REPORTS

International Society for Sexual Medicine's Guidelines for the Diagnosis and Treatment of Premature Ejaculation

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ABSTRACT

Introduction. Over the past 20 years our knowledge of premature ejaculation (PE) has significantly advanced. Specifically, we have witnessed substantial progress in understanding the physiology of ejaculation, clarifying the real prevalence of PE in population-based studies, reconceptualizing the definition and diagnostic criterion of the disorder, assessing the psychosocial impact on patients and partners, designing validated diagnostic and outcome measures, proposing new pharmacologic strategies and examining the efficacy, safety and satisfaction of these new and established therapies. Given the abundance of high level research it seemed like an opportune time for the International Society for Sexual Medicine (ISSM) to promulgate an evidenced-based, comprehensive and practical set of clinical guidelines for the diagnosis and treatment of PE.

Aim. Develop clearly worded, practical, evidenced-based recommendations for the diagnosis and treatment of PE for family practice clinicians as well as sexual medicine experts.

Method. Review of the literature.

Results. This article contains the report of the ISSM PE Guidelines Committee. It affirms the ISSM definition of PE and suggests that the prevalence is considerably lower than previously thought. Evidence-based data regarding biological and psychological etiology of PE are presented, as is population-based statistics on normal ejaculatory latency. Brief assessment procedures are delineated and validated diagnostic and treatment questionnaires are reviewed. Finally, the best practices treatment recommendations are presented to guide clinicians, both familiar and unfamiliar with PE, in facilitating treatment of their patients.

Conclusion. Development of guidelines is an evolutionary process that continually reviews data and incorporates the best new research. We expect that ongoing research will lead to a more complete understanding of the

pathophysiology as well as new efficacious and safe treatments for this sexual dysfunction. Therefore, it is strongly recommended that these guidelines be re-evaluated and updated by the ISSM every 4 years. **Althof SE, Abdo CHN, Dean J, Hackett G, McCabe M, McMahon CG, Rosen RC, Sadovsky R, Waldinger M, Becher E, Broderick GA, Buvat J, Goldstein I, El-Meliegy AI, Giuliano F, Hellstrom WJG, Incrocci L, Jannini EA, Park K, Parish S, Porst H, Rowland D, Segraves R, Sharlip I, Simonelli C, and Tan HM. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. J Sex Med 2010;7:2947–2969.**

Key Words. Premature Ejaculation; Diagnosis of PE; Prevalence of PE; Pharmacotherapy of PE; Psychotherapy of PE

Introduction

Over the past 20 years our knowledge of premature ejaculation (PE) has significantly advanced [1]. Specifically, we have witnessed substantial progress in understanding the physiology of ejaculation [2–8], clarifying the real prevalence of PE in population-based studies [9–13], reconceptualizing the definition and diagnostic criterion of the disorder [14], assessing the psychosocial impact on patients and partners [15], designing validated diagnostic and outcome measures [16], proposing new pharmacologic strategies, and examining the efficacy, safety, and satisfaction of these new and established therapies [17–21]. Given the abundance of high level research it seemed like an opportune time for the International Society for Sexual Medicine (ISSM) to promulgate an evidenced-based, comprehensive, and practical set of clinical guidelines for the diagnosis and treatment of PE.

We were able to identify three sets of clinical practice guidelines for the diagnosis and treatment of PE. They are the *American Urological Association's 2004 Guidelines for the Pharmacologic Treatment of Premature Ejaculation*, the *European Association of Urology Guidelines on Male Sexual Dysfunction: Erectile Dysfunction and Premature Ejaculation*, Updated 2009, and the *Practice Guidelines for the Pan Arab Society of Sexual Medicine* (Disorders of Ejaculation) [22–25]. It was our opinion that the existing guidelines were not sufficiently comprehensive, failed to adequately address both psychological as well as medical interventions and that essential new evidence that has come to light is not included in these documents. Therefore we undertook to develop a contemporary set of practical guidelines primarily targeting front line clinicians, and secondarily sexual medicine specialists.

Guideline Development Process

In September, 2009 the ISSM PE Guidelines Committee met in London for 3 days. The 26-committee members were selected by peer recommendation and further vetted to provide a diversity of discipline, balance of opinion, knowledge, gender and geography. These 22 men and 4 women included most of the world's highly recognized experts on PE and comprised ten urologists, five psychologists, three psychiatrists, two endocrinologists, two primary care physicians, one sexual medicine physician, one genitourinary physician, one internal medicine physician, and one radiation oncologist. The committee was chaired by Stanley Althof, PhD and the meeting facilitated by ISSM President, John Dean, MD. All members were required to declare in advance any potential conflicts of interest with their participation in the committee's work.

A comprehensive review of scientific literature on PE was conducted by ISSM research assistants under the supervision and guidance of the Chairman. Selected original articles were circulated to committee members prior to meeting. Committee members were invited to review all available evidence, not just the articles provided by the ISSM researchers, and prepare a presentation for the meeting on specific topics related to the guidelines. The committee utilized evidence-based medicine grading as the means of integrating individual clinical expertise with the best available external clinical evidence from systematic research. Where available, evidence of important outcomes was collated for each sub-population. Quality of evidence, and the strength of any recommendation was graded using the Oxford Centre of Evidence-Based Medicine system [26]. Figure 2 contains a summary of the relevant evidence-based recommendations of the Committee.

The meeting was supported by an unrestricted grant from Johnson and Johnson, the manufacturer of dapoxetine. However, ISSM required complete independence from industry during the development of the guideline and related resources. There were no industry representatives at the meeting and there was no attempt by industry to influence any part of the development or writing process at any time.

Definitions of PE

Several definitions for PE exist having been crafted by various professional organizations and/or individuals [11,25,27–31] (see Table 1). Most of these definitions include the subtypes of lifelong and acquired (PE symptoms beginning after a period of normal ejaculatory function). The major criticisms of the existing definitions included their failure to be evidenced-based, lack of specific operational criteria, excessive vagueness, and reliance on the subjective judgment of the diagnostician. Nonetheless, three common constructs underlie most definitions of PE: (i) a short ejaculatory latency; (ii) a lack of perceived self-efficacy or control about the timing of ejaculation; and (iii) distress and interpersonal difficulty (related to the ejaculatory dysfunction).

Because of the discontent with the existing definitions of PE, as well as pressure from the regulatory agencies concerning the inadequacy of the PE definitions, the ISSM convened in 2007 a meeting of experts to review the evidence-based literature and to develop a definition grounded in clearly definable scientific criteria [14]. After carefully reviewing the literature, the Committee proposed that lifelong PE is,

> a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy. ***(LOE 1a)***

The definition applies only to intravaginal sexual activity. It does not define PE in the context of other sexual behaviors or men having sex with men. The

Table 1 Definitions of premature ejaculation

Definition	Source
A male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.	International Society of Sexual Medicine, 2008
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.	DSM-IV-TR, 2000
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 seconds) 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.	International Statistical Classification of Disease, 10th Edition, 1994
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.	European Association of Urology. Guidelines on Disorders of Ejaculation, 2001
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.	International Consultation on Urological Diseases, 2004
Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.	American Urological Association Guideline on the Pharmacologic Management of Premature Ejaculation, 2004
The man does not have voluntary, conscious control, or the ability to choose in most encounters when to ejaculate.	Metz and McCarthy [29]
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 percent of their coital connections.	Masters and Johnson [28]
Men with an IELT of less than 1 minute (belonging to the 0.5 percentile) have "definite" premature ejaculation, whereas men with IELTs between 1 and 1.5 minutes (between 0.5 and 2.5 percentile) have "probable" premature ejaculation. In addition, an additional grading of severity of premature ejaculation should be defined in terms of associated psychological problems.	Waldinger et al. [11]

IELT = intravaginal ejaculation latency time.

Committee concluded that there is insufficient information available to extend the definition of PE to these other groups. Additionally, the Committee concluded that there are insufficient published objective data to propose a new evidence-based definition of acquired PE, although it believed the proposed criterion for lifelong PE might be applied to acquired PE as well. ***(LOE 5d)***

Anteportal ejaculation is the term for men who ejaculate prior to vaginal penetration and is considered the most severe form of PE. Such men/couples typically present when they are having difficulty conceiving children. It is estimated that 5% of lifelong PE men suffer from anteprotal PE [18,32,33].

Although not evidenced based, Waldinger proposed two additional "subtypes" for men who are distressed about their ejaculatory function but do not meet the ISSM criterion for PE [31]. These subtypes should be considered provisional; however, we thought it was important to include them because they accurately characterize many men who do not qualify for the diagnosis of PE and are asking for help. We believe these categories may help health-care professionals (HCPs) address these men's concerns.

These two subtypes are termed natural variable PE and premature-like ejaculatory dysfunction. Natural variable PE is characterized by early ejaculations which occur irregularly and inconsistently with some subjective sense of diminished control of ejaculation. This subtype is not considered a sexual dysfunction or psychopathology but rather a normal variation in sexual performance.

Premature-like ejaculatory dysfunction is characterized by: (i) subjective perception of consistent or inconsistent rapid ejaculation during intercourse; (ii) preoccupation with an imagined early ejaculation or lack of control of ejaculation; (iii) actual intravaginal ejaculation latency time (IELT) in the normal range or even of longer duration (i.e., an ejaculation that occurs after 5 minutes); (iv) ability to control ejaculation (i.e., to withhold ejaculation at the moment of imminent ejaculation) may be diminished or lacking; and (v) the preoccupation is not better accounted for by another mental disorder [34]. ***(LOE 5d)***

Prevalence

Reliable information on the prevalence of lifelong and acquired PE in the general male population is lacking. Confounding accurate prevalence estimates are the competing and varying definitions of PE and the manner in which prevalence data was gathered (population-based, self-report, or clinician based). Local and regional variations should be considered in the context of different cultural, religious, and political influences. Additionally, prevalence may vary across different demographics, including geography, ethnicity, and social status [11].

Based on patient self-report, PE is routinely characterized as the most common male sexual dysfunction. Prevalence data derived from patient self-report will be appreciably higher than prevalence estimates based on clinician diagnosis utilizing the more conservative ISSM definition of PE. The following studies demonstrate the varying prevalence estimates ranging from 30% down to 3%.

Data from The Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey investigating the attitudes, behaviors, beliefs, and sexual satisfaction of 27,500 men and women aged 40–80 years, reported the global prevalence of PE (based on subject self-report) to be approximately 30% across all age groups [9,12]. Perception of "normal" ejaculatory latency varied by country and differed when assessed either by the patient or their partner [35].

Differing from the GSSAB study, the Premature Ejaculation Prevalence and Attitude Survey found the prevalence of PE among men aged 18 to 70 years to be 22.7% [10]. PE was categorized by subject self-report. Prevalence was similar across countries (24.0% in the United States, 20% in Germany and Italy) and age groups. Similar results by age groups were also found by Brazilian Sexual Life Study, and PE was reported in 25.8% of 3,332 Brazilian men [36].

A Canadian study, using a study-specific definition of PE, based largely on the Diagnostic and Statistical Manual of Mental Disorders (DSM) III criteria (those who had fair/to poor control over their ejaculation and claimed that time to climax was a problem for them or their partner), classified 16% of males aged 18 to 60 years and above as experiencing PE [37]. Consistently lower rates of PE were reported by female partners, ranging between 9% and 14%.

Applying only the time parameter (IELT approximately 1 minute) of the ISSM definition of PE to a population-based cohort of 500 men with stopwatch measured IELTs, only 1–3% would be eligible for the diagnosis [38,39]. These men were not given measures to assess control or distress. The 1–3% prevalence is considerably different from the previous prevalence estimates of 20–30%

based on self-report or DSM-III diagnosis. The lower prevalence estimates are more consistent with the numbers of men who present for treatment of PE. However, even though some men who present for evaluation of PE will not meet the ISSM diagnostic criteria they should be carefully evaluated and considered for appropriate treatment. ***(LOE 3b)***

Prevalence of PE in Clinical Practice

PE in clinical practice is frequently a self-reported complaint, making it difficult to appreciate its real epidemiology. In addition, in some men/couples PE is diagnosed on the basis of distress rather than as an objective symptom. Another problem is the relative inconstancy of the symptom in many patients. The real prevalence is difficult to assess in clinical practice [38].

Very few PE sufferers seek help (9%); of those who seek help, 91.5% report little or no improvement as a result of seeking treatment; and in most cases (81.9%), it is the sufferer himself who seeks to initiate the conversation [10]. A report on practice patterns of urologists, noted that respondents saw one new PE patient per week and 26% prescribed on-demand SSRI's, 22% daily SSRIs and 11% topical anesthetics [40].

Average Ejaculatory Latency

Only recently have multinational (Netherlands, United Kingdom, United States, Spain, and Turkey) reports of IELT been published [11]. The median IELT was 5.4 minutes (range 0.55–44.1 minutes) and the distribution of the IELT in all five countries was positively skewed. The median IELT decreased significantly with age, from 6.5 minutes in the 18–30 years group, to 4.3 minutes in the group older than 51 years. Median IELT varied between countries, with Turkey having the lowest IELT. The median IELT value was independent of condom use or circumcision status (except in Turkey). A similar study conducted a few years later reported congruent results with a median IELT of 6 minutes (range 0.1–15.2) [39]. ***(LOE 2a)***

Etiology

Over the past two decades several studies have suggested that lifelong and acquired PE may be caused by somatic disorders and/or neurobiological disturbances. Previously it was thought that the condition was primarily psychologically or interpersonally based. Examples of these biological factors include: hypersensitivity of the glans penis [41], a higher cortical representation of the pudendal nerve [42], disturbances in central serotonergic neurotransmission [43,44], erectile difficulties [45], prostatitis [46,47], detoxification from prescribed drugs (e.g., raboxetine [48], citalopram [49]) or recreational drugs [49,50], chronic pelvic pain syndrome [51], varicocele [52], and thyroid disorders [53,54]. It is noteworthy that none of these "organic" etiologies has yet been supported by robust and large-scale studies.

Recent studies have suggested that in some men neurobiological and genetic variations could contribute to the pathophysiology of lifelong PE, as defined by the ISSM criteria and that the condition may be maintained and heightened by psychological/environmental factors [55,56]. In animal experiments serotonin receptors have been implicated in the etiology of lifelong PE and partly in acquired PE. Waldinger et al. hypothesized that lifelong early ejaculation in humans may be explained by either a hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptors [57]. They hypothesized that men with a low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically set at a lower point and ejaculate quickly with minimal stimulation. Additionally, in rapidly ejaculating rats, it has been recently demonstrated that the spinal command of ejaculation differs when compared with "normal" rats [58]. Serotonin dysregulation as an etiological hypothesis for PE may explain only a small percentage (2–5%) of complaints of PE in the general population [55].

Genetics of PE

In his classic article, Bernhard Schapiro noted that some family members of men with PE also have PE [59]. Many years later Waldinger et al. hypothesized that both the IELT and lifelong PE for some men are genetically determined [43]. Supporting this hypothesis was the report of a high prevalence of lifelong PE (defined in terms of and IELT of less than 1 minute) among first degree male relatives of Dutch men with lifelong PE [60].

Models to explain premature and delayed ejaculation were developed based on examination of 1,196 Finish male twins between the ages of 33 to 43 years [56]. The PE model suggested a moderate additive genetic variance of 28%, with no shared environmental variance (0%) and 72% nonshared environmental variance. One possible interpreta-

tion of these findings is that genetic influences may create a diathesis or predisposition in some men to ejaculate prematurely.

The first DNA study on PE was performed in 89 Dutch men with lifelong PE, in whom IELT was measured by a stopwatch [61]. Men with PE were compared with a cohort of mentally and physically healthy Dutch Caucasian men. The data demonstrated an association of the 5-HTLPR gene polymorphism and the duration of the IELT. Men with lifelong PE, defined as IELTs of less than 1 minute, and with the LL genotype ejaculated in a 100% shorter time than PE men with the SL and SS genotype. Additionally, the study showed that there was no difference in the prevalence of the LL, SL, and SS genotypes in men with lifelong PE compared with their prevalence in the general male Dutch population. Given that the distribution of the polymorphism is similar in lifelong premature ejaculators and mentally and physically healthy Dutch men, this study also lends support to a predisposition/diathesis model rather than the conclusion that genetic influences underlie all men with lifelong PE.

In contrast to the aforementioned study [61], a study in Turkish men [62] and Iranian men [63] showed a higher prevalence of SS genotypes in men with lifelong PE. However, the latter studies have been criticized on their methodology and/or use of statistics [64,65]. ***(LOE 2a)***

Thyroid Hormones

Endocrine control of the ejaculatory reflex is still not completely clarified [66]. There is evidence to indicate a link between depression, serotonin, and thyroid hormones [67,68]. Carani reported that 50% of hyperthyroid men had PE and when successfully treated the prevalence of PE fell to 15% [53,54,66].

Prostatitis

Twenty-six to 77% of men with chronic prostatitis or chronic pelvic pain syndrome (CPPS) report experiencing PE [51,69,70]. Prostatic inflammation and chronic bacterial prostatitis have been reported as common findings in men with acquired PE [46,47,71]. Considering the role of the prostate in the ejaculatory mechanism, a direct influence of the local inflammation in the pathogenesis of some cases of acquired PE seems likely [52]. The exact pathophysiology of the link between chronic prostatitis, ED, and PE is unknown. ***(LOE 3a)***

Psychological Factors

There are a range of psychological factors that may precipitate or maintain PE. These factors can be divided into predisposing or historical factors (e.g., sexual abuse, attitude toward sex in the home), individual psychological factors (e.g., body image, depression, performance anxiety, alexithymia), or relationship factors (e.g., intimacy, anger) [72–74]. There has been limited research that investigated the direction of the relationship between the variables given earlier and PE. Most studies are cross-sectional in nature, and associations between the variables have been identified, rather than causative relationships. Care must be exercised in interpreting these relationships, as it is possible that either the psychological factors led to the PE, or vice versa. From a clinical perspective, it is likely that there is a reciprocal relationship occurring, where one condition has led to problems in other areas, and these have, in turn, exacerbated the original condition. For example, performance anxiety may lead to PE, which then further exacerbates the original performance anxiety. ***(LOE 5d)***

Quality of Life Impact of PE on the Man and Partner

Eleven observational, non-interventional studies from 1997 to 2007 were reviewed that report on the psychosocial and quality of life consequences of PE on the man, his partner and the relationship [15]. These studies employed different methodologies, outcome measures, and consisted of both qualitative and quantitative investigations. All studies consistently confirmed a high level of personal distress reported by men with PE and their female partners. The negative impact on single men with PE may be greater than on men in relationships as it serves as a barrier to seeking out and becoming involved in new relationships [75]. Men with PE have significantly lower scores on self-esteem and self-confidence than non-PE men and one-third of men with PE report anxiety connected to sexual situations [76]. It may seem obvious but PE has a direct negative influence on women's sexual experience [10,77]. Both men and their partners affirm negative effects and interpersonal difficulty related to their PE and an overall reduction in their quality of life [15,76,78]. ***(LOE 1a–3a)***

Should Clinicians Specifically Screen for PE

Screening involves testing of a symptomless population in order to detect cases of a disease at an

early stage. Clearly, men affected by PE are not symptomless and, for PE, case-finding might be a better term.

The committee agreed that there was inadequate evidence to recommend screening or case-finding for PE, either in a general population or in most sub-populations. However, it is recommended that men with ED be screened for PE. ***(LOE 5d)***

Improvements in public awareness of sexual health issues, including PE, are required, so that individuals affected by sexual concerns are aware of options and interventions open to them. Physicians have an important role to play in sexual health education and PE should be included within sexual health education programs.

Assessment of PE

History

Patients expect clinicians to inquire about their sexual health [79]. Often patients are too embarrassed, shy, and uncertain if sexual complaints belong in the HCP's office [80]. Inquiry into sexual health gives patients permission to discuss their sexual concerns and also screens for associated health risks (e.g., cardiovascular risk and ED).

Table 2 lists recommended and optional questions that patients who complain of PE should be asked [81]. The recommended questions establish the diagnosis and direct treatment considerations and the optional questions gather detail for implementing treatment. Finally, the committee recommends that the HCPs take a medical and psychosocial history. ***(LOE 5d)***

Figure 1 is a flowchart devised by Rowland et al. detailing the assessment and treatment options for subjects complaining of PE [1].

Assessment of Ejaculatory Latency

Stopwatch Assessment of Ejaculatory Latency (IELT)

Stopwatch measures of IELT are widely used in clinical trials and observational studies of PE, but have not been recommended for use in routine clinical management of PE. Despite the potential advantage of objective measurement, stopwatch measures have the disadvantage of being intrusive and potentially disruptive of sexual pleasure or spontaneity. More recently, studies have indicated that patient or partner self-report of ejaculatory latency correlate relatively well with objective stopwatch latency and might be useful as a proxy measure of IELT [82–85]. As patient self-report is the determining factor in treatment seeking and satisfaction, it is recommended that self-estimation by the patient and partner of ejaculatory latency be accepted as the method for determining IELT in clinical practice. ***(LOE 2b)***

Physical Examination

For lifelong PE, a physical examination is highly advisable but not mandatory and should be conducted in most, if not all, patients. Some patients find it reassuring for the physician to examine them.

Table 2 Recommended and optional questions to establish the diagnosis of PE and direct treatment

Recommended questions For diagnosis	What is the time between penetration and ejaculation (cumming)?
	Can you delay ejaculation?
	Do you feel bothered, annoyed, and/or frustrated by your premature ejaculation?
Optional questions Differentiate lifelong and acquired PE	When did you first experience premature ejaculation?
	Have you experienced premature ejaculation since your first sexual experience on every/almost every attempt and with every partner?
Optional questions Assess erectile function	Is your erection hard enough to penetrate?
	Do you have difficulty in maintaining your erection until you ejaculate during intercourse?
	Do you ever rush intercourse to prevent loss of your erection?
Optional questions Assess relationship impact	How upset is your partner with your premature ejaculation?
	Does your partner avoid sexual intercourse?
	Is your premature ejaculation affecting your overall relationship?
Optional question Previous treatment	Have you received any treatment for your premature ejaculation previously?
Optional questions Impact on quality of life	Do you avoid sexual intercourse because of embarrassment?
	Do you feel anxious, depressed, or embarrassed because of your premature ejaculation?

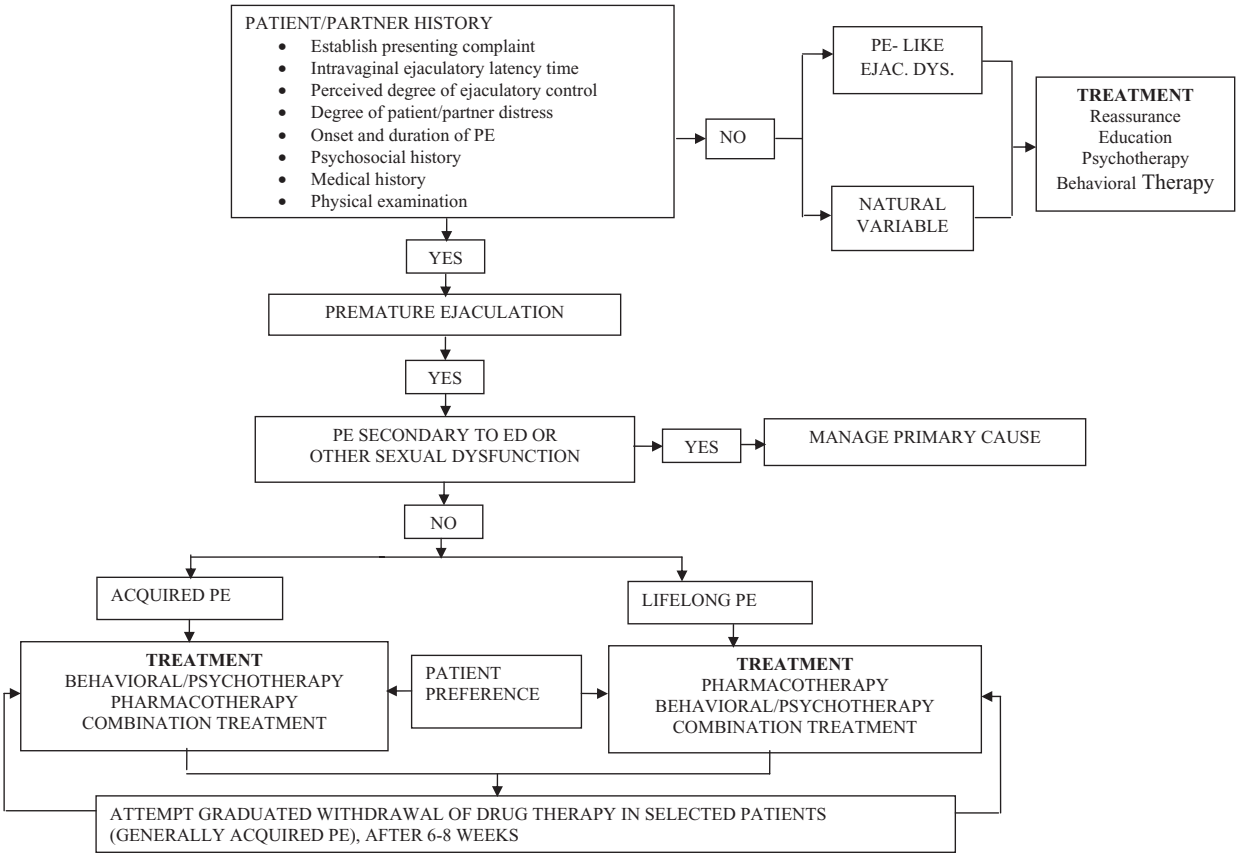

Figure 1 Algorithm for the management of premature ejaculation PE; (with permission of D. Rowland) [1].

For acquired PE, a targeted physical examination is mandatory to assess for associated/causal diseases such as ED, thyroid dysfunction, and prostatitis. ***(LOE 5d)***

Use of Assessment Instruments and Stopwatch Assessments

Standardized assessment measures for PE include the use of validated questionnaires and patient reported outcome (PRO) measures, in addition to stopwatch measures of ejaculatory latency. These measures are all relatively new and were developed primarily for use as research tools. Some have shown good psychometric properties and are potentially valuable adjuncts for clinical screening and assessment. Stopwatch measures of ejaculatory latency, in contrast, have been used extensively in research settings—both clinical trials and observational studies—but have typically not been recommended for use in clinical settings.

Several PE measures have been described in the literature [86–92], although only a small number have undergone extensive psychometric testing and validation. Currently, there are two questionnaires that meet most of the criteria for test development and validation: The Premature Ejaculation Profile (PEP) and the Index of Premature Ejaculation (IPE) [86,88]. A third brief diagnostic measure (PEDT) has also been developed, and is available for clinical use [90]. All three measures can be found in Appendix 1.

Five validated questionnaires have been developed and published to date. Two measures (IPE, PEP) have extensive databases. One measure (PEDT) has a modest database. Two other measures (Arabic, Chinese PE Questionnaires) have minimal validation or clinical trial data available. These latter measures are not recommended for clinical use. Depending on the specific need, the PEP or IPE are currently the preferred questionnaire measures for assessing PE, particularly when monitoring responsiveness to treatment. Overall, these measures may serve as useful adjuncts, but should not substitute for a detailed sexual history performed by a qualified clinician. ***(LOE 2b)***

Treatment

Pharmacological Treatment

Table 3 summarizes all the recommended pharmacological treatments for premature ejaculation. It does not include compounds still in clinical trials. The use of anaesthetics to diminish the sensitivity of the glans penis is probably the oldest known form of treating PE [59]. The introduction of the selective serotonin reuptake inhibitors (SSRIs), paroxetine, sertraline, fluoxetine, citalopram, and the tricyclic antidepressant (TCA) clomipramine has revolutionized the treatment of PE. These drugs block axonal reuptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of postsynaptic membrane 5-HT autoreceptors (Table 3).

Treatment with SSRIs and TCAs

PE can be treated with on-demand SSRIs such as dapoxetine or off-label clomipramine (a TCA), paroxetine, sertraline, and fluoxetine, or with daily dosing of off-label paroxetine, clomipramine, sertraline, fluoxetine, or citalopram.

Dapoxetine

Dapoxetine has received approval for the treatment of PE in Austria, Germany, Italy, Finland, Mexico, New Zealand, Portugal, South Korea, Spain, and Sweden. It is a rapid acting and short half-life SSRI with a pharmacokinetic profile suggesting a role as an on-demand treatment for PE [19,93–95]. No drug–drug interactions associated with dapoxetine, including phosphodiesterase inhibitor drugs have been reported [96]. In RCTs, dapoxetine 30 mg or 60 mg taken 1–2 hours before intercourse is more effective than placebo from the first dose, resulting in a 2.5- and 3.0-fold increases in IELT, increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine was comparably effective both in men with lifelong and acquired PE [97]. Treatment-related side effects were uncommon, dose dependent and included nausea, diarrhea, headache, and dizziness. They were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [98].

There is Level 1a evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of lifelong and acquired PE. (LOE 1a)

Off-Label SSRIs and TCAs

Daily treatment with off-label paroxetine 10–40 mg, clomipramine 12.5–50 mg, sertraline 50–200 mg, fluoxetine 20–40 mg, and citalopram 20–40 mg is usually effective in delaying ejaculation [99–104]. A meta-analysis of published data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline [20].

Ejaculation delay usually occurs within 5–10 days of starting treatment, but the full therapeutic effect may require 2–3 weeks of treatment and is usually sustained during long-term use [18]. Adverse effects are usually minor, start in the first week of treatment and may gradually disappear within 2–3 weeks; they include fatigue, yawning, mild nausea, diarrhea, or perspiration. Hypoactive sexual desire and ED are infrequently reported and appear to have a lower incidence in non-depressed PE men compared with depressed men treated with SSRIs [105]. Neurocognitive adverse effects include significant agitation and hypomania in a small number of patients, and treatment with SSRIs should be avoided in men with a history of bipolar depression [106].

Systematic analysis of RCTs in patients with depressive and/or anxiety disorders indicate a small increase in the risk of suicidal ideation or suicide attempts in youth but not adults [107–109]. In contrast, such risk of suicidal ideation has not been found in trials with SSRIs in non-depressed men with PE. Caution is still suggested in prescribing SSRIs to young adolescents with PE aged 18 years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation [109]. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs, which may be associated with a SSRI withdrawal syndrome [110].

On-demand administration of clomipramine, paroxetine, sertraline, and fluoxetine 3–6 hours before intercourse is modestly efficacious and well tolerated but is associated with substantially less ejaculatory delay than daily treatment in most studies [111–114]. On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low dose daily treatment [112].

A major limitation of treating PE with SSRIs or TCAs is that the PE returns when the medication is discontinued. Additionally, patients are reluctant to begin off-label treatment of PE with SSRIs. Salonia et al. reported that 30% of patients refused to begin treatment (paroxetine,

Table 3 Summary of recommended pharmacological treatments for premature ejaculation

Drug	Daily dose/as needed	Dose	IELT fold increase	Side effects	Status	Level of evidence
Oral therapies						
Dapoxetine [19,95]	As needed	30–60 mg	2.5–3	Nausea Diarrhea Headache Dizziness	Approved in some countries	1a
Paroxetine [104]	Daily dose	10–40 mg	8	Fatigue Yawning	Off label	1a
Clomipramine [99,101]	Daily dose	12.5–50 mg	6	Nausea Diarrhea	Off label	1a
Sertraline [103]	Daily dose	50–200 mg	5	Perspiration Decreased sexual desire	Off label	1a
Fluoxetine [102]	Daily dose	20–40 mg	5	Erectile dysfunction	Off label	1a
Citralopam [100]	Daily dose	20–40 mg	2		Off label	1a
Paroxetine [112]	Daily dose for 30 days and then as needed	10–40 mg	11.6		Off label	1a
Paroxetine [114]	As needed	10–40 mg	1.4		Off Label	1a
Clomipramine [114]	As needed	12.5–50 mg	4		Off label	1a
Topical therapy						
Lidocaine/prilocaine [117]	As needed	25 mg/gm lidocaine 25 mg/gm prilocaine	4–6	Penile numbness Partner genital numbness Skin irritation Erectile dysfunction	Off label	1b

IELT = intravaginal ejaculation latency time.

10 mg daily for 21 days followed by 20 mg as needed) and another 30% of those that began treatment discontinued it. Reasons given included: not wanting to take an antidepressant; treatment effects below expectations; temporary loss of interest in sex because of relationship issues; and side effects [115].

There is Level 1a evidence to support the efficacy and safety of off-label daily dosing of the SSRIs paroxetine, sertraline, citalopram, fluoxetine, and the serotonergic tricyclic, clomipramine, and off-label on-demand dosing of clomipramine, paroxetine, and sertraline for the treatment of lifelong and acquired PE. (LOE 1a)

The decision to treat PE with either on-demand dosing of dapoxetine (where available) or daily dosing of off-label SSRIs should be based upon the treating physician's assessment of individual patient requirements. Although many men with PE who engage in sexual intercourse infrequently may prefer on-demand treatment, many men in established relationships may prefer the convenience of daily medication. Well-designed preference trials will provide additional insight into the role of on-demand dosing.

In some countries off-label prescribing may present difficulties for the physician as the regulatory authorities strongly advise against prescribing for indications in which a medication is not licensed/approved. Obviously this complicates treatment in countries where there is no approved medication and the regulatory authorities advise against off-label prescription.

Topical Anesthetics

The use of topical local anesthetics such as lidocaine and/or prilocaine as a cream, gel, or spray is well established and is moderately effective in delaying ejaculation [21,116,117]. PSD502 is a lidocaine-prilocaine spray currently in clinical trials. Trial results indicated that the treated group reported a 6.3-fold increase in IELT and associated improvements in PRO measures of control and sexual satisfaction [21]. Because of the unique formulation of the compound there were minimal reports of hypoethesias and transfer to the partner. Other topical anesthetics are associated with significant penile hypo-anesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used.

There is Level 1b evidence to support the efficacy and safety of off-label on-demand label topical anesthetics in the treatment of lifelong PE. **(LOE 1b)**

Phosphodiesterase Type 5 Inhibitors (PDE5i)

PDE5i, sildenafil, tadalafil, and vardenafil, are effective treatments for ED. Several authors have reported using PDE5i alone or in combination with SSRIs as a treatment for PE [118–120]. Although a review of 14 studies on the PDE5i drug treatment of PE has failed to provide robust empirical evidence to support a role of PDE5i in the treatment of PE with the exception of men with PE and comorbid ED [121], recent well-designed studies do support a potential role for these agents suggesting a need for further evidence based research [118].

There is Level 4d evidence to support the efficacy and safety of off-label on-demand or daily dosing of PDE5i's in the treatment of lifelong PE in men with normal erectile function. Treatment of lifelong PE with PDE5i in men with normal erectile function is not recommended and further evidence-based research is encouraged to understand conflicting data.

Other Pharmacological Treatments

Treatment with on-demand tramadol, a centrally acting analgesic, or intracavernous injection of vasoactive drugs has been reported in the literature [122–124]. Twenty-five milligrams of tramadol, as needed, increased IELT from 1.17 minutes at baseline to 7.37 minutes after treatment [125]. In another study, 50 mg of tramadol, as needed, resulted in IELT increases from 19 seconds at baseline to 243 seconds at the end of treatment. Twenty-eight percent of the tramadol group vs. 15% of placebo patients reported treatment-related adverse events including nausea, vomiting, and dizziness [124].

There is Level 2d evidence to support the efficacy and safety of these treatments and their use as a treatment for PE <u>cannot</u> be recommended.

Surgery

Several authors have reported the use of surgically induced penile hypo-anesthesia via selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation in the treatment of lifelong PE refractory to behavioral and/or pharmacological treatment [126,127]. The role of surgery in the management of PE remains unclear until the results of further studies have been reported.

There is Level 4 evidence, i.e., no evidence, to suggest that selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation are effective treatments for PE. Surgery may be asso-

ciated with permanent loss of sexual function and is currently not recommended in the management of PE.

Psychological/Behavioral, Combined Medical and Psychological, and Educational Interventions

A wide range of psychological interventions have been developed for the treatment of PE. The majority of the psychotherapy treatment outcome studies are uncontrolled, unblinded trials; none meet the requirements for high level evidence-based studies. The literature is comprised of reports on small to moderately sized cohorts of participants who received different forms of psychological interventions with limited or no follow-up. In most studies, active treatment was not compared with placebo, control, or wait-list groups [128]. The most frequently used behavioral treatments are the squeeze or stop–start techniques [28,129]. Both of these therapies were designed to educate men to recognize midlevel ranges of excitement. Men develop skill at identifying mid-level excitement by a series of graduated exercises beginning with self-stimulation, moving on to partner hand stimulation, then to intercourse without movement, and then to stop/start thrusting. This process gradually leads to an increase in IELT and sexual confidence and self-esteem, although there are few controlled studies to support this claim.

Older uncontrolled studies on the squeeze technique report a failure rate of 2.2% immediately after therapy, and 2.7% at the 5-year follow-up [28]. These results have not been replicated; other studies have found success rates of between 60% and 90% [130]. In a recent study Carufel and Trudel demonstrated an eightfold increase in IELT among men treated with behavioral techniques compared with a wait-list control condition [17].

Psychological interventions are designed to achieve other outcomes beyond simply increasing the IELT. Targeted factors focus on the man, his partner and their relationship. In particular, they include (i) an increase in the man's confidence in this sexual performance, as well as his overall self-confidence; (ii) lowered performance anxiety; (iii) an increase in communication with the partner; and (iv) a resolution of interpersonal problems that may have precipitated or maintained the PE.

There is level 2b evidence regarding the efficacy of psychological/behavioral interventions in the treatment of PE.

Men with natural variable PE (irregular and inconsistent rapid ejaculation with a diminished sense of subjective control of ejaculation) should be educated and reassured. Men with premature-like ejaculatory dysfunction (those whose IELT are within the normal range but who are preoccupied by their ejaculatory control) may require a referral for psychotherapy. More research is necessary to better define the efficacy of reassurance, education, and psychotherapy with these provisional subtypes.

HCPs and mental health professionals have differing levels of interest and training in treating PE. In general all clinicians should be able to diagnose, offer support, and prescribe behavioral exercises. When the situation is complex and/or patients are not responsive to the initial intervention, clinicians should consider referring to a sexual health specialist.

Importance of Partners

Inclusion of the partner in the treatment process is an important but not a mandatory ingredient for treatment success [131]. Some patients may not understand why the clinician wishes to include the partner and some partners may be reluctant to join the patient in treatment. However, if partners are not involved in treatment, they may be resistant to changing the sexual interaction. A cooperative partner can enhance the man's self-confidence, skills, self-esteem, sense of masculinity, and more generally assist the man to develop ejaculatory control. This is, in turn, likely to lead to an improvement in the couple's sexual relationship, as well as the broader aspects of their relationship. There are no controlled studies on the impact of involving partners in treating PE. However, a review of treatment studies for ED demonstrated the important role of including a focus on interpersonal factors on treatment success [132].

Benefits of Combination Medical and Psychological Therapy

There are three studies reporting on combined pharmacological and behavioral treatment for PE [133–135] and one study reporting on consecutive treatment with pharmacotherapy followed by behavior therapy [136]. Each study reported on a different medication- sildenafil, citalopram, clomipramine, or paroxetine (in the consecutive study). Pharmacotherapy was given in conjunction with a behavioral treatment and compared with pharmacotherapy alone. In all three studies, combination

therapy was superior to pharmacotherapy alone on either IELT and/or the Chinese Index of Premature Ejaculation.

For ED, combined treatments have also been found to be more effective than either medical or psychological treatments alone [137–139]. Factors that are not addressable by pharmacotherapy alone can be attended to with a psychological approach include: (i) patient factors (performance anxiety, self-confidence); (ii) partner factors (partner sexual dysfunction); (iii) relationship factors (conflict, lack of communication); (iv) sexual factors in the relationship (sexual scripts, sexual satisfaction); and (v) contextual factors (life stressors).

Combining a medical and psychological approach may be especially useful in men with acquired PE where there is a clear psychosocial precipitant, or lifelong cases where the individual or couple's issues interfere in the medical treatment and success of therapy. Similarly, in men with PE and comorbid ED, combination therapy may also be helpful to manage the psychosocial aspects of these sexual dysfunctions. ***(LOE 2a)***

Role of Education and Coaching

Education on PE (or coaching) may also be useful to address aspects of PE that are not treated with medication [140–143]. Providing education on the prevalence of PE and general population IELT may help to dispel myths about PE. Additionally education may help men with PE who avoid sexual activity, are unwilling to discuss issues with their partner or limit their sexual repertoire because they fear sexual excitement. These educational strategies are designed to give the man the confidence to try the medical intervention, reduce performance anxiety, and modify his maladaptive sexual scripts. ***(LOE 5d)***

Lifelong PE. As lifelong PE is likely to have an organic etiology, a medical intervention with basic psycho-education is initially recommended [31,144]. However, if the PE has resulted in psychological and relationship concerns, graded levels of patient, and couple counselling, guidance, and/or relationship therapy may be a useful adjunct to the medical intervention. ***(LOE 1a)***

Acquired PE. It is recommended that HCPs utilize a combination medical and psychological approach where feasible. Men desire an immediate effect from therapy; therefore medical therapy and amelioration of associated disease factors such as ED will be extremely helpful.

Additionally, education on the nature of PE, helping men improve ejaculatory control with behavioral exercises, addressing restricted/narrow sexual behavioral patterns, and resolving interpersonal issues are likely to be of significant help to men with acquired PE. Once the man's self-confidence and sense of control have improved, it may then be possible to reduce or discontinue the medical intervention [18]. ***(LOE 5d)***

Special Patient Populations

PE and Comorbid ED

Recent data demonstrate that 30–50% of subjects with ED also experience PE [9,10]. Men with ED may require higher levels of manual stimulation to achieve an erection or intentionally "rush" intercourse to prevent early detumescence of erection, resulting in rapid ejaculation. This may be compounded by the presence of high levels of performance anxiety related to their ED, which serves to only worsen their prematurity.

There is evidence to suggest that a PDE5i alone or in combination with a SSRI may have a role in the management of acquired PE in men with comorbid ED [45,145,146]. The high correlation between PDE5i improved erectile function and increased IELTs indicates that reduced PE severity is caused by improved erectile function [145,146]

Although men with mild ED and PE do benefit from treatment with SSRIs, compared with men with no ED, their response to treatment is diminished [45]. Additionally, men with lifelong PE and mild ED were less responsive to treatment than men with acquired PE and mild ED [97].

There is Level 1A evidence to support the treatment of PE and comorbid ED with ED pharmacotherapy. There is Level 3C evidence to support the treatment of PE and comorbid ED with ED pharmacotherapy in combination with PE pharmacotherapy. Further evidence-based research is encouraged.

PE and Hyperthyroidism

Although many patients with hypothyroidism experience erectile dysfunction, few experience PE. Carani et al. found that 50% of hyperthyroid men had acquired PE. Treatment of the hyperthyroidism with thyroid hormone normalization using antithyroid drugs, radioactive iodine or thyroidectomy resulted in normalization of ejaculatory function in 35% of these men [53]. However, the Committee does not recommend routine TSH screening in men with acquired PE.

PE and Chronic Prostatitis

Although antibiotic treatment of chronic prostatitis improves lower urinary tract symptoms (LUTS), there is little published data to suggest a parallel improvement in PE and other sexual dysfunction symptoms [147–149]. Although physical and microbiological examination of the prostate in men with painful ejaculation or LUTS is mandatory, there is insufficient evidence to support routine screening of men with PE for chronic prostatitis.

Outcome

Across all treatments, including daily and as-needed dosing schedules patient's IELT may be expected to increase between three- to eightfold compared with baseline IELT. Similarly, patient's perceived control (self-efficacy) of their ejaculatory timing was significantly improved with treatment. From the patient's perspective, perceived ejaculatory control was a more important outcome variable than IELT alone [150].

Treatment outcome can be addressed in one simple, brief, and validated question known as the Clinical Global Impression of Change (CGIC) [151]. It asks patients, "Compared to before starting treatment, would you describe your PE problem as: much worse, worse, slightly worse, no change, slightly better, better, or much better?" ***(LOE 1b)***

In randomized, placebo-controlled, double-blind trials of dapoxetine for each category of improvement on the CGIC, the magnitude of IELT prolongation increased in concert with the CGIC rating. Additionally, significant positive correlations were noted between CGIC ratings and ejaculatory control and sexual satisfaction and inverse correlation were noted with sexual distress. Control accounted for the greatest proportion of the variance of the CGIC.

Role of the Primary Care Clinician (PCP)

Primary care providers are usually the first line of contact for a patient with the health care system including the diagnosis and treatment of sexual problems. This role includes: (i) initial recognition and evaluation of any undiagnosed sign, symptom, or health concern (the "undifferentiated" patient); (ii) health promotion including disease prevention, health maintenance, counseling, patient education, chronic illness management, and patient advocacy; and (iii) coordination of care promoting effective communication with patients and encouraging the patient to be a partner in health [152]. This model of care is not limited by problem origin, organ system, or diagnosis.

Primary care clinicians are the ideal group to assist the patient with sexual difficulties for several reasons including: (i) the value of the longitudinal and personal relationships with patients in discussing and resolving sexual problems; (ii) the multifactorial issues around sexual problems that can be appropriately evaluated by a generalist clinician; and; (iii) the long-term follow-up routine in primary care is well-suited to being certain that a sexual dysfunction is resolved. The main obligation of the PCP is to recognize PE and make the patient feel comfortable about getting help. Initial work-up and treatment can be planned by the PCP who has good communication skills about sexual activity and who is knowledgeable about first-line treatments. Urologists can be helpful in difficult or complex situations. A mental health professional with experience in sexual problems collaboratively with the clinician increases the chances of therapeutic success by: (i) resolving the sexual difficulty; (ii) teasing out important history; (iii) educating the patient and partner; (iv) suggesting sexual enhancement techniques; and (v) helping the couple resolve individual as well as relationship problems.

Help from a sexual health specialist may be appropriate at varying intervals when managing a man with PE. The major factors in determining when a consultation is needed include (i) the primary care clinician's comfort in discussing and managing treatment options; (ii) the depth of the psychosocial and sexual issues involved; and (iii) the success or failure of the initial intervention efforts. Specific instances in which subspecialty assistance is often useful include (i) treatment failure; (ii) anatomic or complex hormonal issues; (iii) complex issues around sex and/or partnerships; (iv) severe psychological problems; or (v) anytime the treating physician feels that help is needed.

The management algorithm "**ALLOW**" an outgrowth of the PLISSIT model (permission, limited information, specific suggestions and intensive therapy) [153] can help PCPs talk with their patients about sexual health problems and refer patients when appropriate [154]. The physician begins by "**A**sking" about a patient's sexual life and "**L**egitimizes" the importance and potential impact of sexual problems to the patient. The

Topic	Recommendation	Level of Evidence
Definition of Lifelong PE	A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy	1a
Definition of Acquired PE	There are insufficient published objective data to propose a new evidence-based definition of acquired PE, although it believed the proposed criterion for lifelong PE might be applied to acquired PE as well	5d
Prevalence of PE	Statistical analysis of population-based data indicate that 1%-3% of men ejaculate in under 1 minute.	3d
Average Ejaculatory Latency	In multinational studies the median IELT is 5.4 minutes and decreased significantly with age. Median IELT may differ between countries.	2a
Quality of Life	Negative effects on quality of life and interpersonal difficulty related to their PE have been consistently been reported by men and their partners.	1a-3a
Etiology	The etiology of premature ejaculation is not known. To date, no biological factor has been shown to be causative in the majority of men with PE.	
Assessment	The committee agreed that there was inadequate evidence to recommend screening or case-finding for PE, either in a general population or in any sub-population. However, it is recommended that men with ED be screened for PE.	5d
	It is recommended that clinicians utilize the screening questions in Table 2 and that clinicians take a medical and psychosocial history.	5d
	Since patient self-report is the determining factor in treatment seeking and satisfaction, it has been recommended that self-estimation by the patient and partner of ejaculatory latency be routinely assessed in clinical practice when PE is present.	2b
	The PEP or IPE are currently the preferred questionnaire measures for assessing PE, particularly in the context of monitoring responsiveness to treatment.	2b
	For lifelong PE, a physical examination is highly advisable but not mandatory and should be conducted in most if not all patients.	5d
	For acquired PE a targeted physical examination is mandatory to assess for associated/causal diseases such as ED, thyroid dysfunction, or prostatitis.	5d
Treatment	There is robust evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of lifelong and acquired PE. It has been approved in some countries.	1a
	There is robust evidence to support the efficacy and safety of off-label daily dosing of the SSRIs paroxetine sertraline, citalopram, fluoxetine, and the serotonergic tricyclic, clomipramine, and off-label on-demand dosing of clomipramine and paroxetine, for the treatment of lifelong and acquired PE.	1a
	There is good evidence to support the efficacy and safety of off-label on-demand topical anaesthetics in the treatment of lifelong PE.	1b
	There is contradictory evidence to support the efficacy and safety of off-label on-demand or daily dosing of PDE-5 inhibitors in the treatment of lifelong PE in men with normal erectile function. Treatment of lifelong PE with PDE-5 inhibitors in men with normal erectile function is not recommended and further evidence-based research is encouraged to further understand conflicting data.	4d
	Treatment of PE with Tramadol cannot be recommended.	2d
	There is modest evidence supporting the efficacy of psychological/behavioral interventions in the treatment of PE.	2b
	Combining pharmacological and psychological/behavioral treatments may be especially useful in men with acquired premature ejaculation where there is a clear psychosocial precipitant or lifelong cases where the individual or couple's responses to PE are likely to interfere in the medical treatment and ultimate success of therapy.	2a
	There is reliable evidence to support the treatment of PE and co-morbid ED with ED pharmacotherapy. There is level 3c evidence to support the treatment of PE and co-morbid ED with ED pharmacotherapy in combination with PE pharmacotherapy.	1a
	Selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation may be associated with permanent loss of sexual function and is not recommended in the management of PE.	4
Outcome	Treatment outcome can be addressed in one simple, brief and validated question known as the Clinical Global Impression of Change (CGIC). It asks patients, "Compared to before starting treatment, would you describe your premature ejaculation problem as: much worse, worse, slightly worse, no change, slightly better, better, or much better?"	1b

Figure 2 Summary of premature ejaculation (PE) guideline recommendations.

physician then considers his/her "**L**imitations" with regard to managing the sexual dysfunction, and may refer the patient to a sexual health specialist for further evaluation and management. Conversely, if the physician feels comfortable managing the patient's issue(s), he/she then "**O**pens: up the issue(s) for further discussion," and the physician and the patient "**W**ork together to develop a management plan." This methodical approach to "allowing" the patient to discuss sexual issues can be accomplished in as brief or as long a time as the physician has available.

When a clinical situation is encountered in which the primary care clinician needs assistance

in management, two options are available. Patients can be sent to a sexual health specialist for a "consultation." This is a request to answer a specific question with the intention that management will be advanced under the primary care clinician considering the added input. The second option is "referring" the patient to another clinician, usually a sexual health specialist to move further with management. In these situations, a summary of the reason for referral, appropriate history, and related diagnostic studies should accompany the patient. The sexual health specialist will then appropriately advance the management keeping the primary care clinician advised of progress. In a "referral" the care for the referred patient is usually transferred to the sexual health specialist. Communication can be enhanced by the primary care clinician by specifically informing the sexual health specialist about the level of involvement requested [155].

Co-management by the less experienced primary care clinician along with an appropriate sexual health specialist is an excellent way to manage the patient's issues and to increase the primary care clinician's understanding of PE. Good communication between clinicians can improve patient outcome and understanding of planned treatments and monitoring measures. Co-management can be optimized by a clear understanding between the primary care clinician and the sexual health specialist about who will do what. This kind of communication can be ensured by creating "referral agreements" in which a specific referral guideline is used and the responsibilities and activities of each clinician are clearly spelled out [156].

Conclusion

These guidelines have been carefully promulgated by an interdisciplinary international panel of recognized experts in the area of PE with the goal of constructing clearly worded, practical, evidenced-based recommendations for the diagnosis and treatment of PE for family practice clinicians as well as sexual medicine experts. Recognizing that all evidence is not created equal the Committee reviewed and debated the research literature to arrive at its grading of their recommendations according to the Oxford Centre of Evidence-Based Medicine rankings.

Figure 2 lists all the relevant recommendation of the PE Guidelines Committee. These Guidelines affirm the ISSM definition of PE and suggest that the prevalence is considerably lower than previously thought. Evidence-based data regarding biological and psychological etiology of PE are presented, as is population-based statistics on normal ejaculatory latency. Brief assessment procedures are delineated and validated diagnostic and treatment questionnaires are reviewed. Finally, the best practices treatment recommendations are presented to guide clinicians, both familiar and unfamiliar with PE, in facilitating treatment of their patients.

Development of guidelines is an evolutionary process that continually reviews data and incorporates the best new research. We expect that ongoing research will lead to a more complete understanding of the pathophysiology as well as new efficacious and safe treatments for this sexual dysfunction. Therefore, it is strongly recommended that these guidelines be re-evaluated and updated by the ISSM every 4 years.

Finally, it is important to keep in mind that PE causes significant personal and interpersonal distress to the man, his partner and the couple. We are hopeful that these guidelines will assist clinicians in accurately diagnosing and managing their patients who present with complaints of PE.

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Appendix 1

Index of Premature Ejaculation (IPE)

These questions ask about the effects your sexual problems have had on your sex life over the past four weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

— Sexual intercourse is defined as vaginal penetration (you entered your partner).
— Ejaculation: the ejection of semen from the penis.
— Control: ejaculating when you are ready.
— Distress: meaning how frustrated, disappointed, or bothered you are by your premature ejaculation

Mark only one box per question.

1) *Over the past four weeks*, when you had sexual intercourse, how often did you have control over when you ejaculated?
   ☐ No sexual intercourse (not applicable)
   ☐ Almost always or always
   ☐ More than half the time
   ☐ About half the time
   ☐ Less than half the time
   ☐ Almost never or never
2) *Over the past four weeks*, when you had sexual intercourse, how much confidence did you have over when you ejaculated?
   ☐ No sexual intercourse (not applicable)
   ☐ High confidence
   ☐ Moderately high confidence
   ☐ Neither high nor low confidence
   ☐ Moderately low confidence
   ☐ Low confidence
3) *Over the past four weeks*, when you had sexual intercourse, how often was it satisfactory for you?
   ☐ No sexual intercourse (not applicable)
   ☐ Almost always or always
   ☐ More than half the time
   ☐ About half the time
   ☐ Less than half the time
   ☐ Almost never or never
4) *Over the past four weeks*, when you had sexual intercourse, how satisfied were you with your sense of control over when you ejaculated?
   ☐ No sexual intercourse (not applicable)
   ☐ Very satisfied
   ☐ Somewhat satisfied
   ☐ Neither satisfied nor dissatisfied
   ☐ Somewhat dissatisfied
   ☐ Very dissatisfied
5) *Over the past four weeks*, when you had sexual intercourse, how satisfied were you with the length of intercourse before ejaculation?
   ☐ No sexual intercourse (not applicable)
   ☐ Very satisfied
   ☐ Somewhat satisfied
   ☐ Neither satisfied nor dissatisfied
   ☐ Somewhat dissatisfied
   ☐ Very dissatisfied
6) *Over the past four weeks*, how satisfied have you been with your sex life overall?
   ☐ No sexual intercourse (not applicable)
   ☐ Very satisfied
   ☐ Somewhat satisfied
   ☐ Neither satisfied nor dissatisfied
   ☐ Somewhat dissatisfied
   ☐ Very dissatisfied
7) *Over the past four weeks*, how satisfied have you been with your sexual relationship with your partner?
   ☐ No sexual intercourse (not applicable)
   ☐ Very satisfied

☐ Somewhat satisfied
☐ Neither satisfied nor dissatisfied
☐ Somewhat dissatisfied
☐ Very dissatisfied

8) *Over the past four weeks*, how much pleasure has sexual intercourse given you?
☐ No sexual intercourse (not applicable)
☐ Nigh pleasure
☐ Moderate high pleasure
☐ Neither high nor low pleasure
☐ Moderately low pleasure
☐ Low pleasure

9) *Over the past four weeks*, how distressed (frustrated) were you by how long you lasted before you ejaculated?
☐ No sexual intercourse (not applicable)
☐ Extremely distressed
☐ Very distressed
☐ Moderately distressed
☐ Slightly distressed
☐ Not at all distressed

10) *Over the past four weeks*, how distressed (frustrated) have you been about your control over ejaculation?
☐ No sexual intercourse (not applicable)
☐ Extremely distressed
☐ Very distressed
☐ Moderately distressed
☐ Slightly distressed
☐ Not at all distressed

Premature Ejaculation Profile (PEP Items)

Over the past month, was your control over ejaculation during sexual intercourse:
☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good

Over the past month, was your satisfaction with sexual intercourse:
☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good

Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse?
☐ Not at all ☐ A little ☐ Moderately ☐ Quite a bit ☐ Extremely

Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner?
☐ Not at all ☐ A little ☐ Moderately ☐ Quite a bit ☐ Extremely

PE Diagnostic Tool (PEDT)

Patient Instructions

This next questionnaire to help identify men who may have a problem with ejaculating too soon during sexual activity. Even if you do not have difficulties, please answer all the questions:

Please mark X in the box that best represented your answer for each of the questions below.

Please mark only one box for each question.

While your experiences may change from time to time, please report your general experiences with intercourse.

Definition: Ejaculation here refers to ejaculation (release of semen) after penetration (when your penis enters your partner)

(1) How difficult is it for you to delay ejaculation?	Not difficult at all ☐ 0	Somewhat difficult ☐ 1	Moderately difficult ☐ 2	Very difficult ☐ 3	Extremely difficult ☐ 4
	Almost never or never 0%	Less than half the time 25%	About half the time 50%	More than half the time 75%	Almost always or always 100%
(2) Do you ejaculate before you wish?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
(3) Do you ejaculate with very little stimulation?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
	Not at all	Slightly	Moderately	Very	Extremely
(4) Do you feel frustrated because of ejaculating before you want to?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
(5) How concerned are you that your time to ejaculation leaves your partner sexually unfulfilled?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4