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REVIEW

New insights on premature ejaculation: a review of definition, classification, prevalence and treatment

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There are ongoing debates about the definition, classification and prevalence of premature ejaculation (PE). The first evidence-based definition of PE was limited to heterosexual men with lifelong PE who engage in vaginal intercourse. Unfortunately, many patients with the complaint of PE do not meet these criteria. However, these men can be diagnosed as one of the PE subtypes, namely acquired PE, natural variable PE or premature-like ejaculatory dysfunction. Nevertheless, the validity of these subtypes has not yet been supported by evidence. The absence of a universally accepted PE definition and lack of standards for data acquisition have resulted in prevalence studies that have reported conflicting rates. The very high prevalence of 20%–30% is probably due to the vague terminology used in the definitions at the time when such surveys were conducted. Although many men may complain of PE when questioned for a population-based prevalence study, only a few of them will actively seek treatment for their complaint, even though most of these patients would define symptoms congruent with PE. The complaints of acquired PE patients may be more severe, whereas complaints of patients experiencing premature-like ejaculatory dysfunction seem to be least severe among men with various forms of PE. Although numerous treatment modalities have been proposed for management of PE, only antidepressants and topical anaesthetic creams have currently been proven to be effective. However, as none of the treatment modalities have been approved by the regulatory agencies, further studies must be carried to develop a beneficial treatment strategy for PE.
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INTRODUCTION

Even though the first report regarding premature ejaculation (PE) was published more than 100 years ago,[1] the exact pathophysiology of this disorder is still not entirely understood. Studies reporting high prevalence and newly developed pharmacological agents have made PE an attractive target for research and the pharmaceutical industry. Therefore, studies conducted in this field have gained momentum over the past two decades and our understanding of PE has subsequently changed.[2] However, there are still ongoing debates about the definition, classification, prevalence and effective treatment options of PE and this article aims to review the recently accumulated data on these issues.

DEFINITION OF PE

Due to the lack of knowledge about the underlying pathophysiology, attempts to define PE have been a challenging task.[3] Throughout history, PE has been defined in many ways by several professional organisations and individuals[4–9] (**Table 1**). However, most of these definitions are considered to be authority-based rather than evidence-based.[8] Moreover, these definitions lack specific operational criteria and are vague in terms of operational specificity, while they rely on subjective interpretations of these concepts by the clinician.[8]

In order to overcome the shortcomings of former definitions, the International Society for Sexual Medicine (ISSM) *Ad Hoc* Committee of international experts in PE agreed that it is necessary for the new constraints that define PE to consider the length of time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences resulting from PE.[8] They also underlined that objective evidence regarding PE is limited to studies of men with lifelong PE, who engage in vaginal intercourse. Accordingly, the *Ad Hoc* Committee defined lifelong 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;
- inability to delay ejaculation on all, or nearly all, vaginal penetrations;
- negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

Unfortunately, even this definition did not cover all aspects of the problem. First of all, it does not define PE in sexual activities other than vaginal intercourse or PE amongst homosexual men. Secondly, The Committee did not make any recommendations for heterosexual men preferring vaginal intercourse, who complain of ejaculating prematurely, but do not meet the ISSM criteria of lifelong PE, such as men who ejaculate after 1 min of vaginal intercourse, men who occasionally ejaculate prematurely or men who developed PE at some point in their life. Consequently, further studies are necessary to develop similar

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evidence-based definitions and management modalities for these men who do not meet the limited criteria of the current definition.

THE CLASSIFICATION OF PE

The distress caused by ejaculating early varies in severity amongst men who experience this problem. Some men may only report that they have PE when asked during a prevalence study, whereas they may not be bothered enough to seek medical attention. On the other hand, some men with PE may actively seek medical treatment due to negative personal consequences.

Waldinger[10] emphasized that PE has always been considered a male sexual 'disorder' and this has led to debates on diagnosis, classification, epidemiology and treatment of PE. In order to clarify this misconception, he suggests distinguishing the 'complaint' of PE from 'syndromes' of PE.[10–12] Some men may complain about occasional early ejaculation, but may consider this to be a normal sexual variant. On the contrary, some men may have the complaint of ejaculating prematurely, along with a cluster of other complaints, such as ejaculating within 1 min of vaginal penetration, having this inability on (nearly) all vaginal penetrations since first sexual encounters and experiencing negative personal consequences and therefore complete the whole symptomatology of lifelong PE syndrome, as defined by ISSM *Ad Hoc* Committee.[8]

The first attempt at classification of PE was by Bernard Schapiro in 1943 who defined Types A and B.[13] Afterwards, these syndromes were respectively renamed 'lifelong' and 'acquired' PE by Godpodinoff.[14] As these classifications were not well recognized at that time, they were not widely used and it took nearly 20 years to establish the objective criteria for lifelong PE.[8] However, the published objective data regarding acquired PE are still insufficient to define evidence-based criteria for this syndrome. The recent guidelines published by ISSM for the diagnosis and treatment of PE state that the proposed criteria for lifelong PE can also be applied to acquired PE.[2] However, the relevant level of evidence is low. Since men with acquired PE are more often of older age, and have more severe sexual complaints and more comorbidities than those with lifelong PE,[15–18] we believe that further studies are required to establish evidence-based criteria for acquired PE, rather than applying those of lifelong PE. The intravaginal ejaculation latency time (IELT) values in men with acquired PE must be evaluated separately with well-designed observational studies and the differences in their levels of ejaculatory control, distress and interpersonal difficulty must be demonstrated.

In addition to the classifications mentioned above, two more PE syndromes were proposed for men who seek medical help due to distress from short ejaculation time.[10–12] These subtypes are named 'natural variable PE' and 'premature-like ejaculatory dysfunction'. Their properties are listed in **Table 2**, along with the properties proposed of lifelong and acquired PE.[10] Men with natural variable PE experience coincidental and situational rapid ejaculations, whereas men with premature-like ejaculatory dysfunction complain of PE in spite of normal, or even long ejaculation latency time.[10] As the validity of these subtypes is not supported by evidence and their definitions are authority-based, they are recommended to be considered as 'provisional' for researchers, but they are beneficial for patients who do not qualify for the diagnosis of PE and would allow for health-care professionals to address the concerns of these patients.[2]

The variability of help-seeking behaviour in patients with different PE syndromes was brought to attention by Waldinger[10] and has been demonstrated in recent studies,[17,18] which have revealed that most of the patients who sought medical treatment described either lifelong or

Table 1 Definitions of premature ejaculation (PE)

Year	*Source*	*Definition*
1970	Masters and Johnson	The Foundation considers a man a premature ejaculator if he cannot control his ejaculatory process for a sufficient length of time during intravaginal containment to satisfy his partner in at least 50% of their coital connections.
1980	DSM-III	Ejaculation that occurs before the individual wishes it, because of recurrent and persistent absence of reasonable voluntary control of ejaculation and orgasm during sexual activity
1994	*International Statistical Classification of Disease*, 10th edition (ICD-10)	For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required, before or within 15 s) or the occurrence of ejaculation in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.
2000	DSM-IV-TR	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.
2001	European Association of Urology. Guidelines on Disorders of Ejaculation	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.
2003	Metz and McCarthy	The man does not have voluntary, conscious control, or the ability to choose in most encounters when to ejaculate.
2004	International Consultation on Urological Diseases	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.
2004	American Urological Association Guideline on the Pharmacologic Management of Premature Ejaculation	Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.
2005	Waldinger *et al.*	Men with an IELT of less than 1 min have 'definite' PE whereas men with IELTs between 1 and 1.5 min have 'probable' PE. In addition, an additional grading of severity of PE should be defined in terms of associated psychological problems.
2008	International Society of Sexual Medicine	A male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

This table was modified from McMahon.[114]
Abbreviation: DSM, Diagnostic and Statistical Manual of Mental Disorders; IELT, intravaginal ejaculation latency time.

acquired PE. Considering the outcomes of these studies, it may be speculated that the complaints of lifelong and acquired PE patients are more severe than those of natural variable PE and premature-like ejaculatory dysfunction patients. The scores obtained from patient-reported outcome (PRO) measures applied in the study by Serefoglu *et al.*[16] revealed that complaints of patients with acquired PE are more severe, whereas they are least severe among men with premature-like ejaculatory dysfunction. The PRO measure used was the premature ejaculation profile (PEP), which was developed to assess four different domains of PE in large observational studies and drug trials.[19–21] Although the differences among mean PEP scores were not statistically significant in all four measures, the severity of PE complaints seems to follow a continuum, where acquired PE is at the top and lifelong PE is second, followed by natural variable PE and then premature-like ejaculatory dysfunction, respectively.

In a similar study, Porst *et al.*[22] analysed the PEP results of lifelong and acquired PE patients, concluding that the baseline characteristics of acquired and lifelong PE patients are generally similar, without performing any statistical analyses on PROs. The discrepancy between aforementioned studies can partially be explained with different calculation methods used for evaluating PEP results. Porst *et al.*[22] compared the percentage of lifelong and acquired PE patients who reported worse sexual function according to the four questions of PEP, whereas Serefoglu *et al.*[16] compared the mean scores obtained from each of PEP measures, similar to the methodology used in both US and European observational studies.[19,21] By applying the same method to the data of Porst *et al.*,[22] worse scores for acquired PE patients in 'sexual satisfaction' (1.14 ± 0.83 *vs.* 1.22 ± 0.93; $P=0.162$) and 'interpersonal difficulty' (2.09 ± 1.07 *vs.* 1.89 ± 1.17; $P<0.001$) can be detected, whereas lifelong PE patients seemed to report worse 'perceived control' (0.61 ± 0.64 *vs.* 0.77 ± 0.66; $P<0.001$) and 'personal distress' (2.83 ± 0.87 *vs.* 2.80 ± 0.88; $P=0.7$).

Although it is not clear whether lifelong or acquired PE is more severe, it is obvious that these two syndromes have different characteristics and should be managed separately. Moreover, further studies would be of benefit in confirming whether there is a difference in severity of complaints among patients with different types of PE syndromes.

PREVALENCE OF PE

Many studies have been undertaken in order to define the prevalence of PE[15,23–41] (**Table 3**). However, without a valid definition of the disease, it is impossible to carry out accurate prevalence studies. Due to the absence of a universally accepted PE definition, many prevalence studies conducted in the past reported conflicting results.[2,42,43] Additionally, different manners of sampling, data acquisition and response analysis cause further conflicts in the results obtained.

According to trials that used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) definition, PE is recognized as the most common male sexual dysfunction, with a prevalence of 20%–30%.[25,27,28] As the DSM-IV-TR definition uses vague terminology that is not well defined, such as 'complaints' or 'marked distress', the outcomes of these surveys cause ongoing debate, as to whether or not a true rate of PE in the general population has been detected.[10,42] The prevalence of lifelong PE according to the recent ISSM definition was estimated to be between 1% and 5%, and the reason for the high prevalence of PE previously reported in general population surveys was suggested to be mainly secondary to patients with natural variable PE and premature-like ejaculatory dysfunction.[10] These patients do not readily seek medical treatment, but appear in epidemiological studies because of the broad definition being used.[10]

Unfortunately, most recent epidemiological studies were not helpful to resolve the issue. McMahon *et al.*[38] evaluated 4997 men in the Asia-Pacific countries (68% of which were younger than 46 years) and concluded that self-reported PE is more prevalent than self-reported erectile dysfunction (13% *vs.* 8%). However, the authors failed to report the overall response rate, as well as the demographics of non-participants. In this case, the possibility of a participation bias must also be considered, as people who volunteer to participate in health surveys tend to overrepresent the 'worried well' demographic and often believe that they may benefit from participation. Furthermore, the possibility of a selection bias must also be considered, as half of the respondents were 18–35 years old and of higher education.

An online survey of 804 Arabic-speaking internet user men in the Middle East revealed that a total of 82.6% reported various degrees of PE, despite a median IELT of 5 min.[36] As commonly done in previous epidemiological PE studies, the authors accepted people as 'having PE' who reported that they sometimes (45.9%), mostly (21.4%) and always (15.3%) ejaculate before they wish to, in spite of the frequency criterion of the previous definitions.[8] As the authors indicated, online surveys have several advantages compared to face-to-face interviews such as wide-geographic reach, providing privacy/anonymity, and reducing the stress of discussing sensitive issues with a person.

Table 2 Summary of the symptoms of four premature ejaculation (PE) syndromes used in the classification of males with complaints of ejaculating prematurely[9]

Lifelong PE	*Acquired PE*	*Natural variable PE*	*Premature-like ejaculatory dysfunction*
In the majority of cases (80%) within 30–60 s or between 1 and 2 min (20%)	IELT is short (less than 2 min)	Ejaculation time may be short or normal	IELT is in the normal range or may even be of longer duration
From about the first sexual encounter	Early ejaculation occurs at some point in a man's life	Early ejaculations are inconsistent and occur irregularly	Subjective perception of consistent or inconsistent rapid ejaculation
With nearly every woman	The man had normal ejaculation experiences before	Ability to delay ejaculation may be diminished or lacking	Ability to delay ejaculation may be diminished or lacking
Ejaculation occurs too early nearly in each intercourse	The onset is either sudden or gradual	The impression of diminished control of ejaculation	Imagined early ejaculation or lack of control of ejaculation
Remains rapid throughout the lifetime of the subject (neurobiological/genetic cause)	The dysfunction may be the result of urological/thyroid dysfunctions or psychological/relationship problems	Psychotherapy should be considered as first-line treatment	The preoccupation is not better accounted for by another mental disorder

Abbreviation: IELT, intravaginal ejaculatory latency time.

Table 3 The prevalence of premature ejaculation (PE)

Date	*Author*	*Method of data collection*	*Method of sample recruitment*	*Specific operational criteria*	*Prevalence(%)*	*Number of men*
1998	Dunn *et al.*[24]	Mail	General practice registers—random stratification	Having difficulty with ejaculating prematurely	14 (past 3 months) 31 (lifetime)	617 618
1999	Laumann *et al.*[25] (NHSLS)	Interview	NA	Climaxing/ejaculating too rapidly during the past 12 months	31	1410
2002	Fugl-Meyer K and Fugl-Meyer AR[26]	Interview	Population register	NA	9	1475
2004	Rowland *et al.*[39]	Mailed questionnaire	Internet panel	DSM IV	16.3	1158
2004	Nolazco *et al.*[40]	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	28.3	2456
2005	Laumann *et al.*[27] (GSSAB)	Telephone-personal interview/ Mailed questionnaires	Random (systematic) sampling	Reaching climax too quickly during the past 12 months	23.75 (4.26 frequently)	1 3618
2005	Basile Fasolo *et al.*[15]	Clinician-based	Invitation to outpatient clinic	DSM IV	21.2	1 2558
2006	Stulhofer and Bajic[41]	Interview	Stratified sampling	Often ejaculating in less than 2 min	9.5	601
2007	Porst *et al.*[28] (PEPA)	Web-based survey self-report	Internet panel	Control over ejaculation distress	22.7	1 2133
2009	Brock *et al.*[29]	telephone interview	Web-based survey	DSM III Control Distress	16 26 27	3816
2010	Traeen and Stigum[30]	Mailed questionnaire+internet	Web interview+randomisation	NA	27	1 1746+1671
2010	Amidu *et al.*[31]	Questionnaire	NA	NA	64.7	255
2010	Liang *et al.*[32]	NA	NA	ISSM	15.3	1127
2010	Park *et al.*[23]	Mailed questionnaire	Stratified sampling	Suffering from PE	27.5	2037
2011	Vakalopoulos *et al.*[34]	One-on-one survey	Population based cohort	EED ISSM lifelong PE	58.43 17.7	522
2011	Christensen *et al.*[33]	Interview+questionnaire	Population register (random)	NA	7	5552
2011	Serefoglu *et al.*[17]	Interview	Stratified sampling	Complaining about ejaculating prematurely	20.0	2593
2011	Tang and Khoo[35]	Interview	Convenience sampling	PEDT $\geqslant$9	40.6	207
2012	Shaeer and Shaeer[36]	Web-based survey	Online advertisement	Ejaculate before the person wishes to ejaculate	83.7	804
2012	Shindel *et al.*[37]	Web-based survey	Online advertisement targeted to MSM+distribution of invitation to organisations catering to MSM	PEDT $\geqslant$9	NA	1769
2012	McMahon *et al.*[38]	Computer assisted interviewing, online, or in-person self completed	NA	PEDT $\geqslant$11 Self-reported (always/ nearly always)	16 13	4997

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; EED, early ejaculatory dysfunction; GSSAB, Global Study of Sexual Attitudes and Behaviors; ISSM, International Society of Sexual Medicine; MSM, men who have sex with men; NA, not applicable; NHSLS, National Health and Social Life Survey; PEDT, premature ejaculation diagnostic tool; PEPA, Premature Ejaculation Prevalence and Attitudes.

However, internet-based surveys may have disadvantages such as low response rate, overrepresented volunteers (volunteer bias) and sampling bias (individuals recruited from internet panels can afford to buy a computer, use internet and check their e-mails thus they do not represent the population because of their higher income status and educational level).

In an analysis of 522 urban men in Greece, the authors demonstrated that 58.43% reported 'early ejaculation disorders' (EEDs). Also, the prevalence of lifelong PE, according to the ISSM criteria, was calculated as 17.7%.[34] This prevalence was much higher than previous studies, most likely secondary to the unclear criteria of diagnosing both lifelong PE, as well as the authors' unclear criteria of EED. The authors also failed to report IELT, which would have also helped to put their results in proper perspective.

Another recent cross-sectional study conducted at a primary care clinic in Malaysia applied the premature ejaculation diagnostic tool (PEDT) questionnaire and found an extremely high prevalence (40.6%) among patients with various medical conditions.[35] Since all of the subjects recruited were unhealthy, this prevalence cannot reflect the prevalence of PE in the general population. Moreover, the results of this study must be interpreted with precaution because although the sensitivity of PEDT is high, its specificity is found to be low.[16,38]

There have been other recent attempts to further clarify the definition of PE and determine a true prevalence. A recent epidemiological study conducted in Turkey acquired a different approach, as the proportion of men not satisfied with their ejaculation time (men with 'complaint' of PE) was determined.[17] Subsequently, the complaints of these subjects were analysed meticulously, and they were diagnosed

with one of the four PE syndromes, as mentioned above (**Table 2**).[10] Moreover, instead of recruiting subjects with advertisements or internet sources as done in many previous prevalence studies, participating couples were randomly selected by a proportional sampling method, according to postal code lists.[17] Therefore, unlike the majority of previous studies, these subjects were recruited to be representative of the population in terms of distribution across urban and rural settings, geographic regions and age/education/income groups. In this study, the prevalence of the complaint of ejaculating prematurely was reported as 20.0%, which was consistent with previously reported prevalence of PE.[15,28] Furthermore, the prevalences of lifelong, acquired and natural variable PE, and premature-like ejaculatory dysfunction were 2.3%, 3.9%, 8.5% and 5.1%, respectively.[17] To our knowledge, this was the first study to report the prevalence of these syndromes, and it confirmed the assumptions that most of the men who report PE in prevalence studies have natural variable PE and premature-like ejaculatory dysfunction.[10] The very low prevalence of lifelong and acquired PE reveal that 'real' PE patients are no more than 8% of the male population.[17] In fact, the very low help-seeking behaviour of men who report PE in former prevalence studies confirms that the number of patients whom physicians are dealing with is much lower than the reported prevalence.[28] Similar results were reported by Serefoglu *et al.*,[17] where 10.0% of men with PE complaints had seen a doctor, most of whom described acquired PE. It has also been clinically demonstrated that most of the patients who presented to an outpatient clinic with the complaint of PE suffer from lifelong or acquired PE,[18] confirming these findings.

As the current definition of PE is constrained to intravaginal penetration, studies concerning the prevalence of PE in the men who have sex with men (MSM) population have been limited. The prevalence of PE among MSM was recently studied in a cohort of 2640 men in North America. The authors applied PEDT and found that PEDT-diagnosed PE (PEDT $\geqslant$ 11) is consistent within age groups ($\sim$10%). The authors demonstrated that patients with younger age, lower urinary tract symptoms and lower number of lifetime sexual partners were more likely to suffer PE.[37]

PE TREATMENT

A recent survey of urology residents demonstrated that even though approximately 15% of patients presenting to clinics complain of PE, residents still fail to follow the recommendations of current treatment guidelines; this incongruence indicates insufficient training about PE during urology residency programs.[44] It is evident that the needs of PE treatment remain unmet; however, there are many potentially effective management options.[45] Topical anaesthetic creams, selective serotonin reuptake inhibitors (SSRIs) and phosphodiesterase type-5 (PDE-5) inhibitors have been fairly well studied, while newer modalities, such as tramadol and metered-dose aerosol containing topical anaesthetics, require further evidence to support their efficacy.[45,46] Other treatment options include behavioural techniques, psychological therapy, acupuncture, surgical management and combination therapies.[2,43,47]

Psychological therapies may be helpful for patients with the complaint of PE. These therapies should be considered as first-line treatment for patients with natural variable PE and premature-like ejaculatory dysfunction.[10] In spite of the previously reported high success rates,[9] recent reports clearly demonstrated that most of the published papers about psychological approaches for PE are not well controlled or randomized and are lacking in long-term follow-up.[48] Few randomized controlled studies have provided weak and inconsistent evidence regarding the effectiveness of psychological interventions for the treatment of PE.[48] Some advocate that they should be augmented in addition to pharmacotherapy,[49] including sexual counseling as a viable alternative for selected patients, in addition to pharmacotherapy.[50] For example, combining a medical and psychological approach may be especially useful in men with acquired PE with a clear psychosocial precipitant. Similarly, in men with PE and comorbid ED, combination therapy can be used to manage the distress caused by sexual dysfunctions.[51–53] A randomized two-phase study of 2 months of initial medical treatment with paroxetine or lidocaine-based spray, followed by behavioural therapy for another 2 months, during which the pharmacotherapy was discontinued, found an eight-fold delay in IELT after the medication period which deteriorated to 1.7-fold increase during the behavioural program.[54] Considering evidence, pharmacotherapy is superior in reducing PE symptoms when compared to psychological treatment alone, yet pertinent psychological issues should not be overlooked when addressing concerns of the patients.

Behavioural methods include the 'stop–start' program, first developed by Semans[55] and its modification, the 'squeeze' technique, proposed by Masters and Johnson.[9] These methods are postulated to attenuate various stimulus-response connections by gradual exposure of the patient to more intense, prolonged stimulation. Masturbation prior to sexual intercourse also has similar efficacy to the 'start–stop' program.[56] Another possible therapy is pelvic floor rehabilitation exercises, as a small randomized prospective study found that they have similar efficacy to on-demand dapoxetine in treatment of lifelong PE.[57] These behavioural approaches all have the potential to be beneficial when combined with pharmacological treatment; however, further studies are required.[58]

Topical methods are a simple, local treatment modality, and of these, lidocaine-prilocaine cream is the most studied. In a randomized, double-blind, placebo-controlled trial, lidocaine-prilocaine cream 5% significantly increased the IELT when applied for 20 min.[59] In another placebo-controlled study involving 84 men with PE, combination therapy of sildenafil and lidocaine-prilocaine cream showed success rates that were superior to those of placebo and either monotherapy.[60] Recently, a new lidocaine/prilocaine-containing spray has been developed (topical eutectic mixture for premature ejaculation; TEMPE Plethora Solutions Ltd, London, UK). Trial results indicated that IELT increased 6.3-fold, while associated improvements in PRO measures of control and sexual satisfaction were also reported.[61] In the near future, the topical aerosol is likely to be licensed for the treatment of PE, as it has minimal local and negligible systemic side effects.[62] SS-cream is yet another topical anaesthetic agent, made from the extracts of nine herbs.[63] A double-blind, randomized, placebo-controlled study showed improved IELT from 1.37 to 10.92 min, with 82% of patients reporting improved sexual satisfaction.[64] Topical treatments are recommended in the current guidelines, and are a viable option in the management of PE.[2,43]

Of oral treatment modalities serotonergic antidepressants are considered the foundation of PE treatment. Serotonin has been found to exert an inhibitory role on ejaculation throughout various descending pathways, and this process is potentiated by SSRIs.[65] Furthermore, recent studies have displayed significant changes in cortical serotonergic function in patients with PE when compared to normal volunteers.[66] It is important to consider that ejaculation delay may start a few days after daily SSRI intake and maximal delay is not evident until after 1–2 weeks of treatment.[67–70] Several, well-designed, double-blind, placebo-controlled trials support the therapeutic effect of daily SSRIs on PE.[71] Thus, guidelines often recommend medical management as the first-line therapy for lifelong PE.[2,43]

Among various SSRIs, it has been found that paroxetine is superior to fluoxetine, clomipramine and sertraline.[72,73] These daily SSRIs, such as paroxetine, require larger series investigations better understand potential side effects; however, a different treatment modality should be suggested to patients who desire fertility, as this side effect is well documented.[74–78] Published data clearly shows that chronic SSRI treatment has a detrimental effect on spermatogenesis, impairs sperm transportation, damages the sperm cell membrane, alters sperm DNA and/or effects hormonal homeostasis.[74–78] The mechanism of sperm damage from daily SSRI treatment is not yet fully understood, and further studies are needed to investigate if on-demand SSRI treatment can cause detritus effects on sperm as well.

In addition to the risk of infertility, several animal studies have demonstrated that SSRIs may impair erectile function. Angulo *et al.*[79] proposed that paroxetine effects erectile function due to reduced nitric oxide (NO) production and neuronal nitric oxide synthase expression. Similarly, Kadioglu *et al.*[80] postulated that sertraline and fluoxetine release relaxing factors, possibly NO, and that paroxetine has a different NOS inhibitory activity, either on neuronal nitric oxide synthase or endothelial nitric oxide synthase. Other serious limitations associated with serotonergic antidepressants include unwanted sexual side effects, such as decreased *libido*, anorgasmia, impotence and erectile dysfunction which may continue beyond cessation of SSRI treatment.[81,82]

A recently developed SSRI, dapoxetine, has been proven to be quickly absorbed and rapidly cleared.[20] It has been found to increase IELT by a factor of 2.5–3 min with limited and tolerable side effects, allowing this agent to be used as an on-demand treatment option for PE.[62] A recent analysis of five phase III trials of dapoxetine demonstrated that the average IELT increased from baseline (0.9 min) significantly with dapoxetine 30 mg (3.1 min) and 60 mg (3.6 min) *vs.* placebo (1.9 min), at week 12.[83,84] Dapoxetine has been comparably effective in men with lifelong or acquired PE.[22] No drug–drug interactions associated with dapoxetine, including PDE-5 inhibitors, have yet been reported.[85] Findings of the dapoxetine development program demonstrated that dapoxetine is associated with vasovagal-mediated syncope.[86] As on-demand treatment could be assumed to be more convenient, Waldinger *et al.*[87] actually demonstrated that a group of lifelong PE patients favoured an uninterrupted daily drug regimen, as daily treatment guaranteed no interference with the spontaneity of having sex. PE drug treatment research is a young and dynamic field, and the data published on dapoxetine remain a hot topic of debate, especially since many studies are supported by funding by pharmaceutical companies.[88]

PDE-5 inhibitors also have potential to be used in the treatment of PE. In one well-designed, randomized, double-blind, placebo-controlled study, sildenafil was shown to increase confidence, perception of ejaculatory control and overall sexual satisfaction, and decrease the refractory time to achieve a second erection after ejaculation in men with PE, without significant change in IELT.[89] Another randomized, double-blind, placebo-controlled study found that the efficacy of sildenafil was similar to placebo.[60] In contrast, in a randomized, double-blind, parallel group study, sildenafil significantly improved IELT and satisfaction, and reduced overall anxiety compared to several SSRIs and the 'pause–squeeze' technique.[90,91] Limited data are available on the efficacy of other PDE-5 inhibitors (tadalafil and vardenafil) in PE.[90,91] One study comparing sildenafil, tadalafil and vardenafil found that median duration of vibratory stimulation ejaculatory latency time of subjects was significantly longer only in subjects receiving vardenafil compared to placebo.[92] Evidence suggests that a PDE-5 inhibitor alone or in combination with an SSRI can be beneficial in acquired PE in men with comorbid ED.[93] Another recent meta-analysis showed an overall positive effect for the use of PDE-5 as monotherapy, or as a component of a combination regimen in the treatment of PE.[94] PDE-5 inhibitors currently remain a novel treatment; however, this issue will be less controversial when further evidence on the role of NO and PDE5 in the mechanism of ejaculation is better understood.[95]

Alpha-1 adrenergic therapy is another novel treatment postulated for treatment of PE. Currently, there has been little data found to support the effects of alpha-1 adrenergic antagonists, such as terazosin and alfuzosin on PE; however, these medications still exist as novel treatment in theory.[96,97] A recent study of eight patients found that IELT was significantly prolonged (from 3.4 to 10.1 min; $P=0.003$) and all patients answered better (much better) or slightly better for their own PE problem compared with pre-treatment condition.[98] These results may support further randomized controlled trials of this treatment modality.

Tramadol, an opioid which is used as an analgesic, has been shown to be effective for on-demand treatment of PE in several placebo-controlled studies. In two of these trials, tramadol 50 mg significantly increased IELT, as well as measures of sexual satisfaction and ejaculatory control.[99,100] Additionally, it was established that 25 mg of tramadol, as needed, increased IELT from 1.17 at baseline to 7.37 min after treatment.[100] Another single-blind randomized control trial of Tramadol in a group of 60 patients also proved the drug to be effective.[101] Most recently, 600 patients from 62 sites across 11 countries received either placebo or a tramadol orally disintegrating tablet preparation in a double-blind, placebo-controlled trial.[102] There was a significant improvement in IELT with the 62 mg dose, with almost no side effects or tolerability issues. The results were even more pronounced in the men with a baseline IELT$<$1 min (over 300 patients); in this subgroup a significant 2.4-fold increase in IELT was observed with 62 mg tramadol orally disintegrating tablet.[102] Further studies should attempt to include patients with erectile dysfunction (as they were excluded from this study), information on the long-term effect of drug dependence (as Tramadol is an opioid) and the interaction between PDE-5 inhibitors and tramadol orally disintegrating tablet (as this is not yet understood).[103] While the mechanism of action by which tramadol delays ejaculation needs to be elucidated, one should still inform patient complaining of delayed ejaculation who are currently taking tramadol that interruption of tramadol may in fact improve their sexual function.[104]

There are several unconventional methods that have been studied as treatment of PE. Chinese medicine has long attempted to address the process of PE. According to traditional Chinese medicine, the occurrence of PE relates to the dysfunction of the viscera of heart, liver, spleen and kidney, in which the excess or insufficiency of yin and yang in kidney are most common.[105] Sunay *et al.*[106] demonstrated that although less effective than daily paroxetine, acupuncture had a significantly stronger effect on delaying ejaculation than placebo. Few other studies support the efficacy of acupuncture as management of PE.[105]

Surgery is another possible unconventional management option. Several authors have reported the use of surgically induced penile hypoanaesthesia *via* selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation in the treatment of lifelong PE refractory to behavioural and/or pharmacological treatment.[107,108] One recent study involving foreskin remnant removal as management of PE found that IELT significantly increased from 64.25 s before surgery to 731.49 s after the operation.[109] However, the role of surgery in the management of PE will remain unclear until further studies have been completed.[2]

The cause of PE is often multifactorial, thus management of a PE patient is complex and may require a combination of treatment approaches.[110] When deciding on a treatment plan for PE, the physician must consider the severity of symptoms, weigh the side effects of

treatment modalities and also consider combining multiple types of treatment in refractory cases. In clinical practice, treatments for PE are likely to include a combination of pharmacological, psychological and behavioural approaches for the man, as well as including the partner in management when possible.[111] Follow-up forms are an essential component of the overall management of PE, as they help ensure optimal treatment outcomes.[112] Developing a greater understanding of an all encompassing, structured diagnostic approach to PE could lead to better treatment outcomes in the future.[113]

CONCLUSION

By sketching the evidence from the recent studies, it can be concluded that we are now one step closer to gaining a vivid view of PE. The ISSM definition of lifelong PE represents the first evidence-based definition of PE. However, further studies are required in order to obtain objective data to propose evidence-based definitions of acquired PE, natural variable PE and premature-like ejaculatory dysfunction syndromes, as well. Until then, the authority-based definitions for these three syndromes are of clinical value and they are helpful in categorizing patients who report the complaint of PE. Moreover, the severity scale of these syndromes must be confirmed by other studies and appropriate treatment algorithms must be designed. Treatment of PE is complex, and guidelines for treatment are limited due to the lacklustre definition of the disease causing a barrier to standardized evidence-based studies. Currently, it is important for the physician to consider all possible modalities when treating PE, as each patient may respond differently and side effects are variable. Vast improvement has been made in this field; however, clarification of definition and further studies on treatment are required.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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