REVIEWS

Therapeutic Approaches in Premature Ejaculation

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Abstract

Premature ejaculation is an important sexual dysfunction, with a prevalence rate estimated at approximately 20 to 30%. Despite the fact that many men may complain of premature ejaculation, only a small percentage of them will actually seek medical advice, the majority presenting symptoms similar to premature ejaculation, but with normal intravaginal ejaculatory latency time. Due to continuously research regarding this challenging sexual problem, interesting and effective therapeutical options have emerged over the last 30 years. Many treatment options are now available for patients complaining of premature ejaculation: psychotherapy, behavioral therapy, selective serotonin reuptake inhibitors, phosphodiesterase 5 inhibitors, topical anesthetics, tramadol and surgery. Psychotherapy should be considered the first line treatment for patients with natural variable premature ejaculation and premature like ejaculatory dysfunction, whereas pharmacotherapy should be recommended for patients with lifelong and acquired premature ejaculation. The efficacy and safety of selective serotonin reuptake inhibitors have been evaluated in numerous studies, making them the first line option in the management of patients with premature ejaculation. Alternatives such as topical anesthetics, tramadol, phosphodiesterase 5 inhibitors and alpha 1 adrenergic antagonist therapy should be considered for the patients with poor results after selective serotonin reuptake inhibitors treatment.

Keywords: premature, ejaculation, sexual, dysfunction, therapy

Rezumat

Ejacularea precoce este una dintre cele mai frecvente disfuncții sexuale masculine, cu o prevalență estimată între 20 și 30%. În ciuda faptului că mulți bărbați se pot plânge de ejaculare prematură, doar un mic procent se prezintă la medic în vederea recomandării unui tratament. Majoritatea pacienților cu astfel de acuze, prezintă de fapt simptome similare ejaculării precoce, dar cu timp de latență intravaginală normal. Datorită progreselor care au fost făcute în înțelegerea fiziopatologiei ejaculării premature, opțiunile terapeutice au evoluat în mod continuu pe parcursul ultimilor 30 de ani. În momentul de față există multiple opțiuni terapeutice pentru pacienții care prezintă ejaculare precoce: psihoterapie, terapie comportamentală, inhibitori selectivi ai recaptării serotoninei, inhibitori ai fosfodiesterazei 5, topice anestezice, tramadol, precum și intervenții chirurgicale. Eficacitatea și siguranța inhibitorilor selectivi ai recaptării serotoninei au fost confirmate de numeroase studii, aceştia devenind astfel prima linie de tratament pentru pacientii cu ejaculare precoce. Alternative precum topice anestezice, tramadol, inhibitori ai fosfodiesterazei 5 și antagoniști alfa 1-adrenergici, trebuie luate în considerare pentru pacienții care au prezentat rezultate slabe în urma tratamentului cu inhibitori selectivi ai recaptării serotoninei. Psihoterapia şi terapia comportamentală au rolul de ajuta pacienții în ceea ce priveşte modul de a învăța să controleze şi să întârzie ejacularea, de a gestioneza problemele de ordin personal care întreţin această disfuncție, precum şi de a îmbunătăți comunicarea în relația cu partenerul de cuplu.

Cuvinte cheie: ejaculare, precoce, sexuală, disfuncție, terapie

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INTRODUCTION

Premature ejaculation (PE) is a serious health problem with an important impact on male self-confidence, interpersonal relationships and quality of life[1,2].

Although the first description of this debilitating pathology in medical literature dates to 1887, the debate for a correct and complete definition is still open. Over the last decades several definitions for PE have been proposed, but all of them have limitations. According to 2016 *European Association of Urology* (EAU) guidelines the definition of PE should include several critical points, essential in defining PE, points which have been proposed in articles and clinical trials regarding PE: time to ejaculation evaluated by intravaginal ejaculatory latency time (IELT), perceived control, distress and interpersonal difficulty related to ejaculatory dysfunction[3]. We consider that the notion of IELT has its limitations, because it does not include other forms of sexual stimulation. Therefore a more correct criterion in defining PE should be the period of time elapsed from the beginning of the sexual stimulation until ejaculation. Other important aspects in defining PE should be the inability to delay ejaculation and the psychological negative effects of this pathology.

At the beginning of the 1970s Master and Johnson have defined PE as the inability to delay ejaculation long enough that the partner could reach orgasm on 50% of the intercourse events[4,5]. In 2014 the International *Society of Sexual Medicine* (ISSM) defined PE as the inability to delay ejaculation on all or nearly all vaginal penetrations, ejaculation occurring in approximately one minute for the lifelong PE and in three minutes for acquired PE, with important negative personal consequences[4].

The first classification of PE was proposed by Shapiro in 1943 as type A (sexually hypotonic associated with erectile dysfunction) and type B (sexually hypertonic with early ejaculation since intercourse onset)[6]. After analyzing his patients, Schapiro noticed that those with type B PE presented relatives who suffered from PE and he concluded that heredity could be implicated in the etiology of type B PE. He also noticed that in contrast to type A patients, type B patients presented a strong libido, he remarked that erection could occur even with mild sexual stimulation and that type B patients associated an abnormal high sexual tension. Type A patients did not have relatives who suffered from PE and they have previously presented a normal sexual function[6,7].

Later, in 1989 Godpodinoff described PE as lifelong and acquired, the difference between these two types of PE being the onset time of the symptoms[8,9]. Lifelong PE implies early ejaculation in almost every sexual intercourse within approximately one minute from the initiation of sexual stimulation, regardless of the partner, since the onset of sexual activity. Acquired PE appears in patients who have previously presented a normal sexual function and who were able to control and delay ejaculation[1,9]. Acquired PE can be secondary to a psychological factor or due to an urological pathology. In such cases PE management implies treating the causing factor[1].

Anxiety, low frequency of sexual activity, the stress of a new partner may lead to psychogenic PE, therefore the proper treatment should be psychotherapy or behavioral therapy[10]. Organic causes such as drug abuse, alcohol consumption, chronic prostatitis, hyperthyroidism are known for having a major role in the appearance of PE. PE is a complex sexual dysfunction which hasn't been yet completely understood, it is stipulated that hyperarousability, penile hypersensitivity, hyperexcitable ejaculatory reflex, 5-hydroxy tryptamine (5-HT) receptor dysfunction may be implicated in PE appearance[11,12].

The discomfort caused by early ejaculation varies in the population of men who suffer from PE. In 2006 two other PE subtypes were reported: the natural variable PE subtype and premature-like ejaculatory dysfunction[13-15].

Natural variable PE can be regarded as a form of normal sexual performance (ejaculatory latency time may be short or normal, with inconsistent and irregular early ejaculations and with or without a diminished control of ejaculation ability)[4].

Premature-like ejaculatory dysfunction implies the complaint of PE, characterized by a false appreciation of early ejaculation or lack of control of ejaculation, usually with a normal IELT, or even with a long IELT, but the patients have the perception that they suffer from PE[7,11,13-15]. These PE subtypes help to better stratify the patients with PE and to establish a proper treatment.

Several studies have stated that lifelong PE is related to neurobiological and genetic causes, whereas as acquired PE is due to medical factors[16-18]. Psychotherapy should be considered the first line treatment for patients with natural variable PE and premature-like ejaculatory dysfunction, whereas in the cases of the patients with lifelong and acquired PE pharmacotherapy should be the basis of the treatment[1,19].

Recent studies have revealed that the majority of the patients with PE that are looking for medical treatment suffer from lifelong or acquired PE[20,21].

Regarding the severity of PE complains Erfolgu concluded in his studies that acquired PE is on top, followed by lifelong PE, natural variable PE and premature-like ejaculatory dysfunction[22].

NEGATIVE PERSONAL CONSEQUENCES

PE negative impact on the patients' quality of life has been evaluated in several studies. Patrick concluded in a study regarding PE that 64% of the patients in the PE group reported personal distress versus 4% of the patients in the non PE group[23].

In the study „The premature Ejaculation Prevalence and Attitudes (PEPA survey): prevalence, comorbidities and professional help seeking" Porst reported that 20.4% of the patients in the PE group suffered from depression versus 12.4% of the non-PE patients group. 28% of the PE patients group reported excessive stress versus 19% of the non PE group. Anxiety was reported in 24% of PE group cases whereas in the non-PE group anxiety was reported in only 13% of the cases[24].

In a 2005 study regarding the cognitive and partner related factors implicated in rapid ejaculation, Hartmann reported that 58% of the PE patients group stated that the reaction of the partner and their behavior to PE was positive and that only 23% of the patients reported a negative impact secondary to PE[25].

PREVALENCE

The real value of premature ejaculation remains unclear despite the existence of numerous studies regarding it. Several articles have reported PE as the most frequent male sexual dysfunction, with a prevalence rate ranging between 20% and 30%. This problem is most likely secondary to the existing PE vague definitions and to non-standardized data acquisition which leads to discrepancy in the PE prevalence values obtained[11,24,26-28].

In a 2008 study conducted on 1181 Danish men, Anderson reported that the prevalence of PE was 24%, while erectile dysfunction was encountered in only 4.6% of cases[29].

Another study regarding the prevalence of sexual dysfunctions, conducted on 2456 patients, established that the rate of PE was 28.3%, erectile dysfunction 14.1% and anejaculation 6.8%[30].

Due to the research that has been done over the last decade, PE is now classified as longlife PE, acquired PE, natural variable PE and premature-like ejaculatory dysfunction[7].

In a study evaluating the prevalence of PE in Turkish male population Serefolgu concluded that 20% of the men questioned complained of premature ejaculation. Out of these patients 2.3% presented lifelong PE, 3.9% acquired PE, 8.5% natural variable PE and 5.1% premature-like ejaculatory dysfunction[22].

Similar results were found by Gao in his study conducted on the Chinese male population. He reported an overall PE prevalence of 25.80%, out of which 3% of the Chinese patients presented lifelong PE, 4.8% acquired PE, 11% natural variable PE and 7% premature-like ejaculatory dysfunction[31].

Both studies have demonstrated that the percentage of the patients who have presented for medical advice was higher in the acquired PE than in the lifelong PE group.

It is difficult to establish the real value of PE prevalence if we consider the fact that most of the existing PE prevalence data has been obtained by patients self reports and that only a small percentage has been obtained according to international guidelines recommendations[8].

PATHOPHYSIOLOGY OF PE

Ejaculation is controlled by sympathetic, parasympathetic and somatic pathways. Serotonin and dopamine have an important role in the ejaculatory reflex. Ejaculation presents two phases. The first phase, emission, is controlled by the sympathetic nervous system and it implies the contraction of the seminal vesicles and prostate with the deposition of sperm and seminal fluid into the posterior urethra. The second phase, expulsion, is controlled by somatic nerves and consists of sperm ejection out of the urethra[1,32]. The smooth muscle fibers of the bladder neck contract preventing retrograde ejaculation. At the same time the urethral external sphincter relaxes and the pelvic floor muscles, the ischiocavernosus and bulbocavernosus muscles contract allowing sperm ejection[33].

Neuromodulators such as serotonin, oxytocin, dopamine, norepinephrine, gamma-aminobutyric acid and nitric oxide are implicated in the normal pathway of the ejaculatory reflex[16,34].

Since 1976 it was demonstrated that serotonin has an inhibitory effect on the ejaculatory reflex, while dopamine has proven to stimulate ejaculation via D2 receptors[16]. Over the years, research work has established that serotonergic neurons are well represented in the brain and in the spinal cord, and several serotonin receptors have been identified and described: 5-HT1a, 5-HT1b, 5-HT2a, 5-HT2b, 5-HT2C[35].

It has been demonstrated that agonist stimulation of the 5-HT2C receptors determines an increase in the ejaculatory latency, whereas the stimulation of the post-synaptic 5-HT1a receptors leads to the shortening of the ejaculatory latency[36]. The results of several studies have led to the theory that patients suffering from PE may present a hypersensitivity of the 5-HT1a receptors and/or a hyposensitivity of the 5-HT2C receptors[2,37].

Several studies have stated that life-long PE is associated with 5-HT1a receptors hyperfunction and 5-HT2C hypofunction[17].

TREATMENT

Due to the last decades research work regarding PE, several potential effective treatment options have emerged. Many treatment options are now available for treating patients with PE: psychosocial education, behavioral therapy, selective-serotonin reuptake inhibitors (SSRI), phosphodiesterase (PDE)-5 inhibitors, topical anesthetics, selective dorsal neurectomy (SDN), glans penis augmentation (GPA) with hyaluronic acid (HA) gel[32,38,39].

Pharmacotherapy has proven its effectiveness in the treatment of lifelong PE patients and has become the mainstay treatment for such patients. The efficacy of psychotherapy in the treatment of lifelong PE is limited, but it has been demonstrated that if it is associated to pharmacotherapy it significantly improves its efficacy. Patients suffering of acquired PE should undergo psychosexual counseling or should receive pharmacotherapy.

Variable PE or PE-like ejaculatory dysfunction should be managed with psychosexual counseling and patient or couple psychotherapy[16,40].

PSYCHOTHERAPY AND BEHAVIORAL THERAPY

Decades ago premature ejaculation was considered to be a psychological problem and not a physiological one and psychotherapy was the mainstay treatment. The goals of psychotherapy and behavioral therapies are to help patients to learn how to control and delay ejaculation, to resolve personal issues that maintain this dysfunction, to manage the distress that results from this problem and to increase couple communication[41].

Behavioral techniques have been reported since the 1950s. In a 1956 article regarding premature ejaculation, Semans reported the "stop-start" technique, but it has proven to be without success in long-term follow-up for patients with severe PE[42].

The start stop technique implies penile stimulation until the patient feels the urge to ejaculate, followed by cease of stimulation until the ejaculatory sensation passes. Later, in 1970 the "squeeze technique" was first mentioned. This implies that the patients partner should squeeze the penile frenulum when ejaculatory sensation appears for 30 seconds and then the stimulation should be restarted. This maneuver is repeated several times before ejaculation occurs[5,43]. Other techniques such as masturbation prior to sexual intercourse and pelvic floor exercises have been reported to decrease hyperarousability and to improve the ejaculatory control[11].

According to the PE international guidelines psychotherapy should be recommended for the natural variable PE and for the premature-like ejaculatory dysfunction, while lifelong PE and acquired PE should benefit from pharmacotherapy alone or combined with psychotherapy[41,44].

Carmio revealed the superiority of the combined treatment (30 mg dapoxetine and psychotherapy) over pharmacotherapy alone. After 6 months of treatment he concluded that the 30 mg dapoxetine lot presented a two-fold IELT increase, while the lot of patients who have undergone psychotherapy and pharmacotherapy presented a four-fold IELT increase[45]. Similar results regarding the superiority of the combined treatment over pharmacotherapy alone or psychotherapy alone were published[46,47].

In a 2008 study, Steggall evaluated the efficacy of pharmacotherapy alone (paroxetine or lidocaine spray) for two months, followed by another two months of behavioral therapy alone. After the first two months he reported that IELT has increased by eight-fold and that during the second phase of the study- behavioral therapy alone, IELT has decreased. He reported a 1.7 – fold IELT increase during the behavioral therapy phase[48].

With all of these considerations, when comparing the effectiveness of psychotherapy and pharmacotherapy it is clear that pharmacotherapy has better results than psychotherapy alone. Nevertheless, several studies have demonstrated the efficacy of combined treatment when compared to pharmacotherapy alone[49-51].

Pharmacotherapy in the management of PE is based on targeting the neurotransmitters and the receptors involved in the ejaculatory reflex[16,34].

The first molecules used in the treatment of PE were phenoxybenzamine and alpha aminobenzoat, but both of them presented side-effects. The positive effects of the antidepressants agents on PE, were discovered by

chance in the 1970s, during the treatment of patients with depression and pain. Tricyclic antidepressants and SSRI have proven to be effective with tolerable side-effects[52-57].

Since their introduction, SSRIs (paroxetine, sertraline, fluoxetine, citalopram) and serotonergic tricyclic antidepressants (TCA-clomipramine) have revolutionized PE treatment[16].

SSRIs act by blocking the serotonin reuptake from the synaptic cleft via blockage of the 5-HT transporter resulting a high synaptic 5-HT concentration and activation of the post-synaptic 5-HT2C that will lead to ejaculatory latency increase[16,52,58].

The efficacy of SSRI treatment is usually evident after 15 to 20 days of treatment[59-61]. Chronic administration of SSRIs could lead to infertility due to their negative impact on spermatogenesis, sperm-cell membrane damage, sperm-cell DNA alterations and sperm transport impairment[62-65]. Several articles have also reported that SSRIs chronic administration is associated with erectile dysfunction, the mechanisms behind this being a decrease in nitric oxide production[52,66].

With all of these considerations, other therapeutic alternatives should be recommended to the patients who desire to preserve their fertility[52].

Paroxetine, when compared to other representatives of the same drug class, has shown better results with fewer side effects (mild nausea, diarrhea, fatigue, yawning)[58,67,68].

Due to its pharmacological characteristics dapoxetine can be administered when needed. Several studies have reported good outcomes regarding the capacity of 30-60 mg dapoxetine in increasing the ejaculatory latency time, when administered with 1-2 hours before intercourse[69-71].

The use of dapoxetine is approved in over 50 countries. In a phase 3 randomized, placebo-controlled, parallel-groups, double-blind study of dapoxetine, conducted on 1067 patients, McMahon concluded that mean IELT increased from 0.9 minutes to 2.7 minutes in the 30 mg Dapoxetine group, to 3.1 minutes in the 60 mg dapoxetine group and to 1.8 minutes in the placebo group[72].

Buvat concluded in clinical trial conducted on 1162 patients, on a period of 24 weeks, concluded that ejaculatory latency increased from 0.7 minutes to 1.8 minutes for the 30 mg dapoxetine lot, to 2.3 minutes for the 60 mg dapoxetine group and to 1.1 minutes in the placebo group[18].

However, due to effects below expectations, side effects, high costs or no efficacy of the treatment, a rate of 90% of discontinuous treatment within a year from the start of dapoxetine has been reported[73-75].

Due to the small risk of suicidal ideation, it is recommended that physicians should be careful when prescribing SSRIs to patients with depression and suicidal attempts, especially to young patients[75-77].

Regarding side-effects it was reported that these were uncommon and that they depended on the administered dapoxetine dose. Side-effects such as nausea, headache, dizziness and diarrhea can appear[17,69].

It has been observed that SSRIs daily administration is preferred by lifelong PE patients rather than on-demand administration[78].

Good results regarding ejaculation delay have been obtained among patients with lifelong and acquired PE and it has also been reported that dapoxetine has no drug-drug interaction, here including the phosphodiesterase 5 inhibitors[52,71,79].

Clomipramine is a tricyclic antidepressant that blocks the uptake of 5-HT and noradrenaline. One of the first articles regarding the effectiveness of clomipramine in PE treatment was published by Eaton in 1973 and his results were later confirmed by other studies[80].

Several double-blind clinical trials have demonstrated that 25 mg on-demand clomipramine taken with 12 to 24 hours before intercourse has increased IELT by 4 fold, and that daily administration could increase ejaculatory latency even more[57,81-83].

Tramadol is an opioid analgesic that acts at the level of the central nervous system. A number of clinical trials have reported encouraging results regarding 25 to 100 mg tramadol usage[84-86].

In a 2008 study, Salem concluded that 25 mg on-demand tramadol has significantly improved ejaculatory latency, reporting a 6.3 fold increase[85].

Safarinejad reported an important increase of ejaculatory latency and of overall satisfaction in a lot of patients who have received 50 mg on-demand tramadol[87]. With all of these considerations, tramadol could be an effective option in selected patients, but side-effects (somnolence, dizziness, nausea, mouth dryness) and risk of addiction make its use limited. Another important aspect, that we should consider when prescribing tramadol, is that the combination with SSRIs could lead to serotonin syndrome, a potential fatal syndrome[73].

Phosphodiesterase 5 inhibitors (PDE5I) have proven to be effective in patients with erectile dysfunction and who also suffer from PE.

In a 2005 study regarding the efficacy of sildenafil citrate in men with PE, McMahon reported an ove-

rall improved patients satisfaction, despite the fact that a significantly statistical ejaculatory latency increase wasn't achieved[88].

Information regarding PDE5Is effectiveness in PE treatment is limited, but a 2012 meta-analysis concluded that PDE5Is have an overall positive effect[89].

Alpha 1-adrenergic therapy is an option for PE management, but due to the small number of studies conducted on this class of substances, their usage is limited.

However, Sato has reported remarkable results in a 2012 study conducted on 8 patients with PE who have received silodosin. An increase of ejaculatory latency of approximately 7 minutes was achieved[90].

Topical anesthetics were the first medical approach used in PE management[52,91]. The principle behind the use of topical anesthetics is that they decrease glans sensitivity, thus inhibiting the spinal ejaculatory reflex.

In a clinical trial, Dinsmore evaluated the outcome of a lidocaine-prilocaine spray applied on the glans 5 minutes before sexual intercourse and concluded that this is an effective option for PE treatment, reporting a ejaculatory latency improvement of approximately 6 fold[92].

Lidocaine-prilocaine products have shown positive results regarding ejaculatory latency increase and high satisfaction rates. Unwanted secondary reactions such as penile and vaginal numbness and allergic reactions have been reported[52,93].

Busato has evaluated the potential of lidocaine-prilocaine cream in patients with PE. The patients applied the cream 10-20 minutes before sexual intercourse and then they would cover it with a condom. The treatment has significantly improved ejaculatory latency, with approximately 5.6-fold[93].

Considering the limited side-effects and the overall efficacy, topical anesthetics should be regarded as a viable alternative for PE patients.

Another possible drawback could be the fact that the process of applying the product can have a negative impact on sexual spontaneity.

In a double-blind, multi-centre study, Choi evaluated the efficacy of Severance Secret cream (SS Cream-which includes 9 different herbal extracts, some of them with anesthetic properties). He reported that SS Cream has increased the mean IELT from 1.4 minutes to 10.9 minutes[58,91].

Side effects such as local irritation, delayed ejaculation, an-ejaculation and erectile dysfunction have been reported in 12% of the cases[94].

Surgical PE treatment is an unconventional therapeutic option. Due to the possible risk of sexual function permanent loss guidelines do not recommend it. Nevertheless, the efficacy of surgical treatment has been evaluated in several Asian clinical trials.

The goal of PE surgical treatment is to increase ejaculatory latency by reducing penile sensitivity. This goal can be achieved through selective dorsal neurectomy (SDN) or by glans penis augmentation (GPA) with hyaluronic acid (HA). SDN can be used for patients resistant to medical treatment. Several Korean studies have presented good results regarding the efficacy of SDN[95-98].

In a study conducted on 143 patients who have undergone partial neurectomy of the dorsal penile nerve, You reported a significant increase of IELT and a satisfaction rate of 81.8%. Complications such as penile edema, glans pain, wound dehiscence and delayed ejaculation occurred in only 11.8% of cases[95,96].

Zhang reported, in another study regarding PE surgical treatment efficacy, that SDN increased IELT from one minute to approximately four minutes. He also reported that the patients who have undergone SDN have shown an increased ejaculatory latency and that overall satisfaction was significantly improved[39].

The principle behind GPA with HA gel is that the injectable gel creates a barrier between tactile stimuli and dorsal nerve receptors. The advantage of this therapeutic option is that it does not determine sexual dysfunction or permanent sensory loss[98,99].

Kim compared the efficacy of SDN alone, GPA alone and SDN combined with GPA. He reported that no complications were encountered in the GPA lot, while in the SDN lot complications such as penile numbness, paresthesia and pain have been reported by patients[98].

Despite the risk of penile sensory loss, surgical PE approaches and especially SDN have developed over the last decades in Asian countries, especially in South Korea[95].

The efficacy of SDN has been demonstrated in several studies, but despite the good outcomes they remain not recommended in urological guidelines, due to the rare risks of erectile dysfunction and penile sensory loss[16].

CONCLUSIONS

Premature ejaculation is an important sexual dysfunctions, often associated with a negative psychological and social impact.

The debate regarding premature ejaculation definition and prevalence is still open, due to the lack of adequate and efficient diagnosis criteria.

Despite the fact that the prevalence of premature ejaculation has been estimated to be approximately 20-30%, a significant percentage of the patients complaining of PE present normal IELT.

When we evaluate PE patients we should have in mind all the existing therapeutic options.

Psychological therapies should be consider the first line treatment for patients with natural variable PE and premature like ejaculatory dysfunction, whereas medical treatment should be the first line option for patients with lifelong and acquired PE [PE4, PE 4-2.43].

Pharmacotherapy may not have great results in patients with severe PE, therefore the combination of pharmacotherapy with psychotherapy should be considered.

Psychosexual therapy has an important role in reducing sexual related anxiety, in improving communication within the couple and it also helps in building up self-confidence.

The effectiveness of behavioral therapies is usually shortly lived, PE often reappearing.

Numerous studies have demonstrated the efficacy of SSRIs in the management of PE. Daily administration of SSRIs has shown better results on-demand usage. Due to its pharmacokinetic and rare side effects, dapoxetine is ideal for on-demand administration.

Special attention should be given when prescribing SSRIs to patients with depression and suicidal attempts, especially younger patients, due to the small risk of suicidal ideation.

Topical anesthetics can be considered a good alternative to the systemic treatment, because they can be applied when needed and they present fewer unwanted secondary reactions.

Tramadol administration has proven to be effective in the PE management, but the risk of addiction limits its usage as first line treatment.

Over the last years, surgical techniques such as selective dorsal neurectomy and glans penis augmentation with hyaluronic acid gel have developed in Asian countries, with good results, but the risk of penile glans sensory loss makes its use to be not recommended by urological guidelines.

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