De Plas, A., Pattij, T., van Oorschot, R., Coolen, L. M., Veening, J. G., & Olivier, B. (2002). The selective serotonin re-uptake inhibitors fluvoxamine and paroxetine differ in sexual inhibitory effects after chronic treatment. *Psychopharmacology (Berl), 160*(3), 283-289.

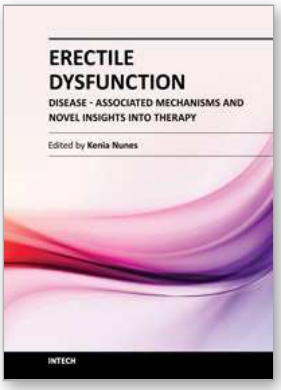
Waldinger, M. D., Zwinderman, A. H., & Olivier, B. (2004). On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. *Eur Urol, 46*(4), 510-515; discussion 516.

Waldinger, M. D., Zwinderman, A. H., Schweitzer, D. H., & Olivier, B. (2004). Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res, 16*(4), 369-381.

Wang, W. F., Chang, L., Minhas, S., & Ralph, D. J. (2007). Selective serotonin reuptake inhibitors in the treatment of premature ejaculation. *Chin Med J (Engl), 120*(11), 1000-1006.

Williamson, I. J., Turner, L., Woods, K., & ., e. a. (2003). The 5-HT1A receptor antagonist robalzotan enhances SSRI-induced ejaculation delay in the rat. *Br J Pharmacol, 138 (Suppl. 1)*, PO32.

World Health Organization. (2004). *Second international consultation on sexual dysfunctions*. Paris: World Health Organization.




**Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy**

Edited by Dr. Kenia Nunes

ISBN 978-953-51-0199-4
Hard cover, 214 pages
**Publisher** InTech
**Published online** 29, February, 2012
**Published in print edition** February, 2012

Erectile dysfunction is a widespread problem, affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. This book contains chapters written by widely acknowledged experts, each of which provides a unique synthesis of information on emergent aspects of ED. All chapters take into account not only the new perspectives on ED but also recent extensions of basic knowledge that presage directions for further research. The approach in this book has been to not only describe recent popular aspects of ED, such as basic mechanism updates, etiologic factors and pharmacotherapy, but also disease-associated ED and some future perspectives in this field.

**How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Tariq F. Al-Shaiji (2012). Premature Ejaculation Re-Visited: Definition and Contemporary Management Approaches, Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy, Dr. Kenia Nunes (Ed.), ISBN: 978-953-51-0199-4, InTech, Available from: http://www.intechopen.com/books/erectile-dysfunction-disease-associated-mechanisms-and-novel-insights-into-therapy/premature-ejaculation-re-visited-definition-and-contemporary-management-approaches

INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821