A review on premature ejaculation

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Abstract

Premature ejaculation (PE) is one of the most important sexual issues in male subjects, which has negative influence on men’s lives and their partners’, as well. There is no common agreement on definition and classification of PE, however, most scientists agreed on three important concepts: Intravaginal ejaculation latency time (IELT), Ejaculation control and negative impact on interpersonal relationship. As there are 4 types of PE – permanent, acquired, Natural and Preterm-like PE- with different pathogenesis and etiologies, practitioners should have different approach to every individual regarding their personality, signs and symptoms, baseline etiologies and the patients’ expectations. A Large number of the patients suffering from permanent PE need medication. In this literature review, we aim to review and cumulate the existing data in this regard; and to provide an informative conclusion on this critical matter.

Keywords: premature ejaculation, Medication, sexual advice, psychotherapy

Introduction

Premature Ejaculation (PE) is one of the most important sexual disorders in male adults (1-4). Studies have demonstrated a wide range of 20-40% prevalence of PE, resulting from differences in societies and difference in PE definition (1, 2, 5-9). However, due to its stigma, the reported percentage could be less than expected. PE is a marriage disorder rather than a sexual or infertility issue; which usually have a non-organic cause. PE is a psychological disorder or a side effect of other medications such as psychological drugs, opium or alcohol (1-2).

Definition: PE had various definitions over time. Some researchers criticize the concept of PE as a sexual disorder, regarding this fact that almost all primates experience ejaculation early at intercourse. The primitive definition of PE was based on an immediate ejaculation in intercourse. Some researchers have indicated a time limit for PE; 1 minute or less from first penile thrust till ejaculation. Others have defined PE as less than 15 penile thrust prior ejaculations (10-13).

“Less than expected time for men” and “sexual contact with less than 50% female desire prevalence” are other descriptions for PE (1). Efforts have been made to characterize PE by organizations such as WHO, APA, EAU, AUA and ISSM, though with no common agreement (14-15).

DSM-IV-TR has defined PE as follow: “resistant ejaculation with the lowest sexual arousal, at, before or after penile thrust, before male partner intention; which can result into marriage breakage and should not be due to organic causes.” This definition is similar to International Society for Sexual Medicine’s (ISSM) and American Urology Association’s (AUA) criteria for PE. All these definitions reveal three criteria for inclusion: 1- limited time between penile thrust and ejaculation, 2- un-controlled ejaculation, and 3- unsatisfactory sexual intercourse for one or both partners. On the other hand, ICD-10 is the only classification, which has an exact cut-off point. In this definition, inability to hinder ejaculation to achieve desirable orgasm; which is experienced as a ejaculation before or a short amount of time (15 second maximum) after first penile thrust. With or without full erection which makes intercourse impossible (15-17).

Regarding the fact that there is no common cut-off point for quantitative researches and there is no WHO-approved accurate evidence for this cut-off point, almost all scientists demonstrated that none of these definitions are sufficient. In 1994, Waldinger et al (18) have introduced the term “Intravaginal ejaculation latency time (IELT)”, which is the time between first penile thrust and ejaculation and a simple chronometer can measure it. Regarding this study, an IELT less than 1 minute is considered as PE. This study provided researchers with a quantiative instrument and has been used in future studies, although it lacks two of the important factors of PE (un-controlled ejaculation and unsatisfactory sexual intercourse) (19). All definitions are presented in table 1.

In 2009, ISSM defined PE as a male sexual disorder with the following criteria (20). This is a clinical, evidenced based and the best definition so far:
1. An ejaculation which mostly occurs less or near 1 minute after penile thrust;
2. Inability to control the time of ejaculation, repeatedly;
3. Negative psychological impact of partners such as undisredness, depression; which result in sexual avoidance.
The Foundation considers a man a premature ejaculator if he cannot control his ejaculatory process for a sufficient length of time during intravaginal containment to satisfy his partner in at least 50% of their coital connections.

Ejaculation that occurs before the individual wishes it, because of recurrent and persistent absence of reasonable voluntary control of ejaculation and orgasm during sexual activity.

For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required, before or within 15 s) or the 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.

Persistent or recurrent ejaculation with minimal sexual stimulation, before, on, or shortly after penetration and before the person wishes it. The condition must also cause marked distress or interpersonal difficulty and cannot be due exclusively to the direct effects of a substance.

Persistent or recurrent ejaculation with minimal sexual 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.

Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.

A male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within 1 min 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.

### Classification and etiologies:

PE was first described and classified by Schapiro in 1943 (21). He demonstrated two “A” and “B” types - not used nowadays - which Godpondinoff et al (22) renamed these into “Acquired” and “Permanent” PE. Permanent PE is a primary disorder, while Acquired PE is a disorder in patients, which had controlled ejaculation before. The etiology of the PE is often unknown. Organic and non-organic causes are discussed in the literature. The difference originates from different approaches to this disorder, which leads us to two different treatments, medication and psychotherapy. Scientists supporting the non-organic etiologies say that PE is a side effect of other psychological disorders such as stress, new or numerous partners, fear from pregnancy or deformed neonates, myths, and etc. are factors which induce PE. However, organic causes such as alcohol and opium sang other drugs like antihypertensive medications (ACE Inhibitors and ARBs) can induce PE; as well as other medical conditions Hyperthyroidism, Chronic prostatitis and Withdrawal syndrome are shown to be the cause of PE. (10-11, 22-23) In these cases, PE can be cured by treatment of underlying disorder or ceasing the improper drug. These scientists believe that PE is initiated by glance hypersensitivity, genetic backgrounds, Hyper-arousability, hyper-excitability ejaculatory reflex, and 5-hydroxytryptamine (5-HT) receptor defect (24).

In 2006, Waldinger and Schwiatser introduced a new classification for PE for DSM-IV and ICD-11. Based on their theory, PE is a syndrome with a collection of symptoms and 2 other types were added: "Natural" and "Preterm-like" PE, which does not need any medication. These classifications are changing through time (25-32).

### Diagnosis:

All types of PE diagnosis is based on medical and sexual history and physical examination regarding the duration needed for ejaculation; however there are clinical trials and epidemiologic studies going on for diagnosing PE with Chronometer and filling out sexual questionnaire (33).

### Treatment:

Treating PE can be challenging for patients and physicians; because its etiology has not been recovered yet. There are many suggested treatment, but not many studies have demonstrated their long-term effects. All studies have indicated that finding the type of PE is the most essential step through treatment; permanent PE should be treated with drugs, acquired PE are treated with treating underlying causes, natural PE patients need psychological support and preterm-like PE needs Psychological advisory and reassurance (10, 21). All treatments are presented in table 2.

<table>
<thead>
<tr>
<th>Year</th>
<th>Source</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>Masters and Johnson</td>
<td>The Foundation considers a man a premature ejaculator if he cannot control his ejaculatory process for a sufficient length of time during intravaginal containment to satisfy his partner in at least 50% of their coital connections.</td>
</tr>
<tr>
<td>1980</td>
<td>DSM-III</td>
<td>Ejaculation that occurs before the individual wishes it, because of recurrent and persistent absence of reasonable voluntary control of ejaculation and orgasm during sexual activity.</td>
</tr>
<tr>
<td>1994</td>
<td>International Statistical Classification of Disease, 10th edition (ICD-10)</td>
<td>For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required, before or within 15 s) or the 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.</td>
</tr>
<tr>
<td>2000</td>
<td>DSM-IV-TR</td>
<td>Persistent or recurrent ejaculation with minimal sexual stimulation, before, on, or shortly after penetration and before the person wishes it. The condition must also cause marked distress or interpersonal difficulty and cannot be due exclusively to the direct effects of a substance.</td>
</tr>
<tr>
<td>2001</td>
<td>European Association of Urology. Guidelines on Disorders of Ejaculation</td>
<td>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.</td>
</tr>
<tr>
<td>2004</td>
<td>International Consultation on Urological Diseases</td>
<td>Persistent or recurrent ejaculation with minimal sexual 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.</td>
</tr>
<tr>
<td>2004</td>
<td>American Urological Association Guideline on the Pharmacologic Management of Premature Ejaculation</td>
<td>Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.</td>
</tr>
<tr>
<td>2008</td>
<td>International Society of Sexual Medicine</td>
<td>A male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within 1 min 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.</td>
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</tbody>
</table>
Non-organic treatment:

Non-organic treatment has been introduced from long time ago and shown to be effective in PE patients

1. Behavioral treatment: "Stop and Start" and "squeeze" techniques have been used for decades and studies have shown 45-65% of treatment, however, 75% of the cured patients were experiencing the problems over time. Masturbating before intercourse is another technique which can induce sexual anesthesia and delayed ejaculation (23, 34-35).

2. Psychological treatment: was considered as first line treatment for PE during 1920 to 1960. There are several case (24, 36-37) reports regarding its success; but there was no fully supported evidence. Most patients with successful treatment had defendant mechanisms regarding sexual issues (24, 36-37).

In fact, SSRIs are widely used and it seems that Psychological treatments are history. However; there are studies that indicate psychological treatment is effective more than before; nowadays, can teach how to make better effects from their drugs. Even with the safest drugs, medication alone cannot be a complete treatment for PE and furthermore, can lower the dose of SSRIs (39-41).

3. Surgery: not so evident, there are some un-controlled and non-randomized trials with successful dorsal neurectomy, frenolctomy and penile glance hyaluronic acid injection. These treatments are not recommended (20, 42-44).

4. Medication: female partner should monitor the effect of these medications with chronometer. Valid and reliable questionnaire may be beneficial (32).

There are 2 types of regimens; Daily and On-demand:

a. Daily usage: Both daily Clomipramine (a tricyclic antidepressant) (45-51) and SSRIs (except fluoxetine) (52-59) can delay ejaculation. Nowadays, daily, or daily plus on-demand treatment in a great choice for this disorder. However, some of these drugs do not have FDA approval for PE. The main reason is the reduction in SSRI sales for depression which drug companies do not comply with this issue easily (60-61).

A systematic review and meta-analysis during 1943 and 2002 showed that analgesic drugs, neurolytic drugs and monoamine oxidase inhibitors (MAOI), sympatholytic drugs, antibiotics and other drugs were tested and used. MAOI and sympatholytic drugs had some positive effects; but were not widely distributed regarding its side effects. Only Clomipramine and SSRIs were approved over time. Other studies also demonstrated the same results (33). One of these studies stated that Paroxetine (OR=8.8) was the best drug in the market; following by Clomipramine (OR=4.6) sertraline (OR=4.1) and fluoxetine (OR=3.9).

For daily usage, 20-40 mg Paroxetine, 10-50 mg Clomipramine, 20-40 mg fluoxetine and 20-40 citalopram are recommended. Delayed ejaculation usually starts few days after the medication use; however, the full effects usually take part at least 1 to 3 weeks afterwards. This effect often remains for a long period but there are cases (5-10%) which have demolished after 6-12 months. The reason is still unknown. Patients should be aware of SSRIs side effects: Fatigue, yawning, slight emesis, loose defecation and hyperhysrosis; most of them disappear in the first one or two week. Unlike SSRI's side effects in depressed patients, these drugs will not result in reduced libido and impotence in a non-depressed individual. Bleeding is a rare side effect and doctors should warn the patients while prescribing NSAIDs. Priapism is another rare condition, which needs emergent interventions (62-63). As there are report which indicates increased risk of suicide in young individuals with SSRIs, these medication in contraindicated in patients younger than 18 years; especially in depressed patients (64). Weight gain and Diabetes are also a chronic side effect. These drugs should not be discontinued without medical supervision and to be tapered for 3 to 6 weeks (65).

As a conclusion, it seems than SSRIs are useful in the medical team.

b. On-demand usage: the aim of this type of treatment is to delay the ejaculation 1 to 2 hours before

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**Table 2. standard treatments of Premature ejaculation (PE)**

<table>
<thead>
<tr>
<th>Oral therapy</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Non-selective SSRI</td>
<td></td>
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<tr>
<td>Clomipramine</td>
<td>25-50 mg/daily, 2-24 h before intercourse</td>
</tr>
<tr>
<td>Selective SSRI</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5-20 mg/daily</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10, 20, 40 mg/daily, 3-4 h before intercourse</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25-200 mg/daily, 4-8 h before intercourse</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20-40 mg/daily</td>
</tr>
<tr>
<td>Dapoxetine</td>
<td>30-60 mg, 1-3 h before intercourse</td>
</tr>
<tr>
<td>Topical Therapies</td>
<td></td>
</tr>
<tr>
<td>Lidocaine/Procaín</td>
<td>2.5%, 20-30 min before intercourse</td>
</tr>
</tbody>
</table>

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intercourse; but ineffectiveness in non-programmed sexual contacts is the important limitation of this approach; furthermore, the side effects of the drugs will appear a few hours after consumption, which is synchronized with intercourse. Most of the studies demonstrated that this kind of treatment does not have sufficient evidence; and there are no meta-analyses due to lack of high quality studies with different planning and methodology. In any case, on-demand SSRIs have landslide less effect than daily consumption. The reason of this fact lies on pharmacological parameters of SSRIs, which results from the time needed for 5-HT receptor’s up-regulation. Using 20–40 mg clomipramine can induce a desirable delay in ejaculation 4 hours after consumption; however, hyperemesis can stand for at least a day (33, 66-67).

Tramadol – as an analgesic compound – can activate opioid receptors and inhibit the reuptake of 5-HT, noradrenaline. FDA does not recommend tramadol for PE, due to high side effects and limited outcome.

The other strategy is to use topical anesthetic drugs such as lidocaine or prilocaine lowering glance sexual sensitivity. This approach has limited usage due to ejaculation problems and vaginal anesthesia, which can be lowered by using a condom (68).

Researches in recent years suggest that short acting SSRIs with small half-time is a better way to utilize on demand approach; such as Dapoxetine. This drug has fewer side effects than other SSRIs regarding to the 3rd phase of clinical trials and is the first approved drug for PE in Europe. Mild headache and hyperemesis are described as its side effects which are tolerated easily; however, Fluoxetine did not overcome the studies to gain approval. A study demonstrated that dapoxetine have a 3-3.6 folded IELT with 30-60 mg dosage (69-73).

There are few 5-PDE inhibitor drugs for on-demand medication. However, a meta-analysis on 14 studies regarding these drugs demonstrated that the validity and reliability of these surveys are compromised and we can come to this conclusion that there are no high quality clinical evidences for these drugs such as sildenafil (74).

Conclusion

PE is one of the most important sexual issues in male subjects; which have negative influence on men’s lives and their partner. The true prevalence of PE is much more that demonstrated. Most scientists agreed on three important concepts: Intravaginal ejaculation latency time (IELT); Ejaculation control and negative impact on interpersonal relationship. There are several standardized types of clinical surveys using IELT (with chronometer), Ejaculation control and self-satisfaction questionnaires.

As there are four types of PE – permanent, acquired, Natural and Preterm-like PE- with different pathogenesis and etiologies, practitioners should have different approach to every individual regarding their personality, signs and symptoms, baseline etiologies and the patients’ expectations. A large number of the patients suffering from permanent PE need medication (However, for better effect, they also need sexual advisors). Patients with acquired PE need different treatment regarding its underlying cause; which may include medication. In natural PE patients, however, usually complains on time-to-time or occasional PE; re-assurance and sexual advises are the most beneficial. Psychotherapy should be considered as a first line treatment in patients with Preterm-like PE. For instance, daily Selective Serotonin Re-uptake Inhibitors (SSRI) or on-demand local anesthetic could be effective in all patients; however, the effect/side-effect balance of these treatments should be considered individually. Recently, short-acting on-demand oral SSRI named “Dapoxetine hydrochloride” has been introduced and viewed a new horizon in treating PE. Other medications such as tramadol, Lidocaine/prilocaine sprays and Phospho di-esterase inhibitors are off-label drugs and should be considered wisely.

References


