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CONSENSUS STATEMENT

Management of premature ejaculation: a clinical guideline from the Italian Society of Andrology and Sexual Medicine (SIAMS)

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Abstract

Premature ejaculation (PE) is the most prevalent male sexual dysfunction, and the most recently defined. PE is often mistakenly considered a purely psychosexological symptom by patients: the lacking awareness in regards to the pathophysiology and treatments often lead to resignation from the patients' side, making PE the most underdiagnosed sexual complaint. However, an ever-growing body of evidence supporting several organic factors has been developed in the last decades and several definitions have been suggested to encompass all defining features of PE. In the present document by the Italian Society of Andrology and Sexual Medicine (SIAMS), we propose 33 recommendations concerning the definition, pathophysiology, treatment and management of PE aimed to improve patient care. These evidence-based clinical guidelines provide the necessary up-to-date guidance in the context of PE secondary to organic and psychosexological conditions, such as prostate inflammation, endocrine disorders, and other sexual dysfunctions, and suggest how to associate pharmacotherapies and cognitive-behavioral therapy in a couple-centered approach. New therapeutic options, as well as combination and off-label treatments, are also described.

Introduction

The inclusion of premature ejaculation (PE) in the radar of science and medicine is relatively recent and still debated: the perception that PE is a psychological or, at the best, sexological symptom, almost exclusively due to behavioral-relational derangements is indeed well-rooted [1–3]. Patients and media are only partially aware of the solid body of evidence produced in the context of diagnosis, pathogenesis and treatment of PE.

Being one of the "youngest" topics for sexual medicine, many aspects of PE still need to be clarified on the basis of adequate evidence. The aim of this clinical guideline is to examine the current findings able to impact on the clinical management of the patient and the couple with PE.

Methods

The Italian Society of Andrology and Sexual Medicine (SIAMS), one of the leading national scientific societies in the related fields, commissioned an expert task force to provide an updated guideline on PE. Following scrutiny and discussion of the best evidence from published literature

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available in PubMed, the authors generated a series of consensus recommendations according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [4]. The strength of recommendations and the quality of the evidence are expressed in four levels: ⊕◯◯◯ denotes "very low-quality evidence", ⊕⊕◯◯ "low quality", ⊕⊕⊕◯ "moderate quality" and ⊕⊕⊕⊕ "high quality". In addition, the number '1' denotes a strong recommendation and is expressed with the phrase 'we recommend', whereas the number '2' denotes a weaker recommendation and it is expressed with the phrase 'we suggest'. The strength also reflects the confidence that authors have that patients and couples with PE who receive recommended care will be better off.

According to SIAMS rulings, these Guidelines have been prepared by a team of experts on the topic coordinated by the senior author and two members of the Guideline Committee of the Society, then sent to the SIAMS Executive Committee and to the Directors of all SIAMS Excellence Centres for revisions and/or approval. Guidelines have then been announced by mail and published for two weeks on the Society's website, siams.info, so that all SIAMS Members could provide further comments and suggest additional minor revisions. Following this last step, the present manuscript has been submitted to the Journal of Endocrinological Investigation for the normal process of international peer reviewing.

Definitions of premature ejaculation

Recommendation #1. We recommend using the International Society of Sexual Medicine (ISSM) PE definitions for experimental and scientific purposes (1 ⊕⊕⊕⊕).

Recommendation #2. We suggest to define PE, for clinical purposes, as: (i) a persistent and recurrent subjective perception of loss of control over the mechanism of ejaculation in presence of proper erotic stimuli; (ii) a subjective, PE-related, distress induced in the patient and in the partner; (iii) a short intravaginal ejaculatory latency time (IELT), from penetration to ejaculation, subjectively perceived and partner-perceived IELT, (PIELT, and PPIELT, respectively) or objectively (stopwatch IELT, SIELT) measured as being lower than 180 s. (1 ⊕⊕⊕⊕).

Note that the order (i), (ii), and (iii) here mentioned reflect the clinical importance of each aspect of the tridimensional definition of PE.

Recommendation #3. We suggest that, in the real-life clinical practice, the same definition could be applied to other sexual stimuli, such as masturbation (MELT), or oral (OELT) and anal (AELT) intercourses, as well to non-heterosexual settings [5] (2 ⊕◯◯◯).

Recommendation #4. We suggest recording the Patients Reported Outcomes (PROs), as resulting from psychometric tests, and when possible, SIELT, PIELT, PPIELT, MELT, OELT, and AELT both during diagnosis and therapeutic follow-up (2 ⊕◯◯◯).

Evidence

The current most widely used definitions are from the International Society of Sexual Medicine (ISSM [6]), from the Diagnostic and Statistical Manual of Mental Disorders, in its fifth revision (DSM-5 [7]), and, more recently, from the 11th Revision of the International classification of diseases for mortality and morbidity statistics (ICD-11) [8]. Table 1 summarize the similarities and differences among the three definitions.

In 2013, DSM defined PE as "a male sexual dysfunction characterized by a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 min following vaginal penetration and before the individual wishes it. The symptoms must have been present for at least 6 months and experienced on almost all (> 75–100%) occasions of sexual activity (situational or generalized contexts). The symptoms cause clinically significant distress in the individual and the sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress and not attributable to substance/medication or another medical condition" [7].

More recently, the ISSM defined PE as a "male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration from the first sexual experience (lifelong premature ejaculation), OR a clinically significant reduction in latency time, often to about 3 min or less (acquired premature ejaculation); 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" [6].

Finally, in 2018, the ICD-11 [8] defines male early ejaculation as characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation occurs episodically or persistently over a period of at least several months and is associated with clinically significant distress. The ICD-11 identifies five categories: (1) lifelong, generalized; (2) lifelong, situational; (3) acquired, generalized; (4) acquired, situational; (5) unspecified (as a residual category).

In respect to cut-offs, the past definitions of PE (including the ICD-10) accounted for the category of severe objective PE, when occurring before penetration

Table 1 Definitions of premature ejaculation

	DSM-V [7]	ISSM [6]	ICD-11 [8]
Definition of ejaculation	Early	Premature	Early
Life-long	(✓)[a]	✓	✓
Acquired	(✓)[a]	✓	✓
Subjective/other	–	–	✓
Generalized	✓	✓	✓
Situational[b]	✓	✓	✓
Onset	6 months	–	Several months
Frequency	> 75%	Always or nearly always	Episodically or persistently
IELT	1 min	1 min for generalized 3 min for acquired	–
Associated distress	✓	✓	✓
Control	Ejaculation before the individual wishes it	Inability to delay ejaculation	No or little perceived control over ejaculation
Trigger	Vaginal penetration	Vaginal penetration	Vaginal penetration or other relevant sexual stimulation
Exclusion criteria	Not better explained by a nonsexual mental disorder	–	–

IELT Intravaginal ejaculation latency time

[a]Not in the definition, but encouraged

[b]Situational: in some circumstances, with some partners, or in response to some stimuli, but not in other situations

or with an IELT ≤ 15 s (as opposed to moderate, with an IELT ≤ 1 min; or mild, with an IELT ≤ 2 min). Then, the ISSM, based on epidemiological studies set up a different criterion of < 3 min for the acquired PE. Finally, the most recent ICD-11 abolished cut-offs while introducing the category of "subjective or relational PE" when the loss of voluntary control is experienced with distress by the male or both partners, but the SIELTs is 'normal' (up to around 6 min) [9].

All current definitions recognize that PE is a multifaceted sexual dysfunction, which could be present from the beginning of sexual life (lifelong, LPE) or after a normal ejaculatory control (acquired, APE).

Pathophysiology of premature ejaculation

Several pathological conditions have been associated with PE [5, 10]. Although all these conditions should be considered as possible causes of APE, they can also worsen ejaculatory control in patients complaining of LPE. The most consistently reported associations are hyperthyroidism (HT) and prostate inflammation. Some evidence indicates an association between PE and other conditions, such as varicocele, high testosterone (*T*) and low prolactin (PRL) levels, as well as poorly controlled type 1 diabetes mellitus (T1DM).

Genetics

Recommendation #5. We suggest against the use of non-evidence-based terminologies, such as "innate" or "constitutional" PE, to refer to genetics or penile hypersensitivity (2⊕⊕⊕⊕).

Evidence

The neurobiological nature of PE has long been hypothesized: the clear role of serotonin in centrally limiting the ejaculatory control has been largely demonstrated in animals [11] and inferred in humans from the delayed ejaculation occurring as a typical sexual side-effect of serotoninergic antidepressants. Moreover, some findings in rodents demonstrated a role for genes encoding for the serotoninergic pathway in modulating the ejaculatory control [12]. Despite initial enthusiasm, no clear-cut data have been produced in humans [13].

Similarly, evidence for a role of an innate, genetically determined, or acquired penile hypersensitivity in some cases of PE appears poor and controversial, suggesting that penile sensitive threshold determination is not recommended in the diagnostic workup of PE [14].

Remarks

While no study has proven (nor attempted to investigate) an increase in type-5 phosphodiesterase (PDE5) expression in patients with erectile dysfunction, the hypothesis that selected forms of PE, such as LPE, may be related to a genetic pathogenesis has often been reported in literature, but with limited evidence in support [15, 16]. This was also due to the apodictic perception that a lifelong symptom should have a genetic nature, as well to the exclusive initial interest in LPE, which appeared as the only or at least the most epidemiologically frequent form of PE.

Hyperthyroidism

Recommendation #6. We suggest thyroid-stimulating hormone (TSH) evaluation in all subjects with APE with symptoms of possible thyroid hyperfunction (2⊕⊕◯◯).

Recommendation #7. We suggest treating underlying clinical or subclinical hyperthyroidism to improve PE before any symptomatic treatment (2⊕◯◯◯).

Evidence

Table 2 summarizes the available studies investigating the association between HT and APE. Two types of studies have been performed: (i) investigating the prevalence of HT in subjects with PE [17–20] and (ii) investigating the prevalence of PE in subjects with HT [21, 22]. The prevalence of HT in PE subjects ranged from 2.2 to 15%. In two [17, 19] out of three studies [20], where a control population was investigated, HT was more prevalent in PE subjects than in control [17, 19, 20]. Note that the experimental setting of Waldinger et al. 2005 [20] was limited to the surprising number of > 600 patients with LPE (no APE) and note that lifelong HT is virtually not existing.

Two studies [21, 22] investigated the effect of treating HT on IELT and found that treatment – even in subclinical forms—almost doubles ejaculatory time, therefore strengthening the hypothesis that HT could have a causative role in the pathogenesis of PE.

Remarks

It is important to recognize that available evidence is only derived from observational studies and open label interventional trial, as no Randomized Clinical Trial (RCT) is currently available. In addition, although HT can be associated with APE, the prevalence of HT in overall PE population is quite modest. Hence, TSH measurement should be indicated in the presence of specific symptoms or signs or in patients with acquired forms of PE.

Table 2 Studies investigating the association between hyperthyroidism and premature ejaculation

Source	Type of patient population	Number/mean age (years) patient population	Prevalence of hyperthyroidism in patient population number (%)	Mean IELT (sec) before hyperthyroidism treatment	Mean IELT (sec) after hyperthyroidism treatment	Type of control population	Number/mean age (years) control population	Prevalence of hyperthyroidism in control population number (%)
Waldinger et al. 2005 [20]	Lifelong PE	NR	14/620 (2.2)	NR	NR	General Dutch population	NR	16/620 (2.5%)
Carani et al. 2005 [21]	Men with hyperthyroidism	34/43.2	34/34 (100)	124 ± 30	240 ± 30	NR	NR	NR
Cihan et al. 2009 [22]	Men with hyperthyroidism	43/48.0	43/43 (100)	75.8 ± 99.3	123.2 ± 96.4	NR	NR	NR
Ozturk et al.2012 [19]	Outpatients with PE	107/45.1	14/107(8.4)	NR	NR	Healthy men	94/48.1	4/94 (4.25)
Corona et al. 2012 [17]	Outpatients with PE	855/51.3	Lifelong PE 17/322 (5.3%) Acquired PE 13/530 (2.5%)	NR	NR	EMAS study florentine sample	433/60.1	3/433 (0.5%)
Culha et al. 2019 [18]	Outpatients with PE	53/42.41	8/53 (15.09)	27.25 ± 22.34	NR	NR	NR	NR

PE premature ejaculation, *IELT* Intravaginal ejaculatory latency time

Prostatitis/chronic pelvic pain syndrome

Recommendation #8. We suggest excluding chronic prostatitis/chronic pelvic pain syndrome in all subjects complaining of PE (2⊕⊕◯◯).

Recommendation #9. We suggest a trial with specific antibiotic in patients with PE associated with bacterial prostatitis before any symptomatic treatment of PE (2⊕◯◯◯).

Evidence

Despite the well-known pivotal role of prostate in the mechanism of ejaculation, the individuation of subacute/paucisymptomatic/chronic prostatic inflammations and infections as a possible risk factor of PE was characterized by an initial skepticism from the urological community. Prevalence of PE has been esteemed up to the 77% in patients with male accessory gland inflammation (MAGI) [23–26], being higher in those positive for ultrasound signs [27, 28]. A recent meta-analysis investigated the prevalence of PE in subjects with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [29]. Thirteen observational studies involving 6819 subjects were scrutinized. Pooled effect size was 0.40 (95% CI 0.3–0.5, $I^2 = 98–9\%$, $p < 0.001$) suggesting a 40% increase in the risk of having PE in subjects with CP/CPPS. However, studies included in the meta-analysis were often not excellent in quality, relying on different definitions and instruments for investigating both CP/CPPS and PE. Subjects with PE often show symptoms and signs compatible with CP/CPPS, as confirmed by many different studies [18, 25, 26].

A lower number of studies investigated the effect of treating CP/CPPS on IELT in PE subjects [30–32]. This was most probably due to the heterogenic nature of CP/CPPS that is supported by a demonstrable infection only in a minority of cases. Interestingly, in such cases, antibiotic treatment improved IELT and other PE parameters [30–32].

Remarks

The available evidence was derived mainly from observational studies with obvious methodological limitations, as previously stated. Hence, due to the observational nature of the data, no final causal inference can be drawn. Although the effect of antibiotic treatment on IELT suggests that prostatitis is an organic risk factor for PE, the cohorts investigated were frequently small and interventions were neither randomized nor controlled. However, no other organic risk factor for PE has been studied more consistently, extensively or on a greater number of patients than the inflammation of the prostate.

Other factors

Recommendation #10. Although preliminary evidence suggests an association between PE and varicocele, uncontrolled T1DM, high testosterone and/or low prolactin levels, no specific recommendation can be released at the present time.

Evidence

An association between PE and other conditions, such as varicocele, low PRL and high T levels has been suggested in some studies (see for review in [17, 33, 34]). A single study found an association between PE severity and poor glycemic control (hypoglycemic domain) in T1DM [35].

Remarks

Due to the low quality of the available evidence or its unconfirmed nature, no specific recommendations on these issues can be provided.

Other sexual comorbidities

As many other sexual symptoms and syndromes, PE rarely occurs alone and without other sexual comorbidities. Addressing them is an essential step in the successful management of PE.

Erectile dysfunction

Recommendation #11. We recommend investigating the presence of other sexual comorbidities, particularly erectile dysfunction (ED), in all patients with PE. (1 ⊕⊕⊕◯).

Recommendation #12. We recommend treating ED before PE in patients with both symptoms. (1⊕◯◯◯).

Recommendation #13. We suggest to evaluate clinically and psychometrically PE-related female sexual dysfunctions (FSDs) (2⊕⊕⊕◯).

Evidence

There is solid evidence suggesting a "vicious cycle" linking erectile dysfunction (ED) and PE, with the two symptoms co-occurring in the same subjects in up to 50% of cases [36–38]. The exact mechanisms have not been fully elucidated, although it is generally assumed that some PE patients may develop ED or subclinical ED (SED) [39] while trying to reduce their excitement, and ED/SED patients may develop PE as a consequence of overexcitement [36, 37]. Furthermore, each of the two symptoms can develop as an "adaptation" mechanism of the other: ED is the result of

performance-related anxiety, whereas PE is the biological response to facilitate orgasm in the presence of impaired erectile function, or a consequence of a lack of confidence in the ability to maintain a reliable erection [36, 37, 40].

The benefits of treating ED/SED before PE (or at least together) have not been proven yet. However, they appear logical, and for this reason all other guidelines give the same suggestion. All the symptomatic treatments of PE, either psychosexological/behavioral or pharmacological, aim to reduce the excitement. This may negatively affect the ability of the patient to obtain and maintain the erection and is to be considered a major reason for drop-out in the PE management [41].

Remarks

As ED and PE can co-exist in the same patient in the proposed taxonomic entity of loss of control on erection and on ejaculation (LCEE) [42], both symptoms should be investigated and treated appropriately. In these regards, while the evidence in support is relatively weak, existing guidelines [43, 44] suggest treating ED first, and then, if still necessary, PE. Type 5 phosphodiesterase (PDE5) inhibitors should be considered the first-line treatment of choice [45]. Although not studied yet, the comorbidity of PE with hypoactive sexual desire disorder or, on the contrary, hypersexuality, could be clinically inferred. Note that the former could be caused by PE while the latter could be a risk factor of PE [46, 47].

Finally, we suggest evaluation of the couple as a whole, also using dedicated and validated psychometric tools such as the Female Sexual Distress Scale-Revised-Premature Ejaculation questionnaire [48, 49] and the male and female versions of the Orgasmometer scale [50, 51].

Infertility

Recommendation #14. We suggest investigating sexual function as well as psychological health status of male patients of infertile couples. (2⊕⊕◯◯).

Evidence

It has been proven that infertility can be a major risk factor for PE and ED [52–54]. In these regards, providing adequate treatment and support for infertility can improve sexual symptoms, as well as the psychological and general health status [52, 53].

Remarks

Among the many studies investigating sexual dysfunction in infertile couples, only a minority of studies investigated the prevalence of PE, using both the Premature Ejaculation Diagnostic Tool (PEDT) and not validated questionnaires. Therefore, while it is advisable to investigate sexual dysfunction in infertile patients, the heterogeneity present in such studies does not allow for stronger recommendation.

Diagnosis

Recommendation #15. We recommend using, for PE diagnosis, PROs from validated questionnaires, as well PIELT and PPIELT (1⊕⊕⊕◯).

Recommendation #16. We recommend collecting medical and psycho-sexological history, also with validated questionnaires and performing targeted physical examination in patients complaining for PE (1⊕⊕⊕◯).

Recommendation #17. We suggest to classify the patient with PE according to the following characteristics: (i) clinical/subclinical; (ii) lifelong/acquired; (iii) absolute/relational; (iv) severity (2⊕◯◯◯).

Evidence

The collection of a complete anamnesis and psycho-sexological history with discussion on sexual orientation, and sexual habits, such as the frequency of sexual intercourse and self-masturbation, is of paramount importance for PE diagnosis (Table 3). As claimed by the ISSM, recommended and optional questions are needed for diagnosis, LPE and APE differentiation, and the exclusion of other sexual disorders in both members of the couple (Table 1) [55]. PE diagnosis has been established in case of IELT < 1 min or 3 min for lifelong or acquired forms, respectively [6]. However, as objective IELT assessment using stopwatch measures (SIELT) has been considered disruptive of sexual spontaneity [56], self-estimated (PIELT) or partner-estimated (PPIELT) IELT can be accepted for their good correlation with stopwatch latency [55, 57]. Accordingly, the patient's report is usually reliable as the large majority of patients referring for PE receive a confirmatory diagnosis [58]. More objective assessment measures include extensively validated questionnaires as the Premature Ejaculation Profile (PEP), the Index of Premature Ejaculation (IPE) and the PEDT [59–61]. Negative effects of PE on orgasmic function have also been identified using the Orgasmometer [50]. These questionnaires are dealing with the PROs, which are to be considered extremely important for PE diagnosis as well for the assessment of the severity of the symptom.

Remarks

The use of other questionnaires in the diagnosis of PE to assess possible sexual comorbidities, such as the International Index of Erectile Function (IIEF), is strongly

Table 3 Questions needed for the establishment of PE diagnosis [55]. PE: premature ejaculation

	Items	Questions
Recommended questions	PE diagnosis	What is the time between penetration and ejaculation? 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?
	Assessment of erectile function	Is your erection hard enough to penetrate? Do you have difficulty in managing your erection until you ejaculate during intercourse? Do you ever rush intercourse to prevent loss of your erection?
	Assessment of 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?
	Previous treatment	Have you received any treatment for your premature ejaculation previously?
	Quality of life	Do you avoid sexual intercourse because of embarrassment? Do you feel anxious, depressed or embarrassed because of your premature ejaculation?

encouraged, at least in their abridged form [62]. The use of the male Orgasmometer is also encouraged, as an easy-to-perform tool to assess whether the presence of PE is negatively affecting the orgasmic function of the patient [50].

Psychometry, psychology, psychotherapy

Recommendation #18. We recommend using standardized, validated psychometric tools for the assessment of PE and of the bother related to PE, for both the patient and the partner (1 ⊕⊕⊕◯).

Recommendation #19. We suggest to carefully counsel all patients with PE and, when possible, to associate pharmacotherapies and cognitive-behavioral therapy, actively involving the partner in the treatment process (2 ⊕◯◯◯).

Evidence

The identikit of the PE-patient comprises, among the main characteristic psychopathological traits, the presence of a marked anxiety trait/dysfunction [63]. Nowadays, although interesting evidences remain for the presence of a marked anxiety in the patients suffering from PE [63], representing either a risk factor or a consequence of PE [64], other etiological hypotheses, in the direction of specific organic variables, have been investigated and found [34].

Some recent findings suggest that behaviors and attitudes may influence the ability to control ejaculation [1, 65]: more positive findings are needed, however, before deserving to be strongly recommended in the psychological assessment of PE patients.

Remarks

The psychological impact of PE on the patient, the partner, and more in general on the couple has been clearly documented [66, 67]. Patients suffering from PE experience high levels of distress, often due to the impossibility to give to the partner sexual pleasure. On the other hand, the partner of the patient with PE may experience high levels of sexual distress, and the emotions of anger and frustration may bring to interpersonal difficulties, lack of sexual confidence, and, in about 20% of cases, also to relationship breakup [68]. Specifically, relationship breakups are more present in women with higher sexual distress and in those paying more attention to ejaculatory control. This kind of couple has been defined as "asynchronous" [69]. The asynchronicity is related to the fact that the man ejaculates prematurely in respect to the partner's sexual physiology. Similar findings have been evidenced also in homosexual couples, where, at the same manner as for heterosexual couples, PE impacts negatively on the relationship quality [70].

This evidence supports the utility of a couple sexual assessment and therapy, rather than of a single patient-centered one, in keeping with the Masters and Johnson theory [3]. However, increasing interest is actually paid to sexual dysfunction occurring in the single [71]. Before the beginning of the sex therapy, the psycho-sexologist must investigate, both with clinical assessment, and with specific psychometric tools, the nature and the severity of PE, together with the impact this symptom has on the couple.

We recommend using the questionnaires with a consolidated statistical validation. The most used questionnaires for the evaluation of the patient's symptomatology are: PEDT,

the premature ejaculation profile (PEP), the Arabic Index of Premature Ejaculation (AIPE), and the Chinese Index of Premature Ejaculation (CIPE) [72]. The IIEF and male Orgasmometer provide insight in regards to erectile and orgasmic functioning, respectively, and could be useful additions in the context of psychometric assessment [50, 62]. In addition, we suggest also the evaluation of the partner's PE-related sexual distress, which may bring to a development of partner's sexual dysfunctions, such as low sexual desire, or pain during sexual intercourse [48]. Two new psychometric tools for the evaluation of female sexual distress related to PE are the Female Sexual Distress Scale-revised-PE (FSDS-R-PE) [48] and the female Orgasmometer [51]. Particular attention must also be paid to female sexual dysfunctions, or to relational problems, which in some cases represent the cause of partner's PE.

Counseling about the physiology of ejaculatory control, about the correct expectations regarding sexual performance and about available therapies and their mechanism of action and possible results should be the first psychological intervention [73]. Management of sexual dysfunctions in the medical setting lacking sexological culture and ability to counsel the patient and the couple is a major factor for failure of therapies and drop-outs [74].

The sex therapy protocol for the management of couple's PE implies the adoption of both behavioral approaches for the management of the symptom from a physical point of view (Stop-Start/Pause-Squeeze techniques), and cognitive strategies for the management of dysfunctional beliefs related to sexual performance and sexual intercourse [40, 75–78]. Although the recent literature evidence exists in regard to the benefits in the adoption of an integrated psychological and medical treatment approach for PE [40, 76, 77], systematic meta-analyzed data, although more dated, show an inconsistent effectiveness of psychological (behavioral) interventions for the treatment of PE [79]. However, these data have to be considered cautiously due to the lack of randomized controlled studies on the psychotherapy efficacy for PE treatment, and the frequency of studies with small sample size.

On-label therapies

Recommendation #20. We recommend the use of dapoxetine as first choice, on-demand, on label, oral therapy for both LPE and APE (1 ⊕⊕⊕⊕).

Recommendation #21. We suggest the starting dose of dapoxetine 30 mg, assumed with a full glass of water 1–3 h before the intercourse, and we suggest not to titrate to 60 mg or to any other treatment or association before at least 6–8 full sexual attempts in a congruous erotic environment (2 ⊕⊕◯◯).

Recommendation #22. We recommend the use of eutectic lidocaine/prilocaine spray as on label local therapy for LPE (1 ⊕⊕◯◯).

Evidence

Dapoxetine is a short-acting selective serotonin reuptake inhibitor (SSRI) with a short half-life which accounts for the inability to affect mood, as other antidepressants do [80], and it is the only oral drug currently approved in plenty of countries for the treatment of PE. The rationale of the use of dapoxetine resides on well-known central role of serotonin in the ejaculatory control [81]. An integrated analysis of the first two double blind placebo-controlled, phase III, RCTs showed that dapoxetine 30 mg or 60 mg assumed on demand 1–3 h before the intercourse resulted in a significantly higher mean IELT when compared to placebo [82].

Similar results were reported in a further analysis including five phase III trials and involving 6081 men. Dapoxetine at both dosages showed from a 2.5- to 3-fold increase in IELT [83]. Accordingly, a number of meta-analyses examining findings on dapoxetine RCTs unanimously agree that the drug is significantly superior to placebo in term of IELT and PROs (feeling of ejaculatory control, distress), as well as in term of the patient global impression of changes [84–88]. The same analyses confirmed that dapoxetine treatment could induce mild side effects, similar to other SSRIs, although of lower severity, frequency, and overall clinical impact (nausea, diarrhea, headache, and dizziness [82, 89]). Additionally, while other SSRIs have known major class-related adverse effects on sexual function, such as hypoactive sexual desire disorder and ED [90], these symptoms are much less frequent in patients treated with dapoxetine. While the IELT increase is highly statistically significant with respect to placebo, it is lower than other SSIRs: however, dapoxetine treatment can be considered a safe treatment in regards to male sexual function, being the only "erection-sparing" SSRI.

The only local therapeutic option approved by the European Medicine Agency (EMA) for PE, but exclusively in its lifelong form, is a combination of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) used as a metered-dose aerosol spray [91]. Two phase III 12-week studies involving 795 subjects, showed that application of the spray five minutes before sexual intercourse resulted in an a six–sevenfold increase in the geometric mean IELT, compared to placebo [92, 93], with positive outcomes in ejaculatory control, sexual satisfaction, and distress. No systemic adverse events were reported, whereas only local side effects, including desensitization of the genitalia in subjects or in their sexual partners, have also been reported [92, 93].

Remarks

We place a high value on the recognition that dapoxetine and eutectic lidocaine/prilocaine spray are the only on label treatment option for PE. Despite the evidence arising from phase III trials and large post marketing studies [94], some other controversial post-marketing data showed high dropout for dapoxetine. In a first 52-week prospective open label study [95] it has been reported that less than 10% of men who were prescribed dapoxetine were still assuming the treatment at the study end-point. Similar results were reported by Park et al. [96] in a more recent observational 2-years prospective study involving 182 subjects. Interestingly, inefficacy or side effects have not been frequently mentioned as main reasons for drop-out, which instead include high cost, disappointment in the need for continual treatment, and other undefined personal reasons [96]. Hence, these data cannot be used to discourage the use of dapoxetine, but further stress the need of a careful counseling. Recently, a nomogram aimed to identify patients who might be suitable for Dapoxetine treatment has been developed: while still lacking external validation, the nomogram might be helpful to reduce the chances of drop-out [97]. In regards to the use of eutectic lidocaine/prilocaine spray, we suggest caution in men with LCEE, as desensitization of the penile glans can negatively affect erectile function [42].

Off-label therapies

Recommendation #23. We suggest the off-label combination between dapoxetine and PDE5i to improve ejaculatory control in patients with LCEE (2⊕◯◯◯).

Recommendation #24. We suggest the off-label combination of dapoxetine and lidocaine/prilocaine in difficult patients' refractory to a single therapy (2⊕◯◯◯).

Recommendation #25. We recommend using PDE5i in case of ED or SED when comorbid with PE (LCEE) (1⊕◯◯◯).

Recommendation #26. We suggest to use SSRIs on demand, i.e. paroxetine or fluoxetine, whenever PE is refractory to first line treatments and in the absence of psychiatric contraindications demonstrated by a psychiatric consultation and by psychometry (2⊕◯◯◯).

Recommendation #27. We suggest to use clomipramine or SSRIs, i.e. paroxetine or fluoxetine, daily whenever PE is refractory to first line treatments, or on demand SSRI, in the absence of psychiatric contraindications and demonstrated by a psychiatric consultation and psychometry (2⊕◯◯◯).

Recommendation #28. We recommend not to prescribe off-label antidepressant without a careful screening for depression and determination of the endogenous or reactive nature of the depression (1⊕◯◯◯).

Recommendation #29. We recommend to obtain written and signed informed consent in all patients treated with SRRI or off-label drugs or associations (1⊕⊕⊕⊕).

Recommendation #30. We do not recommend to use α-1 adrenergic receptor blockers as second line therapy in men with PE/LUTS (1⊕◯◯◯).

Recommendation #31. We do not recommend to use tramadol in PE patients (1⊕◯◯◯).

Recommendation #32. We suggest to associate counselling to all pharmacological PE therapies and to associate psychosexological therapies when indicated (2⊕⊕◯◯).

Evidence

Numerous drugs have been found to improve some parameters of PE, although lacking a specific indication for treatment. This use is technically defined as "off-label" treatment. Pharmacotherapy for PE predominantly targets neurotransmitters and receptors involved in the central control of ejaculation, including serotonin, dopamine, oxytocin, norepinephrine, gamma amino-butyric acid (GABA) and nitric oxide (NO) [98]. Peripherally, the ejaculatory mechanism is controlled by the sympathetic nervous system. While α − 1 adrenergic receptor blockade by selective antagonists (i.e. terazosin, alfuzosin and silodosin) may be potentially useful for delay ejaculation, treatment cannot be recommended until the results of large well-designed RCTs are obtained [99]. As mentioned, PDE5i, by increasing NO availability, may influence ejaculation through different mechanisms [100]: (1) delaying ejaculation by reducing the contractions of the vas deferens and the seminal vesicles; (2) slightly reducing glans sensitivity; (3) increasing the duration of the erection, thus changing the post-ejaculatory refractory time; (4) reducing performance anxiety and adrenergic hypertonia often present in young subjects with PE [101]. Whenever PE is supposed to be caused by hypersensitivity of the glans penis, central analgesic drugs (e.g. tramadol) or topical anesthetics (lidocaine) appear more effective than placebo, paroxetine and sildenafil at increasing IELT even if methodological quality of the existing RCT evidence base is uncertain [102].

The cornerstone of drug therapy remains the use of SSRIs or tricyclic antidepressants with serotonergic activity, such as clomipramine. Citalopram, fluvoxamine and nefazodone are mostly ineffective; good results have been reported in small patient samples with fluoxetine, paroxetine [103] and sertraline. It should be noted that none of these drugs have been approved by regulatory agencies for the treatment of PE, and their use must therefore be subsequent to obtaining an informed consent from the patient.

Notably, PE duration, NIH-CPSI score, and IIEF-5 score are risk factors of depression in men with PE, suggesting the need to check the nature (reactive or endogenous) of the depression itself in PE patients [104]. This screening

is to be considered mandatory when using off-label serotoninergic antidepressants and in particular SSRI, which are strongly and consistently associated with significant suicide risk. Surprisingly, although admitting the mentioned risk, the current guidelines do not recommend such screening before prescribing antidepressants for PE. On the contrary, the role of the psychiatrist could be considered pivotal for recognizing the reactive nature of depression (and anxiety), i.e. generated by PE, with respect to the endogenous depression (also known as major depression). While the former could be easily improved by a successful PE treatment, the latter needs a specific psychiatric management. SSRIs could be considered by the clinician in case of relevant anxious or depressive symptoms, as derived by psychometric tests and psychiatric consultation. In that case, SSRIs not only will treat the aforementioned psychiatric symptoms, but also will ameliorate PE.

The combination of dapoxetine and PDE5is in LCEE has been suggested for increasing ejaculatory control and reducing the risk of worsening a pre-existing ED [42]. However, while a major warning is still present on dapoxetine drug label due to the possible risk of syncope [105], recent data have demonstrated the absence of this adverse event in large post-marketing studies [94] and that the combination between dapoxetine and PDE5Is is well tolerated, and the side effects are negligible [105].

Finally, as dapoxetine is acting on the central nervous system by increasing serotoninergic signaling while lidocaine/prilocaine acts on the peripheral reflex arc controlling ejaculation, the association of these two medications could be hypothesized. However, the association may increase the risk of ED and consequently drop-out: therefore, combination treatment might be considered in patients with perfect control of erection only.

Remarks

The Post-SSRI sexual dysfunction (PSSD) is a novel clinical entity characterized by long term sequelae of SSRIs on sexual function (desire, arousal, ejaculation, and orgasm) not yet well studied, but surely alarming [106]. A petition to the European Medicines Agency (EMA) has been formulated to collect patients reporting PSSD [107]. Several theories (epigenetics? neurotoxicity? downregulation of the serotoninergic receptors? hormonal derangements?) have been formulated so far, but definite evidence in support or against these theories is still lacking. Unfortunately, PSSD frequently appears to be severe and symptoms might persist for many years following drug discontinuation [108]. Although this specific risk is largely underestimated, we recommend, in the interest of both the patient and of the prescribers, to consider off-label SSRIs only in selected patients really unresponsive to on-label prescriptions coupled with counseling and psychotherapy (either alone, or associated).

The treatment of PE, as far as possible, should be pursued for a long time since its high relapse rates after withdrawal. In our experience, the second-choice daily dosing of SSRIs, although risky, is likely to be associated with obvious superior fold increases in IELT compared to on-demand SSRIs. The association of pharmacotherapy and psychotherapy is supposed to achieve superior treatment outcomes in the majority of patients [75]. Treatment with PDE5i alone should be limited to men with APE secondary to co-morbid ED [109]. The use of a combined treatment with PDE5i and dapoxetine, also mentioned in the most recent revision of the EAU guidelines [44], is sometimes preferred by patients to simultaneously improve PE and ED. As previously stated, the association of counselling to pharmacological and psychological treatment is highly suggested to improve the chances of success and reduce the risk of drop-outs, as well as to manage patients' and couples' expectations [73].

Association of available treatments, traditional approaches such as acupuncture [110], but also new behavioral therapies [111] or new deliveries of drugs [112], oxytocin receptor antagonists [113], on-demand rapid acting SSRIs, and single agents that target multiple receptors [99] may form the foundation of more effective future PE management.

Surgical treatment

Recommendation #33. We suggest against routinely performing circumcision and frenulectomy in patients with PE. (2 ⊕⊕◯◯).

Evidence

Frenulum breve has been considered a risk factor for PE, and as such frenulectomy has long been advocated as the best treatment for LPE [114]. However, evidence in support of these statements is rather scarce. On the contrary, penile scars resulting from surgery can act as an irritative "trigger" for ejaculation, therefore actually worsening sexual symptoms [115]. For similar reasons, circumcision has therefore been excluded from the list of recommendations [116].

Conclusion

PE is a frequent and multifaceted symptom, which has only recently been considered of interest for the physician. As a consequence, only few drugs have been developed and approved yet for PE, and in many countries no treatment has been approved so far. Hence, management of PE remains

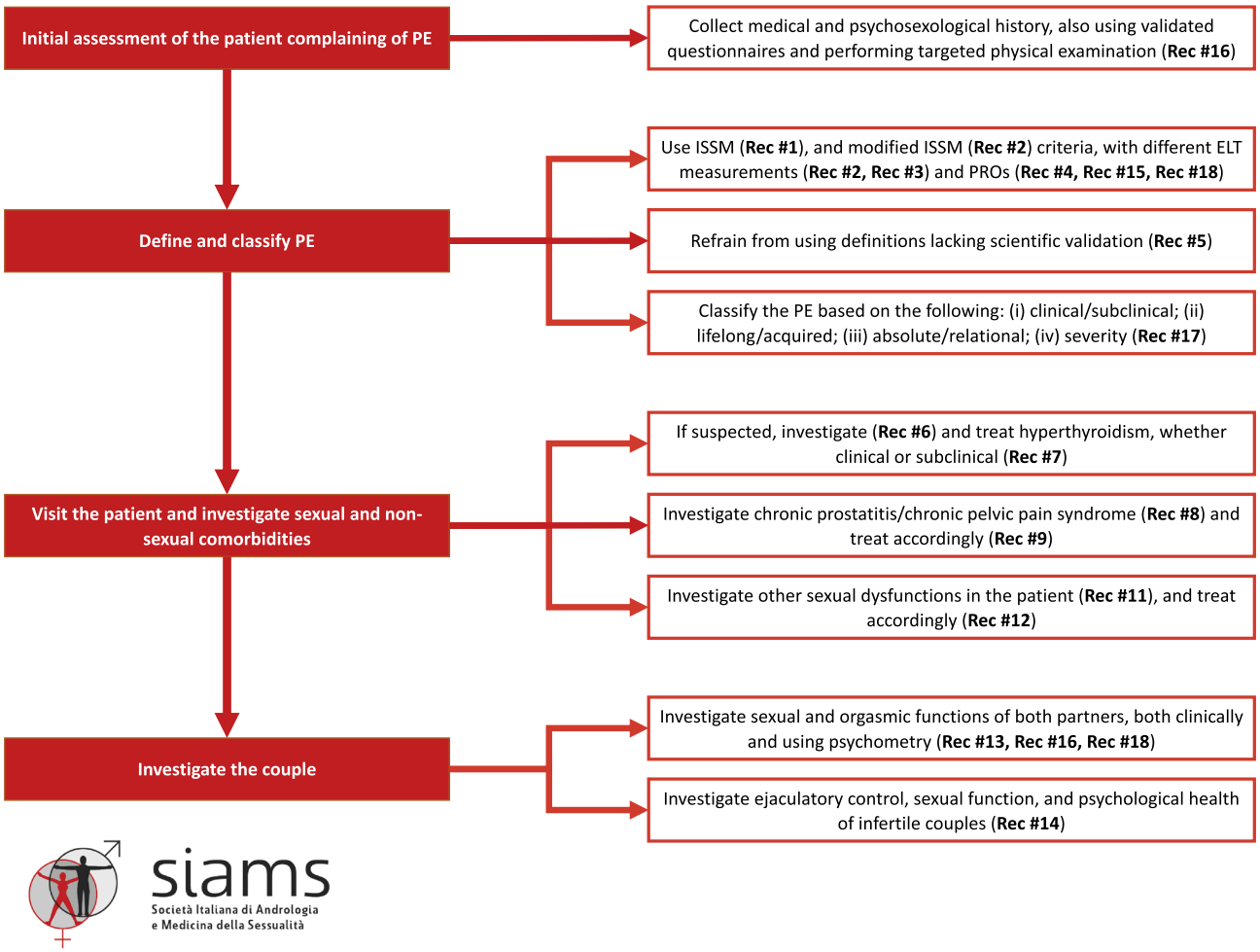

Fig. 1 Flowchart depicting the suggested approach to PE diagnosis. *PE* premature ejaculation, *ISSM* International Society of Sexual Medicine, *ELT* ejaculatory latency time, *PRO* patient-reported outcome

relatively complex and might become a source of dissatisfaction for both patients and clinicians. While DE is destroying the quantitative aspect of sexuality, being the intercourse impossible in the majority of impotent men, PE is affecting the quality of sex itself. Many patients are apparently refractory to simple pharmacological treatment or psychological therapy alone. Hence, its management and the patient and partner expectations appear more difficult, possibly explaining the disappointment encountered by many doctors with a simplistic approach to PE. While PE should always be thoroughly investigated by a specialist, all physicians can (and should) ask their patients whether any sexual dysfunction is present in their life: a flowchart summarizing most of the present guidelines' recommendations could be helpful to guide all necessary steps in diagnosis and treatment (Figs. 1 and 2). Our clinical guideline has been therefore developed to introduce new elements which are likely to have critical repercussions for the daily clinical practice and for the successful treatment of PE.

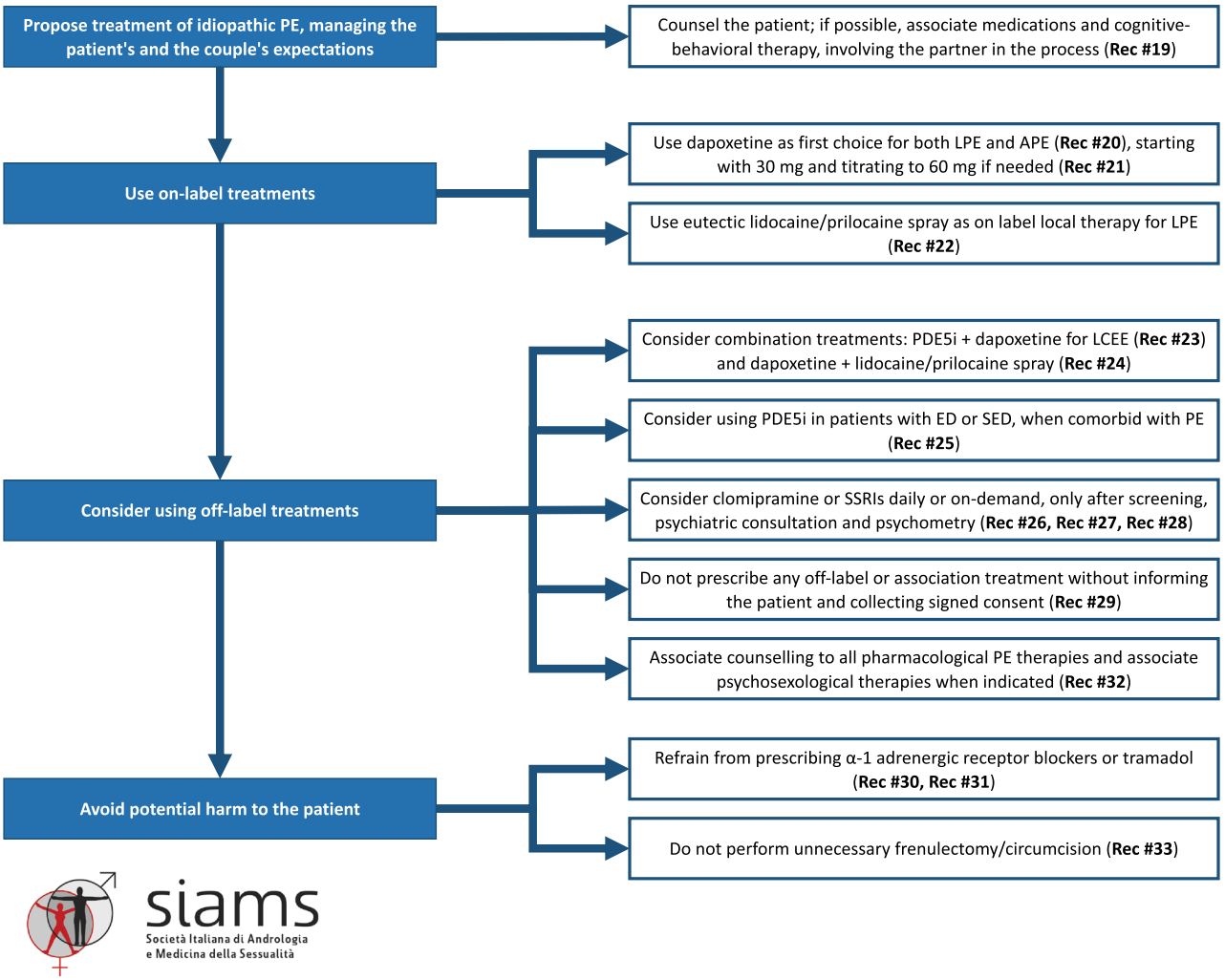

Fig. 2 Flowchart depicting the strategies for PE treatment. *PE* premature ejaculation, *LPE* lifelong premature ejaculation, *APE* acquired premature ejaculation, *PDE5i* phosphodiesterase type 5 inhibitor, *LCEE* loss of control on erection and ejaculation, *ED* erectile dysfunction, *SED* subclinical erectile dysfunction, *SSRI* selective serotonin reuptake inhibitor

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Compliance with ethical standards

Conflict of interest AS, AA, GC, ADF, AMI, SLV, MMa and MMe declare no competing interests for the present article. EL is or has been paid consultant and/or speaker for Pfizer and Shionogi. EAJ is or has been paid consultant and/or speaker for Bayer, Ibsa, Lundbeck, Otsuka, Meniarini, Pfizer and Shionogi.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

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