

## Review Article

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# British Society for Sexual Medicine (BSSM) Position Statement on Premature Ejaculation

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To provide an evidence based consensus on the diagnosis and management of premature ejaculation (PE). The British Society for Sexual Medicine (BSSM) takes issue with the advice to use off label treatments, such as daily selective serotonin reuptake inhibitors treatment, favoring on-demand dapoxetine. There is increasing evidence for the use of PDE5 inhibitors which are superior to a placebo for the treatment of PE. A recent meta-analysis of international PE guidelines supports the need for research to investigate the association of PE with erectile dysfunction (ED), prostatitis and thyroid disease, and supports the early use of PDE5 inhibitors either alone or in combination with dapoxetine or psychosexual interventions. Topical agents and non-pharmacological treatments also have a place, with new agents in the pipeline. The United Kingdom (UK) lacks formal guidance from the National Institute of Clinical Excellence (NICE) on any of the common male sexual dysfunctions, namely ED, PE, ejaculatory disorders, and male hypogonadism. As a result, general practitioners in the UK have relied on local guidance, and international guidelines which are heterogeneous, indicating diagnostic and therapeutic approaches that are often inconsistent. The aim of this position statement is to improve the management of PE in the UK.

**Keywords:** Erectile dysfunction; Guideline; Premature ejaculation; Therapeutics

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## SUMMARY

Currently there are no formal National Institute of Clinical Effectiveness (NICE) Guidelines on any of the common male sexual dysfunctions, namely erectile dysfunction (ED), premature ejaculation (PE) and other ejaculatory conditions, along with male hypogonadism. In recent years, general practitioners (GPs) in the United Kingdom (UK) have relied on Guidance from local Joint Area Prescribing Committees (JAPCs). There are currently several guidelines from various scientific societies on the topic (Diagnostics 2024;14:1819) [1]. These

are heterogeneous, indicating diagnostic and therapeutic approaches that are often inconsistent, as is the guidance from JAPCs. The aim of this position statement is to improve the management of PE in the UK.

## DEFINITIONS OF PREMATURE EJACULATION

- A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of penetration, and the inability to delay ejaculation on all or nearly all

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- penetrations, and
- Negative personal consequences, such as distress, bother, frustration
- and/or the avoidance of sexual intimacy [2]

This definition was revised in 2013 from the previous 2 minute cut off to 1 minute to avoid the risk of including men and couples with little or no distress because of the overlap of patients in the low normal range who were being include in a “disease category” purely on the basis of ejaculatory timing. “Vaginal” was later removed from the definition to include a wider range of sexual preference, even though the bulk of clinical trials leading to current product licenses were conducted in heterosexual couples when the “2 minute or less” definition was in place.

## CLASSIFICATIONS

- Lifelong PE exists with all sexual activity but often less so with masturbation.
- Recent research has suggested a Genetic basis, associated with 5HT (5 hydroxytryptamine/Serotonin) transmission involving.
- Serotonin transporter (Serotonin-transporter-linked promoter region) 5-HTTLPR and dopamine transporter protein (DAT) gene polymorphism leading to hyposensitivity of 5-HT<sub>2c</sub> and/or hypersensitivity of 5HT<sub>1c</sub> receptors [3-6].

The problem is often associated with performance anxiety and secondary ED.

**Lifelong** PE generally has a lower response to medication and is more likely to be a long-term problem.

**Acquired** PE occurs in men with a previously normal sex life in relation to ejaculation and erection. It is commonly associated with:

- Hyper excitability of glans, foreskin and frenulum [7,8]
- Often ED associated (33%) [9,10]
- Hormonal changes, hyperthyroidism, raised Prolactin and Leptin levels [11,12]
- Chronic Prostatitis, lower urinary tract symptoms (LUTS), and Chronic Pelvic Pain [13,14]
- Psychological factors. Sexual conditioning, stress, social phobias, depression and alexithymia [15-19]
- Metabolic syndrome [20]
- Poor sleep quality [21]
- Poor glycaemic control in type 1 diabetes and type 2 diabetes [22,23]

Waldinger [24] introduced the terms, variable and subjective and reported that men with acquired PE were more likely to seek treatment.

Better outcomes from therapy and the need for long-term therapy is less likely to be required, if associated comorbidities and risk factors are adequately managed.

## PATIENT ASSESSMENT

Diagnosis is based largely on a detailed history. Hypothyroidism and chronic prostatitis are the important clinical conditions to exclude (Table 1).

A focused physical examination is required to detect comorbidities such as thyroid disease, BPH, and prostatitis. Genital examination is recommended to exclude testicular disease and Peyronie’s Disease, but, most importantly, for patient reassurance.

Laboratory tests are generally not required unless associated ED is suspected. In such cases total and free testosterone levels should be checked along with HbA1c to exclude diabetes plus a cardiovascular risk and LUTS assessment.

The Premature Ejaculation Diagnostic Tool (PEDT) [25] ([https://www.baus.org.uk/\\_userfiles/pages/files/Patients/Leaflets/PEDT.pdf](https://www.baus.org.uk/_userfiles/pages/files/Patients/Leaflets/PEDT.pdf)) is a five-item questionnaire based on focus groups and interviews from the USA, Germany, and Spain assesses control, frequency, minimal stimulation, distress and interpersonal difficulty. A total score of >11 suggests a diagnosis of PE, 9 or 10 suggests a probable diagnosis, and <8 indicates a low likelihood of PE.

Other questionnaires used to characterize PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [26] (<https://sals3.patientpop>).

**Table 1.** The European Association of Urology (EAU) recommendations for the diagnostic evaluation of premature ejaculation (PE) (2023)[43]

- 
- Perform the diagnosis and classification of PE based on medical and sexual history, which should include assessment of intra-vaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to ejaculatory dysfunction. STRONG
  - Use patient reported outcomes in clinical practice. WEAK
  - Include physical examination in initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions particularly erectile dysfunction. STRONG
  - Do not perform laboratory or neuro-physiological tests. They should be directed by specific findings from history or examination. STRONG
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com/assets/docs/83263.pdf), Index of Premature Ejaculation (IPE) [27], and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [28]. Currently, their role is optional in everyday clinical practice. The Masturbatory Premature Ejaculation Diagnostic Tool (MPEDT) [29] has also been recently proposed, due to fact that PE patients report longer intravaginal ejaculatory latency times (IELTs) and lesser bother/distress during masturbation than partnered sex; however, further validation studies are required before the routine use of this questionnaire in this population.

## PREVALENCE

There have been many large epidemiological studies reviewing PE at the population level in many parts of the world. Not surprisingly, these studies yielded widely variable results, with the overall PE prevalence being from 2% to 60% [30,31].

Such a wide disparity is related to differences in the selected study population, *e.g.*, hospital- *versus* community- *versus* population-based, age, survey methodology, participant population size, data collection method, definition of disorder or symptoms, and culture or ethnicity.

The Global Study of Sexual Attitudes and Behaviours calculated that approximately one-third of all men may have PE (Table 2), but there were significant geographical differences. For example, the lowest prevalence was reported in the Middle East (12.4%), whereas the highest recorded prevalence occurred in Southeast Asia (30.5%) [32].

Researchers in Poland more recently used the PEDT,

to estimate PE prevalence in 3,000 men, and reported a PE prevalence of 19.3% to 38.1% [33].

In the United States Global Online Sexuality Survey study that also was based on the PEDT, 49.6% of respondents were classified as having PE [34]. In contrast, with the same instrument the PE prevalence was 12.1% in a Korean cohort of married couples [35]. These results agree with those reported from Italy, where PEDT-assessed PE prevalence was estimated to be 15.6% [36], and Australia where it was 16% [37].

As demonstrated by the Korean cohort [35], consideration should be given to the fact that the clinical trials were usually conducted in men in stable relationships for longer than 6 months, which is likely to be a different population from those seen in a clinical setting.

## THERAPEUTIC OPTIONS

Before commencing any treatment, it is essential to define the subtype of PE and discuss patient and partner expectations thoroughly. Pharmacotherapy is usually the first option for lifelong PE, whereas treating associated comorbidities is important in acquired PE. Various behavioral techniques are more likely to be effective for subjective PE, or for patients who wish to avoid drug treatment. However, the evidence for effectiveness and long-term benefit for psychological interventions is limited (Table 3, 4).

### 1. Oral medications

The only licensed oral medication for PE is dapoxetine at a dose of 30 to 60 mg taken 30 to 60 minutes prior to intercourse. The licensed indication is as fol-

**Table 2.** Self-reported rates of experiencing various sexual problems for 2 out of the past 12 months by region among sexually active men aged 40 to 80 years

Region	Lack of interest in sex	Inability to reach orgasm	Orgasm reached too quickly	Pain during sex	Sex not pleasurable	Trouble maintaining or achieving an erection
Northern Europe	12.5	9.1	20.7	2.9	7.7	13.3
Southern Europe	13.0	12.2	21.5	4.4	9.1	12.9
Non-European West <sup>a</sup>	17.6	14.5	27.4	3.6	12.1	20.6
Central/South America	12.6	13.6	28.3	4.7	9.0	13.7
Middle East	21.6	13.2	12.4	10.2	14.3	14.1
East Asia	19.6	17.2	29.1	5.8	12.2	27.1
Southeast Asia	28.0	21.1	30.5	12.0	17.4	28.1

Adapted from the article of Laumann et al (Int J Impot Res 2005;17:39-57) [32] with original copyright holder's permission.

This study included 20,000 sexually active adults.

<sup>a</sup>Non-European West includes Australia, Canada, New Zealand, South Africa and the United States.

**Table 3.** Summary of pharmacological treatments for premature ejaculation

Drug	Frequency of administration	Dose	IELT fold increase	Prescribing status	Side effects
Paroxetine <sup>a</sup>	Daily	10–40 mg	8	Off-label	- Nausea
Clomipramine <sup>a</sup>	Daily	12.5–50 mg	6	Off-label	- Fatigue
Sertraline <sup>a</sup>	Daily	50–200 mg	5	Off label	- Yawning
Fluoxetine <sup>a</sup>	Daily	20–40 mg	5	Off-label	- Diarrhea
Citalopram <sup>a</sup>	Daily	20–40 mg	2	Off-label	- Perspiration
Paroxetine <sup>a</sup>	Daily for 30 days, then as needed	10–40 mg	11.6	Off label	- Decreased sexual desire - Erectile dysfunction
Paroxetine <sup>a</sup>	As needed	10–40 mg	1.4	Off-label	
Clomipramine <sup>a</sup>	As needed	12.5–50 mg	4	Off label	
Dapoxetine <sup>a</sup>	As needed	30-60 mg	2.5–3	Locally classified as DNP (do not prescribe)	- Nausea - Headache - Dizziness - Diarrhea
Topical therapy <i>e.g.</i> lidocaine + prilocaine (EMLA) <sup>b</sup>	As needed	25 mg/g lidocaine +25 mg/g prilocaine	4.6	Off-label	- Penile numbness - Partner genital numbness - Skin irritation - Erectile dysfunction

Adapted from the International Society for Sexual Medicines Guidelines for the Diagnosis and Treatment of PE, this table summarizes the pharmacological treatments used in clinical trials, compares different treatment options, and supports JAPCs decision to classify dapoxetine as black.

IELT: intravaginal ejaculatory latency time, PE: premature ejaculation.

<sup>a</sup>Level of evidence 1a. <sup>b</sup>Level of evidence 1b.

**Table 4.** Treatment options for premature ejaculation

Treat erectile dysfunction, other sexual dysfunction or genitourinary infection such as prostatitis first.

**Lifelong PE**

Dapoxetine or lidocaine/prilocaine spray first line for lifelong premature ejaculation.

Use daily PDE5 inhibitor treatment alone or in combination with other therapies in those with or without erectile dysfunction.

**Acquired PE**

Consider dapoxetine as first line licenced treatment.

Consider off label on demand clomipramine.

Consider daily SSRI if frequent intercourse, after discussion of sexual side effects and withdrawal problems.

Psychosexual counselling.

Masturbation training

Biofeedback

Exercise regimes

E-Health techniques, *e.g.* smart phone

Combination therapy, medication with behavioural techniques

- Poor control over ejaculation and;
- A history of PE in the majority of intercourse attempts over the prior 6 months.

**GUIDANCE AND GUIDELINES**

Prescribing guidelines in the UK on the pharmacological treatment of PE [39] states that all the above criteria need to be met, which makes a diagnosis of PE likely before prescribing. The problem is that failing to realize that young men in the current age, who ejaculate quickly each time which causes marked personal distress and interpersonal difficulty are highly unlikely to sustain a relationship for six months, suggesting that they need inflict “misery” on themselves and multiple partners to reach that elusive 6-month milestone.

Experienced clinicians realize that this recommendation was only there for clinical trial purposes as partners were required to time intercourse with a stopwatch and record their own experience in diaries, hence the requirement for a stable relationship. It could therefore be argued that the stable relationship couples recruited to clinical trials bore little relationship to the predominantly unpartnered men with PE attending outpatient clinics or GP surgeries.

lows [38]:

- An IELT of less than 2 minutes (the criteria at the time of license) and;
- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the man wishes and;
- Marked personal distress or interpersonal difficulty as a consequence of PE and;

The NICE throughout evidence summary [38] concluded that dapoxetine is the only medicine licensed in the UK for the treatment of PE, although other treatments are used off-label for this indication.

The General Medical Council (GMC) advice to use a licensed medicine whenever possible [40] should be taken into consideration (see below). Dapoxetine for PE was not considered appropriate for a NICE technology appraisal and is not currently planned for any other work program.

The European Association of Urology (EAU) guidelines 2021 [41], 2023 [42], and 2024 [43] state the importance of treating suspected ED first and that licensed treatments should be used first line. They point out that dapoxetine and Topical Eutectic Mixture for Premature Ejaculation (TEMPE) which contains lidocaine and prilocaine, are first line options, and all other approaches are off label.

Before commencing any treatment, it is essential to define the subtype of PE and discuss what expectations the patient has. Pharmacotherapy is first-line treatment for patients with lifelong PE, whereas treating the underlying cause (*e.g.*, ED, prostatitis, LUTS, anxiety and hyperthyroidism) must be the initial goal for patients with acquired PE [2]. Phosphodiesterase-5 (PDE5) inhibitors are licensed to treat ED and LUTS, with possible clinical benefit.

Various behavioral techniques may be beneficial in treating variable and subjective PE [44]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [45,46]. The evidence base is weak and inconsistent regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown.

Manufacturer advises maximum dose of 30 mg of dapoxetine with concurrent use of moderate inhibitors of CYP3A4 except in patients verified to be extensive 8CYP2D6 metabolizers where manufacturer recommends max (dose 60 mg; <https://www.medicines.org.uk/emc/product/1269/smpc#gref>).

## 1. Summary

- Of the cytochrome P enzymes, CYP3A4 is not only the most prevalent CYP enzyme in the liver but is used by more than 50% of medications on the market for their metabolism and elimination from the body

- Weak inhibitors of CYP3A4 include cimetidine
- Moderate inhibitors of CYP3A4 include amiodarone, erythromycin, fluconazole, miconazole, diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, conivaptan
- Strong inhibitors of CYP3A4 include Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir. It is important to note that not all drugs within a class of medications are known to be inhibitors of CYP3A4

## 2. Contra-indications

- History of bipolar disorder; history of mania; history of severe depression; history of syncope; postural hypotension; significant cardiac disease; uncontrolled epilepsy

## 3. Cautions

- Bleeding disorders: epilepsy (discontinue if convulsions develop); susceptibility to angle-closure glaucoma

## 4. Side effects

### 1) Common

- Anxiety; asthenia; concentration impaired; constipation; diarrhea; dizziness; drowsiness; dry mouth
- Gastrointestinal discomfort; gastrointestinal disorders; headache; hypotension; mood altered; nausea; paraesthesia
- Sexual dysfunction; sinus congestion; sleep disorders; sweat changes; syncope; tinnitus; tremor; vasodilation; vision blurred; vomiting; yawning

### 2) Uncommon

- Akathisia; arrhythmias; behavior abnormal; confusion; depression; eye pain; feeling abnormal; feeling hot; hypertension; level of consciousness decreased; mydriasis; pruritus; taste altered; thinking abnormal; vertigo
- Hepatic impairment
- Manufacturer advises avoid in moderate to severe impairment
- Renal impairment
- Use with caution if creatinine clearance 30–80 mL/minute; avoid if creatinine clearance less than 30

mL/minute (limited information available). See prescribing in renal impairment

### 3) Pre-treatment screening

- Test for postural hypotension before starting treatment

### 4) Treatment cessation

- The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment)

### 5) Patient and carer advice

- Postural hypotension and syncope
- Patients should be advised to maintain hydration and to sit or lie down until prodromal symptoms such as nausea, dizziness, and sweating abate

## THE IMPORTANCE OF LICENSED MEDICATION

As stated above, there is still no NICE guidance on PE, but current EAU guidelines [43] stress the importance of prescribing licensed medications wherever possible.

Current GMC guidelines (section 103/104) state [40]: “You should usually prescribe licensed medicines in accordance with the terms of their license. However, you may prescribe unlicensed medication where, on the basis of an assessment of the individual patient, you conclude, or medical reasons, that it is necessary to do so to meet the specific needs of the patient.”

Critically, there is no mention here of “cost of medication.” A detailed review of multiple Clinical Commissioning Group (CCG) guidance published on websites [47] shows that “off label” daily (selective serotonin reuptake inhibitors [SSRIs]) are recommended as first line continually citing cost savings as the main reason and strongly advising against the licensed product, dapoxetine, even though they acknowledge efficacy and a lower list of side effects and very low risk of habituation. There is an acknowledgement that low sexual desire, orgasmic difficulty, and ED are frequent side effects of SSRIs, and withdrawal can be problematic [48]. This is very concerning given the strong associations of ED and PE. Of even greater concern, is the recommendation of daily paroxetine as first line, quoting

the longest prolongation of IELT, it seems illogical to prescribe a daily drug to treat PE that has well known sexual side effects, however there are a small number of men having very frequent intercourse with PE in whom daily treatment might be appropriate.

## OFF-LABEL SSRI ANTIDEPRESSANTS

Table 2 below (adapted from the International Society for Sexual medicine [ISSM] guidance [2]) highlights the high-level evidence that SSRIs prolong IELT, and that paroxetine is the most effective. SSRIs need to be given daily, for at least the first month but some patients can later switch to on-demand therapy. Efficacy is usually seen within a few weeks. The tricyclic antidepressant, Clomipramine 25 to 50 mg appears to be the most effective on-demand drug from day one. Tramadol 25 to 50 mg has been shown to be effective but recent reports of the risk of habituation have created considerable concern, and the British Society for Sexual Medicine (BSSM) do not recommend. It is interesting that the chart below highlights the effectiveness of licensed on-demand dapoxetine, but recommends against use, based on cost, a situation likely to change in 2024.

Strangely paroxetine, reported as showing a mean 11-fold increase in IELT is not reported to have delayed or anejaculation as a side effect, when in clinical practice, increasing the duration on penetrative sex from 2 to 22 minutes or above, is likely to create difficulties in maintaining erection, not to mention sexual problems in the partner. Paroxetine has one of the highest risks of habituation and is currently banned under 18 in the UK because of 3-fold increased risk of suicide. As with other antidepressants, suddenly stopping paroxetine can lead to a discontinuation syndrome characterized by feelings of sickness, diaphoresis, asthenia, myalgia, paraesthesia, fatigue, electric shock sensations, depression (including suicidality), anxiety, insomnia, headache, chills, stomach ache, nausea, vomiting and diarrhea [49]. Step-wise dose reduction involving slowly tapering down the drug over a period of at least two weeks is recommended for both discontinuation and cross tapering with another antidepressant [50].

Hence, recommending such a drug as first line medication in vulnerable young men unable to sustain sexual relationships is considered by BSSM to be ill advised. The risks of ED and reduced sexual desire are

clearly stated but seem to be perceived as low significance.

The widespread use of daily SSRIs to treat PE in young men, also risks “stigmatisation” with the inevitable assumption that they are under treatment for depression, especially as they are unlikely to deny this fact and offer PE as their clinical diagnosis. Of greater concern is that several commercial websites are offering direct to the public sales of paroxetine for PE, based on the local CCG guidance, following a few basic online questions. The more that we treat PE as a “lifestyle” issue, the more this practice will increase.

Physicians also need to be aware that they may be required to justify prescribing of label medications and offering “cheap” as their clinical indication is likely to be acceptable. Medical defense organizations frequently ask about “off label prescribing” and load insurance premiums accordingly. Doctors involved in treating men with sexual problems on a regular basis with off label indications, might, in effect, be funding CCG savings from their own pockets. Unfortunately, “cheapness” is seldom an effective medicolegal defense.

The patent of dapoxetine expires in 2024/25, and prices are likely to fall dramatically. Unfortunately, CCG drug reviews only occur in cycles over several years, meaning that guidance might not change as quickly as might be expected.

## **THE IMPORTANCE OF TREATING CO-EXISTING ERECTILE DYSFUNCTION FIRST**

Multiple clinical studies [51] have demonstrated that ED occurs in conjunction with PE, either as a primary or secondary factor. As ED develops, patients may ejaculate quickly as an adaptive process, realizing that their erection is failing. With PE, either primary or secondary, it can be impossible for a patient to assess whether they could have maintained an erection for 10 minutes if they ejaculate within 30 seconds. It is also likely that therapy aimed exclusively at prolongation of IELT will lead to unsatisfactory responses as erections are unlikely to last for several minutes if the duration of intercourse has been less than a minute for several months or years. This can lead to a spiral of performance anxiety.

Using validated questionnaires, such as the IIEF-5 or Sexual Health Inventory for Men does not help, as

these were not studied in men with PE:

Q1. “How would you rate your confidence that you could keep an erection?” This will be answered as “low” because of early ejaculation.

Q3. How often are you able to maintain the erection after you have entered your partner?” This will be answered as “almost never” because the erection is lost with ejaculation.

Q5. “When you attempted intercourse, how often was it satisfactory for you?” This will be answered “almost never,” as the experience only lasted a matter of seconds, and they perceive little satisfaction for their partner.

Therefore, these men will score as having severe ED, and there is effectively no way of reliably separating the two issues, hence the EAU guidelines suggest a “daily PDE5 inhibitor” essentially, tadalafil 5 mg daily as first line in most cases. Suggestions that this statement is “off-label use” can be dismissed on the basis that the patient has clearly scored as having ED on the most reliable diagnostic tool. Of relevance is that all other PE treatments (licensed or unlicensed), SSRIs or topical anesthetics list ED, and/or loss of sexual desire as common side effects. Clearly daily PDE5 inhibitors are highly likely to improve erectile function scores from the baseline levels. Daily therapy is preferable in younger men, attempting to establish new relationships are more likely to desire frequent and spontaneous sexual activity, often driven by spontaneous erections, which are also beneficial in terms of masturbatory training recommended by therapists. In the case of a patient seeking sex or ejaculation more than once per week, daily tadalafil 5 mg results in lower total doses, fewer side effects, improvement in urinary symptoms and even improvement in depression scores. In practice, it is highly unlikely that the new partner of a 19–29-year-old would be happy with a sex-life reliant on “on-demand” medication before pre-planned sex.

These important aspects of human sexuality are best appreciated by clinicians, experienced in dealing with sexual problems in single men and couples, rather than by allied health professionals such as community pharmacists with previously no direct patient experience, unless they have had training in sexual medicine. These issues are highlighted in the diagnostic and treatment algorithm below, taken from the latest EAU guidelines [43], although the BSSM takes issue with the advice on off label treatments, such as daily SSRI

treatment.

## PDE5 INHIBITORS FOR PE

A 2024 review demonstrated that PDE5 inhibitors, both as lone agents and together with SSRIs or topical agents, were superior to a placebo for the treatment of PE [52].

This endorsed a 2020 review that concluded that PDE5 inhibitors were significantly more effective than placebo in the treatment of PE [53].

### Summary:

Diagnosis based on clinical history from patient and ideally partner (determine whether lifelong or not).

Time to ejaculation IELT

Degree of control

Degree of bother, distress and interpersonal difficulty

Onset

Medical history and appropriate blood testing, e.g. diabetes, and psychosocial history

Targeted physical examination, to exclude anatomical abnormality, e.g. phimosis.

Proceed with education and discussion of treatment options (pharmacotherapy for lifelong PE).

A 2023 study (Fig. 1) compared tadalafil 5 mg on demand (group A) with dapoxetine (group B) showing a 4.5-fold prolongation of IELT at 4, 8, and 12 weeks for both drugs and a 6.5-fold prolongation with both (group C), well maintained at 12 weeks. Erectile Function (EF) and International Prostate Symptom Score (IPSS) scores were not recorded. Adverse events were mild, and discontinuation rates were low. Given the huge cost advantage and long-term safety profile of tadalafil, this study strongly supports the use of tadalafil as first line therapy, especially with the difficulty in excluding concomitant ED in the presence of severe PE [54].

A study by Mohseni Rad et al [55], included 120 patients with PE. Patients were randomly assigned into 4 groups: dapoxetine was given to the first group, paroxetine to the second, and tadalafil, on demand, with dapoxetine to the third, and the fourth received paroxetine combined with tadalafil for one month. The mean pre-treatment and post-treatment IELT among groups were  $57.8 \pm 34.2$  vs  $204.4 \pm 82$  in group 1,  $59.4 \pm 32$  vs  $208.8 \pm 65.1$  in group 2,  $56.1 \pm 31$  vs  $269.9 \pm 100.4$  in group 3, and  $54.6 \pm 30.9$  vs  $259.3 \pm 83.4$  in group 4. They concluded that combination therapy (tadalafil with dapoxetine or paroxetine) was associated with better improvement in the IELT than monotherapy. No significant differences

were detected between the groups regarding the side effects except for headache and flushing which were significantly higher in the groups who received a combination therapy.

Another placebo-controlled study of 60 patients randomized to daily tadalafil 5 mg placebo for 3 months found EF score improved from 9.5 to 16.1. IELT from 2.2 to 3.4 minutes and IPSS from 14.1 to 10.4. Tadalafil 5 mg once daily treatment was effective in improving IELTs and Patient Reported Outcome Measures or up to 2 years [56].

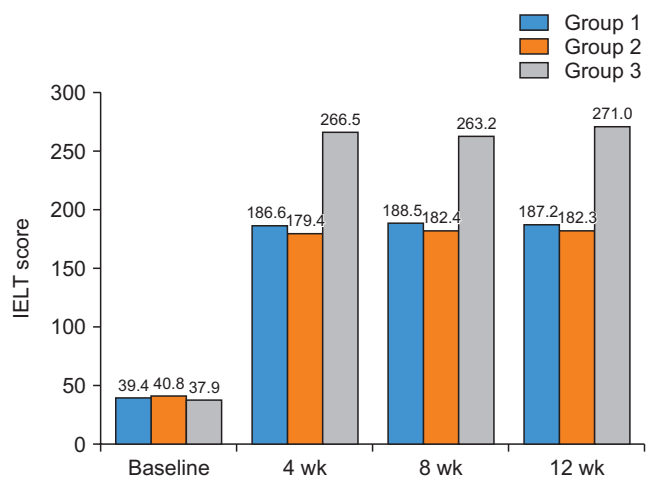
These studies show the importance of patient selection and the over-reliance on IELT as the primary endpoint, whereas overall sexual satisfaction for the patient and partner may be preferable as confidence in ability to maintain an erection is at least as important.

In terms of side effects, we know that after 27 years' experience, especially with daily tadalafil, these are usually mild, self-limiting and more acceptable for the management of a potentially long-term problem in younger men.

Open label studies [54,55] have shown that a combination of PDE5 inhibitors and SSRIs is superior to SSRI monotherapy, which has also been recently confirmed by a Bayesian network meta-analysis [57].

## TOPICAL TREATMENTS

A eutectic mixture of lidocaine and prilocaine in



**Fig. 1.** Prospective comparison of tadalafil 5 mg (group 1), dapoxetine 30 mg (group 2), and the combination of both (group 3) in the treatment of premature ejaculation. Comparison between pre-treatment and post-treatment IELT in the studied groups. IELT: intravaginal ejaculatory latency time. Adapted from the article of Hasan et al (Arab J Urol 2023;22:81-8) [55] with original copyright holder's permission.

an aerosol spray (TEMPE) is the only licensed topical preparation for PE (since 2006). In clinical trials this produced a 2.5-fold increase *versus* placebo and was well tolerated [58]. Expense has been a major drawback, especially as cheaper unlicensed preparation such as Eutectic Mixture of Local Anaesthetics cream and topical lidocaine sprays (*e.g.* Promescent or Stud 100) are available via the internet. Numbness (patient and partner) is the major adverse event with topical anesthetic products and recommendation for condom use is a major drawback.

## FUTURE TRENDS

Current treatments only provide a temporary delay in the ejaculation latency time, and PE tends to recur when the treatment is stopped. An effective treatment for PE is therefore still elusive. The efficacy and safety of topical anesthetics and SSRIs in delaying ejaculation have been confirmed in many well-designed controlled trials, and studies on new-generation SSRIs are ongoing. Moreover, promising results came from clinical trials in which the efficacy of on-demand PE therapies targeted neurotransmitters other than serotonin, such as  $\alpha$ 1-adrenoceptor antagonists. Oxytocin antagonists are currently under development for PE as is oral KH-001 a natural alkaloid derived from the *Sceletium tortuosum* plant also known as Kanna, used for centuries in South Africa for mood and performance enhancement.

Surgical intervention and neuromodulation have been proposed as potential treatment options for PE; however, current PE guidelines do not recommend these treatments owing to lack of controlled clinical trials and safety concerns [59]. Clearly there is a place for such interventions in severe intractable cases, including selective dorsal neurectomy, cryoablation, radiofrequency and hyaluronic acid injections, but the lack of controlled studies with sufficient patients does not enable formal endorsement in an evidence based guideline.

## NON-PHARMACOLOGICAL INTERVENTIONS

Psychological and couple therapy, and double condom use was the mainstay of treatment throughout the 20th century, but publications usually involved small

numbers and non-standardized approaches.

Psychosexual interventions, whether behavioral, cognitive, or focused on the couple, are essentially techniques to control/delay ejaculation, to gain confidence in sexual performance, thereby reducing anxiety, and promoting communication and problem-solving within the couple [44].

The earliest study was published in 1974 and involved 4 couples treated with an average 1.5-hour psychotherapy and 2 couples regained normal function, and the other 2 couples reported improvement in relationships [60]. Another study evaluated 18 couples reporting PE for a mean 5 years. After 15 to 20 sessions of pelvic floor exercises, 11 (61%) were able to control their ejaculation and 7 (39%) were unchanged [61]. A further publication reported results from 12 one-hour in 16 patients full-immersion virtual reality sessions and reported benefits lasting 12 months [62].

Small uncontrolled studies have shown benefits from increased physical activity (running for 30 minutes 5 days per week for 30 days) compared with dapoxetine. The researchers concluded that, a moderate physical activity longer than 30 min at least 5 times a week leads to ejaculation delay and appears as an alternative to dapoxetine on demand for the treatment of PE [63].

Other studies have looked at desensitizing of the penis with frequent masturbation. One study used the Tenga Flip masturbation device, five times per week for 6 weeks, resulting in a 57% increase in IELT with masturbation and 79.9% increase with intercourse [64].

One study of 224 patients, penile allograft graft surgery increased IELT 8 from 1 minute 17 seconds to 17 minutes. Sixty patients were treated by cutting the bulbospongiosus muscle bilaterally and frenular delta excision with a 96% success rate with IELT prolongation off 200% to 1,000% [65].

Five patients treated with CT guided pudendal nerve block increased ejaculation from 22 to 215 seconds [66].

One study evaluated transcutaneous posterior tibial nerve stimulation in 11 patients 3 times per week for 12 weeks. IELT increased 4.8, 6.8, and 5.4-fold at 12, 24, and 48 weeks [67].

Interventions with a focus on sexual education or acceptance have also been shown to be effective [68].

Recent evidence suggests that start-stop exercises, combined with psychoeducation and mindfulness techniques improve PE symptoms, PE-associated distress,

anxiety, and depression [69]. Mindfulness alone also has some positive data [70].

A study of a smartphone-delivered psychological intervention, aimed at improving behavioral skills for ejaculatory delay and sexual self-confidence, had positive effects, supporting the use of E-health in the context of PE [71].

All the above behavioral therapies may be most effective when used in combination with medical interventions.

## CONCLUSIONS

Different international and local guidelines on PE are currently in force. They have several similarities but also many differences that reflect prevalence rates and cultural variations. The latter appear particularly evident when analyzing the definitions of PE and the recommendations on the management of the patient with PE. The authors have arrived at a consensus for management of PE in the UK, and the BSSM takes issue with the advice to use off label treatments, such as daily SSRI treatment, favoring on-demand dapoxetine. There is increasing evidence for the use of PDE5 inhibitors which are superior to a placebo for the treatment of PE. A recent meta-analysis of international PE guidelines [1] supports the needs for research to investigate the association of PE with ED, prostatitis and thyroid disease, supporting the early use of PDE5 inhibitors either alone or in combination with dapoxetine or psychosexual interventions. Topical agents and non-pharmacological treatments also have a place, with new agents in the pipeline.

## Conflict of Interest

The authors have nothing to disclose.

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## Author Contribution

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