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Current premature ejaculation treatments
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·*Review*·

Premature ejaculation: current and future treatments

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Abstract

Premature ejaculation (PE) is recognized to be the most common male sexual disorder. PE provides difficulties for professionals who treat this condition because there is neither a universally accepted definition nor a medication approved by the Food and Drug Administration (FDA). Despite these shortcomings, physicians continue to diagnose their patients with PE according to major guidelines and treat them with either behavioral therapies or off-label medications. This review focuses on current and emerging treatment options and medications for PE. Advantages and limitations of each treatment option are discussed in the light of current published peer-reviewed literature. *(Asian J Androl 2008 Jan; 10: 102–109)*

Keywords: premature ejaculation; male sexual disorder; ejaculation

1 Introduction

Although premature ejaculation (PE) is recognized to be the most common male sexual disorder, it provides difficulties for the professionals who treat men with PE because there is neither a universally accepted definition nor a medication approved by the Food and Drug Administration (FDA) with which to treat it. The lack of a globally accepted definition causes difficulties in determining the prevalence, which has been cited as being anywhere from 4% to 66%. Most authorities accept that around 25%–40% of all men suffer from this condition at some point of their life [1]. The following review will focus on non-medical and medical treatment options of this common male sexual disorder including the off-label use of medications.

Clinicians tend to use definitions of PE as described in one of the major guidelines, such as The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR), The International Consultation on Urological Disease or The American Urological Association Guideline. The DSM-IV-TR [2] has defined PE as "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it". This definition of PE requires that the condition "must also cause marked distress or interpersonal difficulty", and states that it "is not due exclusively to the direct effects of a substance". Very similar definitions are given in The International Consultation on Urological Disease and The American Urological Association (AUA) Guideline. The former defines it as "persistent or recurrent ejaculation with minimal stimulation before, on or shortly after penetration and before the person wishes it, over which the sufferer has little or no voluntary control which causes the sufferer and/or his partner bother or distress". The latter defines PE as ejaculation that "occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners" [3]. All of these definitions share three main qualifications: short time interval between penetration and ejaculation, lack of control over ejaculation and distress by one or both partners. Only the International Classification of Diseases, Tenth Edition [4] issued by the World Health Organization (WHO), gives us a quantified cut-off point as it describes PE as "the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 s of the beginning of intercourse) or ejaculation oc-

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curs in the absence of sufficient erection to make intercourse possible". For the most part, researchers are dissatisfied with these definitions, as the former three are based on subjective complaints and fail to define an objective cut-off point that can be easily used in a study while the latter fails to provide peer-reviewed literature to support any defined cut-off value.

In 1994, Waldinger and colleagues [5] introduced and defined the term "intravaginal ejaculatory latency time" (IELT)-the time from vaginal penetration to the start of intravaginal ejaculation-as an objective outcome measure. The IELT is positively skewed with a median of 5.4 min. The 0.5 percentile equates to an IELT of 0.9 min and the 2.5 percentile an IELT of 1.3 min [5]. It is generally accepted but not included in most guidelines that men with an IELT of less than 1 min have "definitive" PE. Although IELT covers only one parameter of PE, namely "short time interval between penetration and ejaculation", and ignores other patient-reported outcomes (PROs) such as "lack of control over ejaculation" and "distress experienced by one or both partners", it was welcomed by the research community as it provided a tool to objectively assess the efficacy of pharmacological or surgical interventions. For this review, we will employ IELT as the main measure for comparing different treatment options as it is the most universally accepted tool and newly developed PE questionnaires are in need of further validation in larger scale studies. It should be noted that PE questionnaires such as the Premature Ejaculation Questionnaire (36 items), The Index of Premature Ejaculation (10 items) or The Chinese Index of Premature Ejaculation (10 items) take evaluation one step further, as they include questions about perception of control over ejaculation, interpersonal distress, and overall sexual satisfaction. We do not believe the use of IELT is reliable as the only parameter for defining treatment success in a clinical setting. PE has a significant impact on men and their partners' sexual life and the goal for treatment of PE should be improvement in patient and partner satisfaction in relation to sexual intercourse and quality of life [3].

2 Non-medical treatment of PE

Historically, and through the early 1990's, PE was considered to be a psychological (rather than a physiological) problem and behavioral psychosexual therapies were considered the treatment of choice. In 1956, urologist Semans [6] described one of the earliest behavioral interventions, namely the "stop-start technique". 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. A similar technique was proposed by sex therapists Masters and Johnson in 1970 [7]. 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. Although the teaching of these specific techniques to delay ejaculation seems to be the mainstay of psychosexual therapy, the primary goals of traditional psychosexual treatment for PE are to aid the male in regaining confidence in his sexual performance, reduce performance anxiety, resolve any interpersonal difficulties and increase couple communication. Typically, these psychological approaches have high initial success rates (45%–65%); however, the effects are not long-lasting. Hawton and colleagues [8] reported that 75% of men with PE who initially responded to behavioral therapy showed no long lasting improvement after 3 years of follow-up. Ejaculation is actually a spinal reflex under strong control from higher spinal and cortical centers, much like urination and defecation. Control can be learned and is greatly influenced by past experiences and the present context under which the response is occurring. However, as demonstrated by Waldinger and colleagues, the patients with real PE occupy the far left edge of a normal distribution curve which may suggest a genetically inherited physiological response that may be caused by inherited serotonin receptor sensitivities. This proposal is based on animal studies and is not universally accepted. However it gives us a reason for the failure of psychosexual treatment strategies as the capacity of the higher centers to control ejaculation is not without limits, e.g. when sexual stimulation becomes so intense the ejaculation can no longer be inhibited [9]. From an evolutionary perspective, some authors suggest that PE might provide a survival advantage in regards to natural selection as rapid copulation allows for passage of genes to one's progeny. Other possible organic factors that can be treated include alterations in sex hormone levels and diseases of the genital organs (primarily prostatitis) [10].

Combination therapy is currently the suggested solution for patients with severe PE. These patients need more than pharmacotherapy to overcome obstacles to effective sexual activity and require targeted psychoeducational interventions termed "coaching" [11]. Recently, Althof [10] and Perelman [11] independently described combination therapy as a "concurrent or stepwise integration of psychological and medical interventions". Clinicians and non-MD healthcare professionals (i.e. sex therapists) act as a multidisciplinary team to treat patients suffering with recalcitrant PE [11].

3 Medical treatment of PE

Although sex therapy is effective, it is labor-intensive and requires involvement of a cooperative partner. For this reason pharmacological options have become popular for treating PE. However, it should be noted that all of the medications currently used for treatment of PE were originally developed to treat other medical disorders such as depression or erectile dysfunction (ED). Their use is considered "off-label" as they have not been approved by the regulatory bodies in America or Europe for the treatment of PE.

Current accepted pharmacological treatment options include topical desensitizing agents, antidepressives, phosphodiesterase type 5 (PDE-5) inhibitors and alpha-blockers. Combined uses of these medications are not included in this review as they usually exhibit non-synergistic effects and generally have a higher incidence of adverse events.

3.1 Topical desensitizing drugs

The oldest form of therapy for PE is the use of local anesthetic agents as described by Schapiro [12] in 1943. The rationale for use has traditionally been based on penile hypersensitivity in patients with PE [13]. However, a recent study failed to show any significant correlation between IELT and penile sensitivity [14]. Topical desensitizing drugs likely act by diminishing pleasurable sensations for men in order to prolong time of sexual intercourse, a questionable trade-off. In comparison with systemic treatments, topical agents exhibit a low systemic side effect profile. They are recognized to cause penile hypoaesthesia, ED, female genital anaesthesia, and skin reactions. Disruption of spontaneity is another drawback for some couples. Topical drugs for PE include lidocaine-prilocaine cream, SS cream, lidocaine-prilocaine spray and dyclonine-alprostadil cream.

3.1.1 Lidocaine-prilocaine cream

Although lidocaine and prilocaine are both crystalline solids at room temperature, when mixed together in equal amounts they form a liquid eutectic mixture with a 16ºC melting point and thus can be formulated into preparations without the use of a non-aqueous solvent. This allows for higher concentrations of active ingredients within the preparation, in this case 2.5% each for EMLA® (AstraZeneca, London, UK). Although this product is widely available and frequently used to treat PE, the literature on its effects is scant. Two relevant publications include a 2002 study designed in a single blind, placebo-controlled, randomized fashion to determine the optimum time that anesthetic cream should be on the penis before vaginal intercourse, in this case 20 min [15]. Prolonged administration resulted in penile numbness and eventual loss of erection in all patients after 45 min. A second randomized, double-blind, placebo-controlled study aimed to determine the efficacy of EMLA cream in treating PE [16]. Although 42 patients were initially recruited, only 29 completed the study; however, none of the drop-outs were due to adverse effects. The treatment resulted in a 5.6-fold increase in IELT. Of the patients completing the study in the treatment arm, 11 of 16 reported very good or excellent sexual satisfaction. Results showed 16% of patients experiencing adverse effects with two patients having penile numbness and associated retarded ejaculation, two men reporting penile irritation and one female complaining of decreased vaginal sensitivity.

3.1.2 SS cream

SS cream® (Cheil Jedan Corporation, Seoul, Korea) is applied to the glans penis 1 h before intercourse and is washed off before sexual intercourse. The major disadvantage of the product is the unpleasant color and smell. This cream is comprised of nine different compounds, some with local anesthetic and vasodilatatory properties. SS cream is available for use only in Korea, and to date all eight studies conducted on its efficacy were published by the same group and took place there. These studies demonstrated success rates of 89.2% with an 8-fold increase in IELT. However, at the optimum dose of 0.2 g cream, almost 19% of episodes were associated with localized irritation [17]. Because of the unpleasant smell and color, a reformulation was designed by the producers that contains only two of the main components present in the original cream. Unfortunately, only animal data is available for this new formulation which claims higher efficacy than the original formulation [18].

3.1.3 Lidocaine-prilocaine spray

The topical eutectic mixture for PE (TEMPE®, Plethora Solutions Holdings PLC, London, UK) is a metered-dose spray of lidocaine and prilocaine under development. It delivers 7.5 mg lidocaine and 2.5 mg prilocaine per dose. 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. The product is incapable of penetrating keratinized skin, hence only anesthetizing the glans and reducing the incidence of penile numbness related anejaculation. There are only two studies on this product and among them only the phase-II study has a prospective, double-blind, placebo-controlled design. Besides focusing on objective outcome measures, this study uses questionnaires to evaluate control over ejaculation and quality of sex life. A treatment regime of three self-administered applications onto the glans penis 15 min before sexual intercourse was chosen for this study. Results indicate a 2.4 times higher IELT for TEMPE compared to placebo and a significant improvement in control over ejaculation. TEMPE was generally well tolerated with 12% of pa-

tients experiencing numbness of the penis and one man experiencing erectile dysfunction. Although TEMPE provides a significant improvement in IELT with a rise from 1.0 min at the baseline to 4.9 min, its effectiveness is somewhat lower than EMLA cream, but with a better adverse effect profile [19].

3.1.4 Dyclonine/Alprostadil

A preparation which combines the local anesthetic, dyclonine, with the vasodilator, alprostadil, is under development. This product is applied 5–20 min before intercourse to the tip of the penis in the region of meatus. The one pilot study claims the combined preparation produces a synergistic effect but fails to provide baseline IELT and details about adverse effects observed. Further studies are needed before any conclusions about this product can be made.

3.2 Oral medication

Oral treatments for PE consist mainly of selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressant, clomipramine. The PDE-5 inhibitors and tramadol are also included as these medications are subject to scientific research.

3.2.1 Clomipramine

Clomipramine (Anafranil®, Mallinckrodt Pharmaceutical Products, Hazelwood, MS, USA) is a tricyclic antidepressant with the greatest effect on the serotonergic system. In the midst of the era when behavioral psychotherapy was the main treatment option for PE, Eaton [20] published his novel report on the efficacy of clomipramine in 1973 and numerous subsequent publications have confirmed its effectiveness. The meta-analysis by Waldinger [21] showed that, if used on a daily basis, clomipramine increases IELT 4.6 fold which is not statistically different from sertraline or fluoxetine.

On-demand use of clomipramine is effective if used 3–6 h prior to intercourse. The only head to head study evaluating on-demand use of paroxetine 20 mg and clomipramine 25 mg revealed a 4.05- and 1.41-fold increase in IELT for clomipramine and paroxetine, respectively [22]. The most common adverse side effect is nausea which is experienced on the day of sexual intercourse and the day after. Patients with initial ejaculatory latencies over 60 s, self-reported sexual satisfaction of 5 or higher (on a seven-point scale) and ejaculation frequency of twice or more weekly were more likely to benefit from on-demand 25 mg clomipramine therapy [23].

3.2.2 SSRIs

Although none of the SSRIs are approved by regulatory bodies for the treatment of PE, their common "adverse effect" of delaying ejaculation in 30%–50% of otherwise healthy depressed patients has made them the preferred "off-label" treatment option for PE [24]. The effect of this class is not restricted to PE patients as use by otherwise healthy subjects can also significantly delay ejaculation [25]. Currently four different SSRIs are used commonly in the treatment of PE, namely fluoxetine (Prozac®, Eli Lilly and Company, Indianapolis, IN, USA), sertraline (Zoloft®, Pfizer, New York, NY, USA), paroxetine (Paxil®, GlaxoSmithKline PLC, Philadelphia, PA, USA) and citalopram (Celexa®, Forest Laboratories, New York, NY, USA). Among the SSRIs, fluvoxamine [26] and venlafaxine [27] have been shown to be ineffective. Developers of dapoxetine (Johnson & Johnson, New Brunswick, NJ, USA), another molecule of this class with a unique pharmacokinetic profile, are seeking to obtain formal approval for the treatment of PE.

The first publication about the delaying effect of paroxetine was in 1994 and numerous studies have since confirmed the effectiveness of each of the aforementioned SSRIs in treating PE. However, none of these agents have gained regulatory approval for this indication, most likely because of concerns about the negative impact of emphasizing a side effect in the marketing for its major indication, depression. This class of drugs is generally well tolerated by PE patients, who exhibit a slightly different side effect profile than depressed patients using the same medications. SSRIs have different short term and long term adverse effects. The most commonly observed short term adverse effects are yawning, mild nausea, excessive perspiration, fatigue and loose stools. These adverse effects are generally mild and gradually disappear within 2–3 weeks of use in most patients. Less well known adverse effects that have been reported in depressive patients include bleeding [28], priapism [29], weight gain related type II diabetes mellitus [30] and bone mineral density loss with prolonged treatment [31], and these certainly need to be taken into account when treating PE patients. Decreased sexual desire and erectile dysfunction are frequently reported in patients being treated for depression [32], while these are not as common in PE patients without depression. The reason for this difference is not entirely clear [33]. Patients must be advised not to abruptly discontinue long term SSRI use in order to prevent possible SSRI discontinuation syndrome [34]. The use of SSRIs, especially in young depressed patients, is reported to increase the suicide rate [35]. While this issue is currently controversial, great caution should be taken when treating this subgroup of PE patients, and psychiatric consultation is recommended [36].

Although the efficacy of this class of drugs is well established, there are a number of unanswered questions such as "Is daily or on-demand treatment better?",

"Which is the most effective medication?", or "What is the preferred dosing regimen?".

A meta-analysis regarding the use of SSRIs between 1943 and 2003 was published in 2004. An obvious drawback of this meta-analysis is its reliance on IELT and absence of patient reported outcomes (PROs) in its evaluation of efficacy [37]. On a daily treatment basis paroxetine revealed the highest efficacy with a geometric mean fold increase of 8.8, followed by sertraline (4.1) and fluoxetine (3.9). This increase was significant compared to the 1.4-fold increase achieved with placebo [38]. A new molecule, citalopram, and its S-enantiomer, escitalopram (Lexapro®, Forest Laboratories, New York, NY, USA), have recently been subject to studies in the treatment of PE and have provided inconsistent results [39, 40]. Of the currently available SSRIs, escitalopram has the highest selectivity for the human serotonin transporter relative to noradrenalin and dopamine transporters. In a recent randomized, placebo-controlled, double-blind study, treatment with escitalopram demonstrated a 4.9 fold increase in geometric mean IELT [41]. Both of these molecules increased sexual intercourse satisfaction and sexual intercourse frequency. On a daily treatment scheme, the onset of effect usually takes 2–3 weeks. The onset of efficacy is gradual and some patients experience a change in as early as 5–7 days. Generally this class is effective but some patients will not respond to the treatment and even when they do respond some men lose efficacy over time [42]. Neither this phenomenon, called tachyphylaxis, nor the lack of efficacy has a satisfying scientific explanation to date.

There are only a limited number of publications focusing on on-demand use of SSRIs for PE and the data available is difficult to compare as it is heterogeneous in terms of medications used, study design and outcome reporting. This makes it difficult to draw any absolute conclusions about the efficacy of a particular medication. However it can be stated that the overall efficacy achieved by daily treatment is generally higher than by on-demand treatment. Paroxetine appears to be the most effective medication again; however, well designed head to head trials are needed for confirmation.

Dapoxetine, a new SSRI with a unique pharmacokinetic profile, is promising for on-demand treatment of PE. 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 [43].

Two phase III, randomized, placebo controlled studies that enrolled 2 614 PE patients showed that dapoxetine increased IELT, perception of control over ejaculation and satisfaction with sexual intercourse of both the man and his partner. The IELT increase was 2.8 and 3.3 fold for the 30 mg and 60 mg group, respectively, whereas it was 1.8 fold for placebo. While the efficacy was lower than with daily SSRIs this agent is convenient and fast acting for on-demand use [44]. Approval by the FDA has not been granted in its initial application.

A related study examined patient preferences for PE treatment. In this study, PE patients were offered an anesthetic ointment, on-demand use of an SSRI or daily continuous treatment with an SSRI. Eighty-one percent of patients preferred daily treatment whereas 16% and 3% preferred on-demand SSRIs and anesthetic ointment, respectively. Those patients who initially preferred daily treatment did not change their view after receiving standard information about efficacy and side effects, while nine of 17 men who initially preferred on-demand treatment switched their preferences to daily treatment. The conclusion that all patients prefer daily treatment over on-demand needs to be interpreted with caution [45] based on this single study as patients were offered only conventional SSRIs which need to be taken 4–6 h before intercourse which interferes with the spontaneity of sex. Preference profiles will likely be different with a PE medication with a fast onset of action.

3.2.3 Tramadol

Tramadol (Ultram®, Johnson & Johnson, New Brunswick, NJ, USA) is an effective analgesic that has been on the market for a number of years. Tramadol is a centrally acting analgesic with two distinct mechanisms of action: one enantiomer exerts a predominantly weak μ-opioid effect, whereas the other inhibits norepinephrine and serotonin reuptake, activating descending monoaminergic inhibitory pathways. Peak plasma concentrations are attained within 1.6–1.9 h after oral administration. Initial distribution half life is 6 min followed by a second phase of 1.7 h. It is mainly excreted by the kidneys with a mean elimination half-life of 5–6 hours. Currently, only two publications are available on the use of tramadol in the treatment of PE. The double-blind, placebo-controlled, fixed-dose, randomized study by Safarinejad *et al*. [46] demonstrated a 13-fold increase in IELT for the on-demand use of 50 mg tramadol. 28.1% of the participants in the tramadol arm reported adverse effects including nausea, vomiting and dizziness while 15.6% of the patients in the placebo arm reported similar adverse effects [46]. Another study by Salem *et al*. [47] was a single blind, placebo-controlled, cross-over, two-period prospective study to evaluate the efficacy of on-demand 25 mg tramadol. The treatment group experienced a 6.3 fold increase in IELT compared to a 1.7 fold increase in the placebo group. 13.3% of the patients reported adverse effects with tramadol including dyspepsia and mild somnolence [47]. Although initial studies are encouraging, further studies are needed.

3.2.4 PDE-5 inhibitors

At least 30% of PE men have concomitant ED [48]. Successful 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.

A study comparing the effectiveness of sildenafil with the squeeze technique and on-demand use of two different SSRIs (paroxetine and sertraline) and clomipramine in primary PE patients was preformed in a double-blind, prospective, cross-over design. A placebo arm was not included in the study. All medications were used 3–5 hours prior to sexual intercourse. The study demonstrated a 15-fold increase in IELT for the sildenafil group whereas SSRIs, clomipramine and the squeeze technique caused a 2–4-fold increase. Sexual satisfaction increased dramatically with sildenafil treatment. Adverse effects were more common in the clomipramine group (25%) whereas 17.9% of the patients with sildenafil treatment reported adverse effects, mainly headaches and flushing [49].

Another study compared the effectiveness of a PDE-5 inhibitor (sildenafil) with a daily SSRI (paroxetine) and the squeeze technique in primary PE patients without concomitant ED. This head to head, non-placebo controlled study also evaluated intercourse satisfaction using a questionnaire. At 6 months follow-up there was a 5.7-, 4.4- and 2.5-fold increase in IELT for sildenafil, paroxetine and the squeeze technique, respectively. Improvements in sexual satisfaction for both patient and partner were highest in the sildenafil group. Adverse effects were more frequent in the sildenafil and paroxetine groups compared to the squeeze technique group. The most frequent adverse effects were headache (11.7%) and nasal congestion (8.3%) for sildenafil [50].

The only placebo-controlled, randomized, double-blind, prospective multicenter study evaluating the effectiveness of sildenafil in the treatment of PE in potent men failed to demonstrate a significant increase in IELT. The 2.6-fold increase in IELT was not statistically different from placebo. However using the Index of Premature Ejaculation questionnaire, there was a significant increase in ejaculatory control, ejaculatory confidence and improved overall sexual satisfaction scores [51]. A related study comparing placebo, sildenafil, EMLA cream and a combination of EMLA cream and sildenafil treatment arms failed to demonstrate a significant difference between placebo and the sildenafil treated groups [52].

In summary, these studies failed to demonstrate any significant benefit in PE patients who did not have ED. PDE-5 inhibitors are not of benefit in the first line therapy of primary PE patients, however they may be in men with ED and secondary PE [53, 54].

In this context, intracavernosal injections have been proposed as a treatment for PE. The benefit is achieved by providing rigidity after ejaculation. Limited study has been done on this topic [55].

3.2.5 α1-adrenoceptor antagonist

As ejaculation is controlled by the sympathetic nervous system peripherally, it has been hypothesized that α-blockers, which are commonly employed to improve obstructive urinary symptoms, might also be effective in treating PE. This hypothesis has been supported by animal studies demonstrating a decreased vasal and seminal vesicle pressure in response to hypogastric nerve stimulation [56]. One clinical study demonstrated significant improvement in 50% of PE patients resistant to psychotherapy [57]. Although the number of patients in this study was too small to draw any conclusions about the efficacy of α-blockers, its use in the PE patient with concomitant lower urinary track symptoms may be of benefit [58].

4 Experimental treatment options

Besides behavioral and pharmacological treatment options, researchers are searching other avenues on the treatment of PE. 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 [59]. Another 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 [60]. A surgical approach consisting of a dorsal neurectomy with glandular augmentation using hyaluronic acid gel has been reported [61]. While these preliminary reports are interesting, they are not considered standard treatment options.

5 Emerging treatment options for PE

The ideal drug for PE should be an on-demand-dosed treatment with a high rate of efficacy and a short onset of action, should not interfere with sexual spontaneity, and should not have sexual side effects [62]. Two areas of interest are being investigated.

The first is a purely pharmacological approach. The concept is to mimic the desensitization of the 5-HT$_{1A}$ receptor agonist during chronic administration of SSRIs. For this purpose, two 5-HT$_{1A}$ receptor blockers, namely WAY-100635 [63] and Robalzotan [64], were used in animal models of ejaculation and both drugs delayed ejaculation acutely when administered together with an SSRI. However, when used alone they had no effect on ejaculation. This confirms the hypothesis that the 5-HT$_{1A}$ receptors are activated in response to elevated extracellular serotonin levels after acute SSRI administration. Although this pharmacological combination is very promising, further clinical research is needed to evaluate

potential adverse effects of this combination.

A second approach is to increase the success of treatment by using combined behavioral and physiological therapies. PE is a multidimensional condition and most likely reflects a predetermined physiological response in conjunction with intrapsychic and interpersonal issues. Perelman suggests that physicians and sex therapists working together could significantly improve initial and long term treatment response rates for PE by combining the two treatment modalities. There is growing evidence that combination therapy using new pharmaceuticals and psychotherapy will become the treatment of choice [10].

6 Conclusion

PE is a self reported disorder and one in which the diagnosis is mainly based on history. Currently none of the guidelines recommend any formal diagnostic testing. A history should include all three aspects of PE, namely short IELT, lack of control and distress for both partners. Although our methods of diagnosis are in evolution, currently available questionnaires that document PROs and determination of IELT are sufficient to make a correct diagnosis. Therapy should be tailored for each patient as one treatment does not fit all. Each treatment option should be discussed with the PE patient including the success rate and possible adverse effects such that the patient participates in the decision making. This will improve compliance and success of therapy. In recalcitrant PE, collaboration between physicians and sex therapists will improve success rates.

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