An Evidence-Based Unified Definition of Lifelong and Acquired Premature Ejaculation: Report of the International Society for Sexual Medicine (ISSM) Second Ad Hoc Committee for the Definition of Premature Ejaculation

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Abstract

Introduction: The Ad Hoc International Society for Sexual Medicine (ISSM) Committee for the Definition of Premature Ejaculation developed the first evidence-based definition for lifelong premature ejaculation (PE) in 2007 and concluded that there was insufficient published objective data at that time to develop a definition for acquired PE.
Aim: The aim of this article is to review and critique the current literature and develop a contemporary, evidence-based definition for acquired PE and/or a unified definition for both lifelong and acquired PE.
Methods: In April 2013, the ISSM convened a second Ad Hoc Committee for the Definition of Premature Ejaculation in Bangalore India. The same evidence-based systematic approach to literature search, retrieval and evaluation used in the original meeting was adopted.
Results: The committee unanimously agreed that men with lifelong and acquired PE appear to share the dimensions of short ejaculatory latency, reduced or absent perceived ejaculatory control, and the presence of negative personal consequences. Men with acquired PE are older, have higher incidences of erectile dysfunction, comorbid disease, cardiovascular risk factors and a higher intravaginal ejaculation latency time (IELT). A self-estimated or stop-watch IELT of 3 minutes was identified as a valid IELT cut-off for diagnosing acquired PE. On this basis, the committee agreed on a unified definition of both acquired and lifelong PE as "… a male sexual dysfunction characterized by

- ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration from the first sexual experiences (lifelong PE), or, a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE), 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

Conclusion: The ISSM unified definition of lifelong and acquired PE represents the first evidence-based definitions for these conditions. These definitions will enable researchers to design methodologically rigorous studies to improve our understanding about acquired PE.

Key Words: Premature Ejaculation; Definition; Lifelong Premature Ejaculation; Acquired Premature Ejaculation; Intravaginal Ejaculatory Latency Time; Ejaculatory Control; Sexual Satisfaction; Personal Distress; Interpersonal Distress; Negative Personal Psychological Consequences

Introduction

Research into the treatment and epidemiology of PE is heavily dependent on how PE is defined. The medical literature contains several univariate and multivariate operational definitions of PE.[1-10] Each of these definitions characterise men with PE using all or most of the accepted dimensions of this condition: ejaculatory latency, perceived ability to control ejaculation, reduced sexual satisfaction, personal distress, partner distress and interpersonal or relationship distress. In the last decade, substantial progress has been made in the development of evidence-based methodology for premature ejaculation (PE) epidemiologic and drug treatment research using the objective intravaginal ejaculatory latency time (IELT) and subjective validated patient-reported outcome (PRO) measures.
The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM III/IV-TR) definitions of PE were largely accepted by the medical community with little discussion, despite having no evidence-based medical support. [11-13]

Following the introduction of evidence-based PE pharmacotherapy, the validity of the DSM definitions was the subject of debate with a substantial polarization of opinion. The inclusion of words such as "persistent", "recurrent", "minimal" and "shortly after" rendered the DSM definitions as vague, multi-interpretable and lacking in objective and quantitative criteria.[14-16] Concerns about the validity and application of the DSM-IV-TR definition was also expressed by regulatory agencies such as the United States Food and Drug Administration (FDA) who regarded the lack of evidence-based criteria as an obstacle in interpretation and assessment of data from clinical trials of investigational drugs for PE.

The absence of a specific ejaculation time cut-off point to operationalize "shortly after penetration or before the person wishes" leads to ambiguous application of the DSM criteria for PE in epidemiological and clinical research.[17-20] Giuliano et al. reported the IELT of men with DSM-IV-TR diagnosed PE ranged from 0 seconds (*ante portas* ejaculation) to almost 28 minutes, with 44% of subjects having an IELT ≥ 2 minutes and 25% ≥ 4 minutes. [20] This study demonstrates that a subject diagnosed DSM-IV-TR diagnosed PE has a 44% risk of not having PE if a PE diagnostic threshold IELT of 2 minutes, as suggested by community-based normative IELT trial, is used. [21]

Waldinger et al., in a number of studies in cohorts of heterosexual men with lifelong PE with prospective stopwatch IELT measurement showed that about 90% of men seeking treatment for lifelong PE ejaculated within 1 minute after penetration, and about 10% ejaculated between 1 and 2 minutes [17]. These data were confirmed by McMahon in a retrospective questionnaire analysis of a large cohort of men with lifelong PE. [22] These data support the proposal that lifelong PE is characterized by an IELT of less than or about 1 minute after vaginal penetration.

In October 2007, the International Society for Sexual Medicine (ISSM) responded to these concerns and convened a meeting in Amsterdam of the Ad Hoc ISSM Committee for the Definition of Premature Ejaculation. The committee included 21 international experts in PE who were charged with the development of the first contemporary, evidence-based definition of lifelong PE. Evidence-based definitions seek to limit errors of classification and thereby increase the likelihood that existing and newly-developed therapeutic strategies are truly effective in carefully selected dysfunctional populations.[4] After critical evaluation of the published data, the committee unanimously agreed that the constructs that are necessary to define lifelong PE are time from penetration to ejaculation, inability to delay ejaculation, and negative personal consequences from PE. The following definition was

agreed upon: "*Lifelong PE is a male sexual dysfunction characterized by the presence of all of these criteria: 1) ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration; 2) the inability to delay ejaculation on all or nearly all vaginal penetrations; and 3) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy."* [10] The committee was, however, unable to identify sufficient published objective data to craft an evidence-based definition of acquired PE.

In April 2013, the International Society for Sexual Medicine (ISSM) convened a second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation in Bangalore, India. The brief of the committee was to evaluate the current published data and attempt to develop a contemporary, evidence-based definition of acquired PE and/or a single unifying definition of both acquired and lifelong PE.

This article chronicles the development of current definitions of PE and details their strengths and weaknesses. Included are critiques of the evidence in support of the constructs of ejaculatory latency, ejaculatory control, sexual satisfaction and personal distress. The epidemiology, etiology and presenting symptoms of lifelong and acquired PE are compared and a new, unifying definition for both acquired and lifelong PE is proposed.

Definition Development Process

The second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation was supported by an unrestricted research grant from Johnson and Johnson. However, ISSM required complete independence from industry during the development of the new definition of PE. There were no industry representatives at the meeting and there was no attempt by industry to influence any part of the development process at any time. The same evidence-based systematic approach to literature search, retrieval and evaluation used in the original meeting was adopted.[23]

The Committee was chosen by peer-recommendation and comprised 19 experts appointed to achieve a balance of opinion, knowledge, gender and geography. These 19 included several of the world's most highly recognized experts on PE and comprised 6 psychologists or psychiatrists, 8 urologists, 2 sexual health physicians, 1 primary care physician, 1 endocrinologist and 1 radiation oncologist. All of the attendees were ISSM members. The meeting was organized, chaired and facilitated by the current ISSM president, Chris G McMahon.

The Need for an Evidence-Based Definition of Acquired Premature Ejaculation

The lack of consensus as to what constitutes acquired PE has continued to hamper clinical practice, basic and clinical research into the etiology and management of this condition. The results of PE epidemiological and drug treatment clinical trials are only reliable, interpretable and capable of being generalised to patients when consistent objective physiological measures or sensitive, validated outcome assessment instruments are used as study endpoints in well defined and consistent populations where lifelong, acquired PE or PE with comorbid ED are treated as separate PE subgroups. [24]

The original Ad Hoc ISSM Committee for the Definition of Premature Ejaculation concluded that there was insufficient published evidence to propose an evidenced-based definition of

acquired PE.[10] The committee anticipated that future studies would generate sufficient data to develop an evidence-based definition for acquired PE. The committee suggested that a post-hoc review of baseline data from phase 3 dapoxetine drug trials might provide preliminary exploratory data on the dimensions of acquired PE which might assist in future research and the development of an evidence-based definition for acquired PE. This data was interpreted as suggesting that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress to men with lifelong PE, and raised the possibility of a single unifying definition of PE. [25]

However, as acquired PE generally manifests later in life and is likely to have a different etiology [26], it may be that the presenting patient characteristics and/or symptoms reported by men with acquired PE differ from those with lifelong PE. Additional information regarding differential symptomatology and/or sexual history experiences in men with acquired PE may facilitate the development of a definition and assist in the diagnosis of acquired PE. A more accurate definition may improve design of research and assist in selecting the best treatments for this PE subtype.

Operationalization of PE Variables and Constructs

The original Ad Hoc ISSM Committee for the Definition of Premature Ejaculation (2007) agreed that errors of PE diagnosis and classification are minimised by the development and clinical application of a multivariate definition which captures and operationalizes (i.e. to develop an identifying measure, procedure, or operation) the key PE constructs of rapidity of ejaculation, perceived ejaculatory self-efficacy or control, and negative personal and interpersonal consequences (e.g., distress).[10]

The committee determined that operationalization was inherently difficult and that the constructs were inter-related and potentially confounded by each other and by multiple other variables. [10, 27] The following measures were identified as adequately but not precisely capturing the essence of each construct. [10, 27]

1. Rapidity of ejaculation-patient estimation or stop-watch measurement
2. Perceived ejaculatory-improvements in ejaculation latency time during attempts to delay ejaculation or by the measurement of the subjective feeling of ejaculatory control using patient report or validated single/multi-item multi-domain PE inventories
3. Negative personal consequences-patient report or measurement using validated single or multi-item multi-domain PE inventories of sexual or global levels of distress, bother, frustration, anxiety, depression, confidence, self-esteem and quality of life

The International Society for Sexual Medicine (ISSM) Definition of PE (Lifelong and Acquired PE)

Members of second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation (2013) unanimously agreed that lifelong and acquired PE are distinct and different demographic and etiological populations: however, they can be jointly defined, in part, by the constructs of time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences from PE. The committee agreed that the presence of these mutual constructs was sufficient justification for the development of a single

unifying definition of both lifelong and acquired PE. Finally, the committee determined that the presence of a a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less was an additional key defining dimension of acquired PE.

The second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation (2013) defined premature ejaculation (lifelong and acquired PE) as a male sexual dysfunction characterized by…

- Ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE), or, a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE), 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

The Committee agreed that published objective evidence on PE is limited to studies of men with PE engaging in vaginal intercourse. There is insufficient information to objectively define problematic early ejaculation in the context of oral sex, anal sex, and same-gender sexual activity.

History of Definitions of PE

During the period of 1920 to 1960, the absence of any scientific publications proposing a definition of PE reflects the scarcity of prevalence data. Based upon the limited published literature, a man was considered to suffer from PE when he ejaculated within seconds or within about a minute of vaginal penetration. [28] In the 1970s, despite an absence of any empirical data, Masters and Johnson rejected this ejaculation latency proposal and defined PE as a man's inability to satisfy his female partner on more than 50% of sexual events.[1] In spite of their noteworthy accomplishments, Masters and Johnson's definition was seriously flawed in that the diagnosis was determined by the female partner's response rather than the sexual function of the man. Additionally, their rejection of the ejaculation time criterion has led to a debate on "objective criteria" and "subjective criteria" of PE [29]. Typical "objective" criteria include the ejaculation latency time and the number of penile thrusts. "Subjective" criteria are measures of self-efficacy including "diminished feelings of control" and "ejaculation at moments without wishing it".

These opposing constructs have served as the framework for the development of the various definitions proposed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) by the American Psychiatric Associations. [12, 13].

Diagnostic and Statistical Manual of Mental Disorders (DSM III/IV) Definitions of PE : *The first official definition of PE was established in 1980 by the American Psychiat*ric Association (APA) in the DSM-III [30]. PE was defined as "*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*" [30]. However, because of disagreement on the criterion of "reasonable voluntary control", this criterion was removed in the subsequent DSM-III-R and DSM-IV definitions [31, 32], and replaced by the criterion of a "*short ejaculation time*". The DSM-IV-TR, defined PE as a "*Persistent or recurrent*

ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect the duration of the excitement phase such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity" and requires for the diagnosis that "*the disturbance causes marked distress or interpersonal difficulty*" [32]. As such, DSM-III contains the criterion of control but not time, whereas subsequent DSM-III-R, DSM-IV and DSM-IV-TR definitions contained the criterion of time but not control. [12, 13]

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Definition of PE: Based upon the same data that supported the ISSM definition of lifelong PE, the recently published DSM-5 definition of PE now includes an objective ejaculatory latency criterion. DSM-5 defines PE by four major criteria: *"A. A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minutes following vaginal penetration and before the person wishes it. B. The symptom in Criterion A must have been present for at least six months and must be experienced on almost all or all (approximately 75% -100%) occasions of sexual activity (in identified situational contexts or if generalized, in all contexts) C. The symptom in Criteria A causes clinically significant distress in the individual. D.The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance /medication or another medical disorder.*" [33].

The DSM-5 definition of PE requires clinicians to specify PE as either lifelong or acquired, and as generalized or situational. In addition, the DSM-5 definition of PE distinguishes between mild PE (ejaculation occurring within approximately 30 seconds to 1 minute of vaginal penetration), moderate PE (ejaculation occurring within approximately 15-30 seconds of vaginal penetration) and severe PE (ejaculation occurring prior to sexual activity, at the start of sexual activity, or within approximately 15 seconds of vaginal penetration).

International Classification of Diseases (ICD-10) Definition of PE: The World Health Organization (WHO) 1992 ICD-10 defines PE as *"The inability to control ejaculation sufficiently for both partners to enjoy sexual interaction* and *as "an inability to delay ejaculation sufficiently to enjoy lovemaking, and manifest as either of the following: (1) occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) and (2) ejaculation occurs in the absence of sufficient erection to make intercourse possible" "* [3].The ICD-10 uses both the criterion of "control" and a "very short" ejaculation time, and quantifies the ejaculation time to maximally 15 seconds after penetration. Although the ICD-10 provides an objective definition of PE, evidence to support a latency cut-off of 15 seconds was not provided. [12, 13] Furthermore, the ICD-10 use of the criterion of ejaculation that occurs within 15 seconds restricts the application of the criterion of control. [12, 13]

Classification of PE

In 1943, Schapiro [34] proposed a classification of PE into two types, types B and A. Type B (the sexually hypertonic or hypererotic type), represented a consistent tendency to ejaculate rapidly from the first act of intercourse, and type A (the hypotonic type) was associated with the development of ED. In 1989, Godpodinoff [35] renamed both types as

lifelong (primary) and acquired (secondary) PE. Over the years, other attempts to specify subtypes have occurred (e.g., global vs. situational, due to the effect of a substance, etc).

Community-based normative IELT research and observational studies of men with PE demonstrated that although IELTs of less than 1 minute have a low prevalence of about 2.5 % in the general population. However, a much higher percentage of men with IELT greater than one minute report PE. [19-21, 36]

In order to take account of this disparity, Waldinger and Schweitzer [13, 29] proposed a new classification of PE in which four PE subtypes are distinguished on the basis of the duration of the IELT, frequency of complaints, and course in life. In addition to lifelong PE and acquired PE, this classification includes variable PE and subjective PE. Men with variable PE occasionally experience an early ejaculation. It should not be regarded as a disorder, but as a natural variation of the ejaculation time in men [37]. On the other hand, men with subjective PE complain of PE, while actually having a normal or even extended ejaculation time [37]. The complaint of PE in these men is probably related to psychological and/or cultural factors. In contrast, the consistent early ejaculations of lifelong PE suggested an underlying neurobiological functional disturbance, whereas the early ejaculation of acquired PE is more related to underlying medical and/or psychological and interpersonal causes. Serefoglu et al. [38, 39] confirmed the existence of these four PE subtypes in a cohort of men in Turkey. Recently, Zhang et al. [40] and Gao et al. [41] using a similar methodology confirmed similar prevalence rates of the four PE subtypes in China to that reported by Serefoglu et al. [38, 39]. This new classification and continued research into the diverse phenomenology, etiology and pathogenesis of PE is expected to provide a better understanding of the four PE subtypes. [29]. Although the pathogenesis of lifelong and acquired PE differs, the presence of shared dimensions such as a lack of ejaculatory control and the presence of negative personal consequences, suggest a potential for a single unifying definition of both lifelong and acquired PE. With continued research into the two other PE subtypes, variable PE and subjective PE, it may be appropriate to expand this unifying definition in the future.

The Rationale for the ISSM Definition of Lifelong PE

The multivariate ISSM evidence-based definition of lifelong PE captures the key PE constructs of ejaculatory latency, perceived ejaculatory control, and the presence of negative personal consequences from PE. [10].

Rationale for Inclusion of "…ejaculation always or nearly always occurs prior to or within about one minute of vaginal penetration IELT less than about 1 minute": Operationalization of PE using the length of time between penetration and ejaculation (IELT) forms the basis of most current clinical studies on PE. [42] IELT can be measured by a stopwatch or estimated (Table 1). Several authors report that estimated and stopwatch IELT correlate reasonably well or are interchangeable in assigning PE status when estimated IELT is combined with PROs. [43, 44]

Several studies suggest that 80-90% of men seeking treatment for lifelong PE ejaculate within 1 minute. [17, 22, 45] Waldinger et al. (1998) reported IELTs <30 sec in 77% and <60 sec in 90% of 110 men with lifelong PE with only 10% ejaculating between 1 and 2 minutes [17]. These data are consistent with normative community IELT data, support the notion that IELTs of less than 1 minute are statistically abnormal and confirm that an IELT cut-off of 1 minute will capture 80-90% of treatment seeking men with lifelong PE. [21]

Further qualification of this cut-off to "about one minute" affords the clinician sufficient flexibility to also diagnose PE in the 10-20% of PE treatment seeking men who ejaculate within 1-2 minutes of penetration without unnecessarily stigmatising the remaining 80-90% of men who ejaculate within 1-2 minutes of penetration but have no complaints of PE.

Rationale for Inclusion of "…The inability to delay ejaculation on all or nearly all vaginal penetrations":
The ability to prolong sexual intercourse by delaying ejaculation and the subjective feelings of ejaculatory control comprise the complex construct of ejaculatory control. Virtually all men report using at least one cognitive or behavioral technique to prolong intercourse and delay ejaculation, with varying degrees of success, and many young men reported using multiple different techniques [46]. Voluntary delay of ejaculation is most likely exerted either prior to or in the early stages of the emission phase of the reflex but progressively decreases until the point of ejaculatory inevitability [47, 48].

Several authors have suggested that an inability to voluntarily delay ejaculation defines PE. (Table 2) [49-52] Patrick et al. reported ratings of "very poor" or "poor" for control over ejaculation in 72% of men with PE, compared to 5% in a group of normal controls [19]. Lower ratings for control over ejaculation were associated with shorter IELT with "poor" or "very poor" control reported by 67.7%, 10.2% and 6.7% of subjects with IELT <1 min, >1 min and >2 min respectively. However, Grenier and Byers failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control. [46, 53] Several authors report that diminished control is not exclusive to men with PE and that some men with a brief IELT report adequate ejaculatory control and vice versa, suggesting that the dimensions of ejaculatory control and latency are distinct concepts.[19] [46, 54]Furthermore, there is a greater variability in changes in control compared to IELT in men treated with SSRIs. [55] Contrary to this, several authors have reported a moderate correlation between the IELT and the feeling of ejaculatory control. [19, 20, 43, 56] Rosen et al. reports that control over ejaculation, personal distress and partner distress was more influential in determining PE status than IELT. [43] In addition, the effect of IELT upon satisfaction and distress appears to be mediated via its direct effect upon control. [57] However, despite conflicting data on the relationship between control and latency, the balance of evidence supports the notion that the inability to delay ejaculation appears to differentiate men with PE from men without PE.[19, 20, 58]

Rationale for Inclusion of "…negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy": Several authors have reported an association between PE and negative psychological outcomes in men and their female partners (Table 3) [19, 20, 58-70]. Patrick et al. reported significant differences in men with and without PE in the PRO measures of personal distress (64% versus 4%) and interpersonal difficulty (31% versus 1%), suggesting that this personal distress has discriminative validity in diagnosing men with and without PE.[19] The personal and/or interpersonal distress, bother, frustration and annoyance that results from PE may affect men's quality of life and partner relationships, their self-esteem and self-confidence, and can act as an obstacle to single men forming new partner relationships [19, 20, 58-70]. McCabe reported that sexually dysfunctional men, including men with PE, scored lower on all aspects of intimacy (emotional, social, sexual, recreational and intellectual) and had lower levels of satisfaction compared to sexually functional men ($p<0.001$ or $p<0.01$) [63]. Rowland et al. showed that men with PE had significantly lower overall health-related quality of life, total Self-Esteem and Relationship Questionnaire (SEAR) scores and lower confidence and self-esteem

compared to non-PE groups [62]. PE men rated their overall health-related quality of life lower than men without PE ($p \leq 0.001$).

Rationale for Exclusion of Sexual Satisfaction: Men with PE report lower levels of sexual satisfaction compared to men with normal ejaculatory latency. Patrick et al reported ratings of "very poor" or "poor" for sexual satisfaction in 31% of subjects with PE compared to 1% in a group of normal controls. [19] However, caution should be exercised in assigning lower levels of sexual satisfaction solely to the effect of PE and contributions from other difficult to quantify issues such reduced intimacy, dysfunctional relationships, poor sexual attraction, and poor communication should not be ignored. This is supported by the report of Patrick et al. that despite reduced ratings for satisfaction with shorter IELTs, a substantial proportion of men with an IELT <1 min report "good" or very good" satisfaction ratings (43.7%). The current data is limited but suggests that sexual satisfaction is of limited use in differentiating PE subjects from non-PE subjects and was not included in the ISSM definition of PE. [19]

Epidemiology and Pathophysiology of Acquired PE

Prevalence of Acquired PE

The previous lack of a standardized definition and specific operational criteria for PE, has limited evidence-based research into the epidemiology, pathogenesis, characteristics, dimensions and psychological burden of this condition. As a result, different authors report with conflicting prevalence rates for PE. (Table 4) [7, 36-39, 61, 71-92] There appears to be a substantial disparity between the incidence of PE in epidemiological studies which rely upon either patient self-report of PE and/or inconsistent and poorly validated definitions of PE [19, 20, 92], and that suggested by community based stopwatch studies of the IELT. [21] Furthermore, few researchers have focused on the epidemiology and characteristics of acquired PE.

Data from The Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey investigating the attitudes, behaviours, 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.[92] Perception of "normal" ejaculatory latency varied by country and differed when assessed either by the patient or their partner[93]. A core limitation of the GSSAB survey stems from the fact that the youngest participants were aged 40 years, an age when the incidence of PE might be different from younger males. [83]

Fasalo et al. reported that 2,658 of 12,558 men (21.2%) attending a free andrological consultation self-diagnosed PE, the majority describing acquired PE (14.8%) with 4.5% describing lifelong PE. [94] In contrast, Serefoglu et al. [38] reported that the majority of PE treatment-seeking patients described lifelong PE (62.5%) compared to acquired PE (16.1%). Similar findings were reported by Zhang et al. who found that the majority of 1,988 Chinese outpatients described lifelong PE (35.6%) or acquired PE (28.07%).[40] These data provide evidence that lifelong and acquired PE patients comprise the majority of the patients who seek treatment for the complaint of ejaculating prematurely. In addition, there appears to be a disparity between the incidence of the various PE sub-types in the general community and in men actively seeking treatment for PE (Table 5).

Consistent with this notion, Serefoglu et al. subsequently reported an overall PE prevalence of 19.8% comprising lifelong PE (2.3%), acquired PE (3.9%), variable PE

(8.5%) and subjective PE (5.1%).[38] Using similar research methodology, Gao et al. reported that 25.80% of 3,016 Chinese men complained of PE, with similar prevalence of lifelong PE (3.18%), acquired PE (4.84%), variable PE (11.38%) and subjective PE (6.4%).[41] Of particular interest is the report of Serefoglu et al. [38] that men with acquired PE are more likely to seek medical treatment than men with lifelong PE (26.53% vs. 12.77%). This finding was confirmed by Gao et al. who demonstrated that acquired PE patients were more likely to seek (17.12% vs. 14.58%) and plan to seek (36.30% vs. 27.08%) treatment for their complaints compared to men with lifelong PE. [41] These data suggest that the prevalence of acquired PE in the community is approximately around 4% among sexually active adults and that these patients are more likely to seek medical treatment (Table 5). The reasons for increased treatment seeking behaviour in men with acquired PE compared to that seen in men with lifelong PE are unclear. It is possible that men with lifelong PE may reach a degree of accommodation of their rapid ejaculation whereas the additional psychological burden imposed by the bothersome change in ejaculatory latency in acquired PE may prompt treatment seeking.

Etiology of Acquired PE

Acquired PE is most commonly due to sexual performance anxiety[66], psychological or relationship problems[66] and ED[95], and occasionally due to prostatitis [96], hyperthyroidism[97], or during withdrawal/detoxification from prescribed[98] or recreational drugs.[99]

Acquired premature ejaculation and sexual performance anxiety, psychological, or relationship problems: Psychological theories include the effect of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity, and psychodynamic explanations.[69] [100] Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation. [49, 101] Hypoactive sexual desire may lead to acquired PE, because of an unconscious desire to abbreviate unwanted penetration. [100] Similarly, diminished sexual desire can be a consequence of chronic and frustrating PE. [10] Female sexual dysfunctions (such as anorgasmia, hypoactive sexual desire, sexual aversion, sexual arousal disorders, and sexual pain disorders, as vaginismus [101] may also be related to acquired PE.

Acquired premature ejaculation and comorbid erectile dysfunction: Recent data demonstrates that as many as half of subjects with ED also experience PE.[59] [94] Subjects with ED may either require higher levels of stimulation to achieve an erection or intentionally "rush" intercourse to prevent early detumescence of a partial erection, resulting in ejaculation with a brief latency [9]. This may be compounded by the presence of high levels of performance anxiety related to their ED which serves to only worsen their prematurity and erectile function.

Acquired premature ejaculation and prostate disease: Acute and chronic lower urogenital infection, prostatodynia, or chronic pelvic pain syndrome (CPPS) is associated with ED, PE and painful ejaculation. [102-104] Several studies report PE as the main sexual disorder symptom in men with chronic prostatitis or CPPS with a prevalence of 26-77%. [105] The pathophysiologic link between chronic prostatitis, ED and PE is unknown. Prostatic inflammation may result in altered sensation and modulation of the ejaculatory reflex but evidence in support of this hypothesis is lacking. [104] [105, 106] Antibiotic treatment of microbiologically confirmed bacterial prostatitis in men with acquired PE resulted in a 2.6 fold increase in IELT and improved ejaculatory control in 83.9% of subjects. [106]

Premature ejaculation and hyperthyroidism: The majority of patients with thyroid hormone disorders experience sexual dysfunction. Studies suggest a significant correlation between PE and suppressed TSH values in a selected population of andrological and sexological patients. The 50% prevalence of PE in men with hyperthyroidism fell to 15% after treatment with thyroid hormone normalization.[97] Hyperthroidism is relatively rare in men, with a prevalence of 0.2% reported in a community-based study, and is more common in men over 60 years of age.[107] It is very uncommon in the population who present for treatment of PE and routine TSH screening is not recommended unless clinically indicated.[108]

Comparison of Characteristics of Acquired PE with Lifelong PE

Lifelong PE is a syndrome characterized by a cluster of core symptoms including early ejaculation at nearly every intercourse within 30-60 seconds in the majority of cases (80%) or between 1-2 minute (20%), with every or nearly every sexual partner and from the first sexual encounters onwards. [17, 22] Acquired PE differs in that sufferers develop early ejaculation at some point in their life, which is often situational, having previously had normal ejaculation experiences. The main distinguishing features between presentations of these two syndromes are the time of onset of symptoms and the reduction in previously normal ejaculatory latency of acquired PE.

Although men with lifelong and acquired PE appear to share the dimensions of short ejaculatory latency, reduced or absent perceived ejaculatory control and the presence of negative personal consequences from PE, they remain distinct and different demographic and etiological populations. [25]

Demographic Differences between Lifelong and Acquired PE: Consistent with the predominant organic etiology of acquired PE, men with this complaint are usually older. [25, 38-41, 94, 109] Fasolo et al. reported that the mean age of men with acquired PE patients was older compared to patients with lifelong PE (50 vs. 39 years).[94] Both Serefoglu et al. [38] and Zhang et al. [40] confirmed this finding that men with acquired PE were significantly older than other PE syndromes.

Porst et al. reported the results of an integrated analyses of baseline characteristics and treatment outcomes from phase 3 dapoxetine trials in men with acquired or lifelong PE (n= 2,228) who met the DSM-IV-TR criteria for PE, had an IELT ≤2 minutes in ≥75% of intercourse episodes and had mild or no ED (IIEF EF domain ≥21).[25] Statistical analysis was limited to comparison of baseline IELT and premature ejaculation profile (PEP) responses between subjects with acquired PE and lifelong PE with or without ED.

Although formal statistical analysis of baseline demographics was not reported, a slight age-related trend was observed. Subjects with acquired PE, especially those with mild ED were noted to be slightly older than men with lifelong PE. (Table 6) This is consistent with the increased incidence of ED in acquired PE and the epidemiology of ED. Predictably, the overall mean IIEF domain scores in men with acquired PE were slightly lower compared to lifelong PE. Men with acquired PE, appear less likely experience early ejaculation during solitary masturbation and are more likely to benefit from behavioral treatment, consistent with a syndrome associated with situational anxiety symptoms. [25, 109] Porst et al. concluded that with the exception of time of onset and duration of PE and incidence of ED, the characteristics of men with acquired and lifelong PE were sufficiently similar in

terms of demographics, sexual history, and PE symptomatology to preclude their use in discriminating between lifelong and acquired PE.

A post hoc analysis of baseline demographic data from the COUPLE study, a Phase 3 randomized clinical trial of the efficacy and safety of flexible dosed dapoxetine (30/60mg) in men with either lifelong or acquired PE and comorbid ED currently successfully treated with a phosphodiesterase type 5 inhibitor drug (PDE5i-treated IIEF EF ≥ 21), also confirmed that men with acquired PE and comorbid ED were older than men with lifelong PE and comorbid ED (Table 6). [110]

Differences in Comorbid Disease/s between Lifelong and Acquired PE: Godpodinoff [35] noted that 81% of secondary (acquired) PE subjects had "demonstrable organic causes" whereas 18% demonstrated no organic causes but were involved in disturbed or triangular relationships. Recent studies have suggested that in some men neurobiological and genetic variations could contribute to the pathophysiology of lifelong PE, [26, 29, 111-113] but the etiology of acquired PE is both psychological and organic, the latter being commonly associated with other comorbid diseases. [66, 95-99] Men with acquired PE have a higher incidence of ED, other comorbid disease and cardiovascular risk factors. [38-41, 94]

Serefoglu et al.[39], Zhang et al.[40] and Gao et al.[41] reported that patients with acquired PE had a higher mean BMI and a greater incidence of comorbid disease including hypertension, sexual desire disorder, diabetes mellitus, chronic prostatitis, and ED compared to lifelong, variable and subjective PE.

Porst et al. reported the presence of comorbid ED in 15% and 24% of the lifelong and acquired PE subgroups, respectively.[25] Overall, the mean IIEF domain scores were similar for the lifelong and acquired subgroups for erectile function (27.9 vs. 27.1), orgasmic function (8.9 vs. 8.6), sexual desire (7.7 vs. 7.5), intercourse satisfaction (8.2 vs. 7.8), and overall satisfaction (5.1 vs. 5.1). Predictably, slightly lower IIEF domain scores for the orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction domains were observed in men with mild ED. However, this post-hoc analysis has several limitations imposed by the design of the original Phase 3 studies that restrict additional analysis of other factors that may have discriminatory relevance. These limitations include; (1) the use of the authority-based DSM-IV-TR to diagnose PE, (2) the lack of a standardized method used to differentiate lifelong and acquired PE, (3) the application of IELT selection criteria based upon normative IELT data for men with lifelong PE which may have filtered out more substantial differences in average IELT that may exist between these two subtypes in the general population, (4) the exclusion of men with moderate or severe ED (IIEF-EF domain score <21), chronic prostatitis, and lack of information regarding hyperthyroidism.

It is likely that the inclusion of men with moderate or severe ED in the studies comprising the Porst et al. study[25] might have resulted in a statistically significant age trend consistent with the epidemiology of ED, in which prevalence is known to increase with age and statistically different overall IIEF domain scores. The greater disparity in age between these two PE sub-groups observed in the COUPLE study which enrolled men with more severe ED supports this speculation. [109, 114]

Differences in Intravaginal Ejaculatory Latency Times (IELT) between Lifelong and Acquired PE: Porst et al. reported that both the arithmetic (1.1 vs. 0.9 min., P<0.001) and

geometric mean IELT (0.9 vs. 0.7 min., P<0.001) was slightly (but significantly) greater for patients with acquired PE. [25] Several authors have confirmed this preliminary finding by demonstrating that self-estimated IELT is higher in men with acquired PE compared to lifelong PE. [38, 40, 41, 109]

The post hoc analysis of the COUPLE data confirms a statistically significant higher IELT in men with acquired PE and comorbid compared to men with lifelong PE with comorbid ED (52.2 years vs. 45.5 years) (Table 6). [109, 114] Serefoglu et al. [39] reported that self-estimated IELT was lowest in men with lifelong PE and highest in men with subjective PE. (lifelong PE: 20.47±28.90 seconds (2–120 seconds); acquired PE: 57.91±38.72 seconds (90–180 seconds); variable PE: 144.17±22.47 seconds (120–180 seconds); subjective PE:286.67±69.96 seconds (180–420 seconds, *P* = 0.001). Gao et al. [41] and Zhang et al. [40] confirmed that self-estimated IELT follows a continuum among the four PE syndromes and reported a mean self-estimated IELT of 1.65±0.82 minutes and 1.84±1.02 minutes respectively in acquired PE patients. These data suggest 3 minutes as a valid cut-off for either self-estimated or stopwatch IELT for the diagnosis of acquired PE.

Differences in Patient Reported Outcomes (PRO) between Lifelong and Acquired PE: Both Porst et al. [25] and McMahon et al. [109] reported that the majority of patients with acquired and lifelong PE, regardless of comorbid ED, reported perceived control over ejaculation as "poor" or "very poor," levels of satisfaction with intercourse as "fair" or worse, and at least "moderate" levels of personal distress. The COUPLE data demonstrates that men with lifelong PE and comorbid ED have less control, less satisfaction, more distress and interpersonal difficulty than men with acquired PE and comorbid ED. (Table 6) [109, 110]

These findings conflicts with the reports of Patrick et al. [19] and Serefoglu et al. [39] who observed better satisfaction with sexual intercourse and less interpersonal difficulty in the lifelong PE subgroup compared to the acquired PE sub-group. However, caution should be exercised in assigning lower levels of sexual satisfaction solely to the effect of PE and contributions from other difficult to quantify issues such reduced intimacy, dysfunctional relationships, poor sexual attraction, and poor communication should not be ignored. This is supported by the report of Patrick et al. that despite reduced ratings for satisfaction with shorter IELTs, a substantial proportion of men with an IELT <1 min report "good" or "very good" satisfaction ratings (43.7%).

In conclusion, men with lifelong and acquired PE appear to share the dimensions of short ejaculatory latency, reduced or absent perceived ejaculatory control, and the presence of negative personal consequences. Although there are limited published reports, these studies supported by expert opinion suggest that self-estimated IELT appears higher in men with acquired PE compared to lifelong PE and that a self-estimated or stop-watch IELT of 3 minutes is a valid IELT cut-off for diagnosing acquired PE. Men with acquired PE patients are older, have higher incidences of ED, comorbid disease and cardiovascular risk factors and report less sexual satisfaction and more interpersonal difficulty compared to patients with lifelong PE. Further observational studies in men with acquired PE are required to validate the 3 min IELT cut-off and other patient characteristics.

Conclusion

Although the 2007 ISSM Definition of Lifelong PE represented a major development in the application of evidence based methodology in the field of sexual medicine, its application in clinical practice is restricted by it's limitation to men with lifelong PE. Research into the

epidemiology, etiology, features and treatment of acquired PE has been limited by the lack of an evidenced-based definition. An urgent need for standardization of PE observational, intervention and intervention preference trial methodology continues to exist. The lack of an evidence-based definition promotes errors of classification resulting in poorly defined study populations with less reliable and less interpretable data which is difficult to generalise to patients.

The unified ISSM definition of lifelong and acquired PE represents an evidence-based definition for these conditions. This definition should form the basis for both the office diagnosis of lifelong PE and the design of PE observational and interventional clinical trials. It is limited to men engaging in vaginal intercourse because there are few studies on early ejaculation in the context of oral sex, anal sex, and same-gender sexual activity between men.

The evidence suggests that the multivariate evidence-based unified ISSM definition of lifelong and acquired PE will reduce errors of diagnosis and classification by providing the clinician with a discriminating diagnostic tool. The IELT cut-off of about one minute captures the 90% of men with lifelong PE who actively seek treatment and ejaculate within 1 minute but also affords the clinician sufficient flexibility to also diagnose lifelong PE in the 10% of lifelong PE treatment seeking men who ejaculate within 1-2 minutes of penetration.

The Committee reiterated that the 1 minute IELT cut-off point should not be applied in the most absolute sense, as about 10% of men seeking treatment for lifelong PE have IELTs of 1-2 minutes. The phrase, "within about 1 minute" must be interpreted as giving the clinician sufficient flexibility to diagnose PE also in men who report an IELT as long as 90 seconds. Similarly, a degree of flexible clinical judgement is key to the recognition and interpretation of a bothersome change in ejaculatory latency with reduction of pre-morbid latency to ≤ 3 minutes in men with acquired PE. Men who report these ejaculatory latencies but describe adequate control and no personal negative consequences related to their rapid ejaculation do not merit the diagnosis of PE.

This definition intentionally includes a degree of diagnostic conservatism and flexibility for several reasons. First, a conservative and flexible definition provides a more realistic prevalence of the dysfunction. Second, it would help to establish PE as a bona fide sexual dysfunction rather than a lifestyle condition where men are simply seeking to enhance their sexual function. Third, it would help to ensure greater confidence in the efficacy of new and existing treatments and strengthen the likelihood that regulatory agencies might approve new efficacious and safe compounds for this dysfunction.[27]

We wish to thank the ISSM for its leadership for assembling and encouraging the committee members in the development of the evidenced based definition of lifelong and acquired PE. We anticipate that this definition will promote and assist further research into the prevalence of both lifelong and acquired PE, the development of new tools and PRO's for both the diagnosis and assessment of treatment outcomes and the development of new pharmacologic and psychological treatments.

Author Conflicts of Interest

Serefoglu EC	Allergan, Consultant
McMahon CG	Johnson & Johnson-Consultant, Principal Investigator, Advisory Board Member, Speaker Menarini Group-Principal Investigator, Advisory Board Member, Speaker Bayer Schering-Investigator, Advisory Board, Speaker Plethora Solutions-Advisory Board, Speaker Ixchelsis-Consultant
Althof S	Allergan, Consultant, Principal Investigator Abvie, Consultant Eli Lilly, Consultant Ixchelsis, Consultant Menarini, Speaker Palitan- Advisory Board, Plethora- Consultant Sprout, Consultant Trimel, Principal Investigator
Waldinger MD	Emotional Brain B.V., Advisory Board Menarini Netherlands, Advisory Board Pound Int., Advisory Board

Legend of Tables

Bibliography

[1] Masters WH, Johnson VE. *Human Sexual Inadequacy*. Boston: Little Brown; 1970.
[2] American Psychiatric Association. *Diagnostic And Statistical Manual of Mental Disorders, DSM-IV 4th. Ed*. Washington D.C.; 1994.
[3] World Health Organization. International Classification of Diseases and Related Health Problems (10th ed.). Geneva: World Health Organization. 1994.
[4] Metz M, McCarthy B. *Coping with premature ejaculation: how to overcome PE, please your partner and have great sex*. Oakland (CA): New Harbinber Publications; 2003.
[5] Montague DK, Jarow J, Broderick GA, et al. AUA guideline on the pharmacologic management of premature ejaculation. *The Journal of urology*. 2004;**172**: 290-4.
[6] Colpi G, Weidner W, Jungwirth A, et al. EAU guidelines on ejaculatory dysfunction. *European urology*. 2004;**46**: 555-8.
[7] McMahon CG, Abdo C, Incrocci I, et al. Disorders of orgasm and ejaculation in men. In: Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F, eds. *Sexual Medicine: Sexual Dysfunctions in Men and Women (2nd International Consultation on Sexual Dysfunctions-Paris)*. Paris, France: Health Publications; 2004:409-68.
[8] Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Proposal for a definition of lifelong premature ejaculation based on epidemiological stopwatch data. *The journal of sexual medicine*. 2005;**2**: 498-507.
[9] Jannini EA, Lombardo F, Lenzi A. Correlation between ejaculatory and erectile dysfunction. *International journal of andrology*. 2005;**28 Suppl 2**: 40-5.
[10] McMahon CG, Althof SE, Waldinger MD, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. *The journal of sexual medicine*. 2008;**5**: 1590-606.
[11] St Lawrence JS, Madakasira S. Evaluation and treatment of premature ejaculation: a critical review. *International journal of psychiatry in medicine*. 1992;**22**: 77-97.
[12] Waldinger MD, Schweitzer DH. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part I--validity of DSM-IV-TR. *The journal of sexual medicine*. 2006;**3**: 682-92.
[13] Waldinger MD, Schweitzer DH. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part II--proposals for DSM-V and ICD-11. *The journal of sexual medicine*. 2006;**3**: 693-705.
[14] O'Donohue W, Letourneau EJ, Geer JH. *Premature ejaculation*: Simon and Schuster; 1993.
[15] Waldinger MD. The neurobiological approach to premature ejaculation. *The Journal of urology*. 2002;**168**: 2359-67.
[16] Althof SE, Symonds T. Patient reported outcomes used in the assessment of premature ejaculation. *The Urologic clinics of North America*. 2007;**34**: 581-9, vii.
[17] Waldinger M, Hengeveld M, Zwinderman A, Olivier B. An empirical operationalization of DSM-IV diagnostic criteria for premature ejaculation. *Int J Psychiatry Clin Pract*. 1998;**2**: 287-93.
[18] McMahon CG. The DSM-IV-TR definition of premature ejaculation and its impact upon the results of epidemiological studies. *European urology*. 2008;**53**: 887-9.
[19] Patrick DL, Althof SE, Pryor JL, et al. Premature ejaculation: an observational study of men and their partners. *The journal of sexual medicine*. 2005;**2**: 358-67.

[20] Giuliano F, Patrick DL, Porst H, et al. Premature ejaculation: results from a five-country European observational study. *European urology*. 2008;**53**: 1048-57.
[21] Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A Multinational Population Survey of Intravaginal Ejaculation Latency Time. *The journal of sexual medicine*. 2005;**2**: 492–97.
[22] McMahon CG. Long term results of treatment of premature ejaculation with selective serotonin re-uptake inhibitors. *IntJImpRes*. 2002;**14**: S19.
[23] Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;**213**: 71-72.
[24] McMahon CG. Clinical trial methodology in premature ejaculation observational, interventional, and treatment preference studies--part I--defining and selecting the study population. *The journal of sexual medicine*. 2008;**5**: 1805-16.
[25] Porst H, McMahon CG, Althof SE, et al. Baseline characteristics and treatment outcomes for men with acquired or lifelong premature ejaculation with mild or no erectile dysfunction: integrated analyses of two phase 3 dapoxetine trials. *The journal of sexual medicine*. 2010;**7**: 2231-42.
[26] Janssen PK, Bakker SC, Rethelyi J, et al. Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. *The journal of sexual medicine*. 2009;**6**: 276-84.
[27] Althof SE, Rowland DL. Identifying constructs and criteria for the diagnosis of premature ejaculation: implication for making errors of classification. *BJU international*. 2008;**102**: 708-12.
[28] Waldinger MD. The need for a revival of psychoanalytic investigations into premature ejaculation. *J Mens Health & Gender* 2006;**3**: 6.
[29] Waldinger MD, Schweitzer DH. The use of old and recent DSM definitions of premature ejaculation in observational studies: a contribution to the present debate for a new classification of PE in the DSM-V. *The journal of sexual medicine*. 2008;**5**: 1079-87.
[30] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (3rd edition) (DSM-III)*. Washington, DC: American Psychiatric Association; 1980.
[31] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (3rd edition, revised) (DSM-III-R). Washington, DC: American Psychiatric Association; 1987.
[32] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edition, Text Revision) (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.
[33] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5)*. Washington, DC: American Psychiatric Association; 2013.
[34] Shapiro B. Premature ejaculation: a review of 1130 cases. *The Journal of urology*. 1943;**50**: 6.
[35] Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. *Journal of sex & marital therapy*. 1989;**15**: 130-4.
[36] Waldinger MD, McIntosh J, Schweitzer DH. A five-nation survey to assess the distribution of the intravaginal ejaculatory latency time among the general male population. *The journal of sexual medicine*. 2009;**6**: 2888-95.

[37] Waldinger MD. History of premature ejaculation. In: Jannini EA MC, Waldinger MD, ed. *Premature Ejaculation: From Etiology to Diagnosis and Treatment*. New York: Springer; 2013:5-24.
[38] Serefoglu EC, Cimen HI, Atmaca AF, Balbay MD. The distribution of patients who seek treatment for the complaint of ejaculating prematurely according to the four premature ejaculation syndromes. *The journal of sexual medicine*. 2010;**7**: 810-5.
[39] Serefoglu EC, Yaman O, Cayan S, et al. Prevalence of the complaint of ejaculating prematurely and the four premature ejaculation syndromes: results from the Turkish Society of Andrology Sexual Health Survey. *The journal of sexual medicine*. 2011;**8**: 540-8.
[40] Zhang X, Gao J, Liu J, et al. Distribution and Factors Associated with Four Premature Ejaculation Syndromes in Outpatients Complaining of Ejaculating Prematurely. *The journal of sexual medicine*. 2013.
[41] Gao J, Zhang X, Su P, et al. Prevalence and Factors Associated with the Complaint of Premature Ejaculation and the Four Premature Ejaculation Syndromes: A Large Observational Study in China. *The journal of sexual medicine*. 2013.
[42] Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double blind, randomized, placebo controlled study. *Am J Psychiatry*. 1994;**151**: 1377-9.
[43] Rosen RC, McMahon CG, Niederberger C, Broderick GA, Jamieson C, Gagnon DD. Correlates to the clinical diagnosis of premature ejaculation: results from a large observational study of men and their partners. *The Journal of urology*. 2007;**177**: 1059-64; discussion 64.
[44] Althof SE, Levine SB, Corty EW, Risen CB, Stern EB, Kurit DM. A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *The Journal of clinical psychiatry*. 1995;**56**: 402-7.
[45] Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. The majority of men with lifelong premature ejaculation prefer daily drug treatment: an observation study in a consecutive group of Dutch men. *The journal of sexual medicine*. 2007;**4**: 1028-37.
[46] Grenier G, Byers ES. The relationships among ejaculatory control, ejaculatory latency, and attempts to prolong heterosexual intercourse. *Archives of sexual behavior*. 1997;**26**: 27-47.
[47] McMahon CG, Waldinger M, Rowland DL, et al. Ejaculatory Disorders. In: Porst H, Buvat, J, ed. *Standard Practice in Sexual Medicine*. Oxford UK: Blackwell Publishing; 2006:188-209.
[48] Perelman MA. A new combination treatment for premature ejaculation: a sex therapist's perspective. *The journal of sexual medicine*. 2006;**3**: 1004-12.
[49] Kaplan HS, Kohl RN, Pomeroy WB, Offit AK, Hogan B. Group treatment of premature ejaculation. *Archives of sexual behavior*. 1974;**3**: 443-52.
[50] McCarthy B. Cognitive-behavioural strategies and techniques in the treatment of early ejaculation. In: Leiblum SR, Rosen R, eds. *Principles and Practices of Sex Therapy: Update for the 1990's*. New York: Guilford Press; 1988:141-67.
[51] Vandereycken W. Towards a better delineation of ejaculatory disorders. *Acta psychiatrica Belgica*. 1986;**86**: 57-63.
[52] Zilbergeld B. *Male Sexuality*. Toronto: Bantam; 1978.
[53] Grenier G, Byers S. Operationalizing premature or rapid ejaculation. *J Sex Res*. 2001;**38**: 369-78.
[54] McMahon CG, Stuckey BG, Andersen M, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *The journal of sexual medicine*. 2005;**2**: 368-75.

[55] Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *International journal of impotence research*. 2004;**16**: 369-81.
[56] Rowland DL, Strassberg DS, de Gouveia Brazao CA, Slob AK. Ejaculatory latency and control in men with premature ejaculation: an analysis across sexual activities using multiple sources of information. *Journal of psychosomatic research*. 2000;**48**: 69-77.
[57] Patrick DL, Rowland D, Rothman M. Interrelationships among measures of premature ejaculation: the central role of perceived control. *The journal of sexual medicine*. 2007;**4**: 780-8.
[58] Rowland D, Perelman M, Althof S, et al. Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. *The journal of sexual medicine*. 2004;**1**: 225-32.
[59] Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, Alexander J. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *European urology*. 2007;**51**: 816-23; discussion 24.
[60] Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. *Journal of epidemiology and community health*. 1999;**53**: 144-8.
[61] Symonds T, Roblin D, Hart K, Althof S. How does premature ejaculation impact a man's life? *Journal of sex & marital therapy*. 2003;**29**: 361-70.
[62] Rowland DL, Patrick DL, Rothman M, Gagnon DD. The psychological burden of premature ejaculation. *The Journal of urology*. 2007;**177**: 1065-70.
[63] McCabe MP. Intimacy and quality of life among sexually dysfunctional men and women. *Journal of sex & marital therapy*. 1997;**23**: 276-90.
[64] Byers ES, Grenier G. Premature or rapid ejaculation: heterosexual couples' perceptions of men's ejaculatory behavior. *Archives of sexual behavior*. 2003;**32**: 261-70.
[65] Riley A, Riley E. Premature ejaculation: presentation and associations. An audit of patients attending a sexual problems clinic. *International journal of clinical practice*. 2005;**59**: 1482-7.
[66] Hartmann U, Schedlowski M, Kruger TH. Cognitive and partner-related factors in rapid ejaculation: Differences between dysfunctional and functional men. *World J Urol*. 2005;**10**: 10.
[67] Brock GB, Gajewski J, Carrier S, Bernard F, Lee J, Pommerville PJ. The prevalence and impact of premature ejaculation in Canada. *Proceedings of Annual Meeting of the American Urological Association*. Anaheim, CA; May 19-24, 2007.
[68] Althof SE. Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. *The Journal of urology*. 2006;**175**: 842-8.
[69] Althof S. The psychology of premature ejaculation: therapies and consequences. *The journal of sexual medicine*. 2006;**3 Suppl 4**: 324-31.
[70] Rosen RC, Althof S. Impact of premature ejaculation: the psychological, quality of life, and sexual relationship consequences. *The journal of sexual medicine*. 2008;**5**: 1296-307.
[71] Amidu N, Owiredu WK, Woode E, Addai-Mensah O, Gyasi-Sarpong KC, Alhassan A. Prevalence of male sexual dysfunction among Ghanaian populace: myth or reality? *International journal of impotence research*. 2010;**22**: 337-42.
[72] Christensen BS, Gronbaek M, Osler M, Pedersen BV, Graugaard C, Frisch M. Sexual dysfunctions and difficulties in denmark: prevalence and associated sociodemographic factors. *Archives of sexual behavior*. 2011;**40**: 121-32.

[73] Hirshfield S, Chiasson MA, Wagmiller RL, Jr., et al. Sexual dysfunction in an Internet sample of U.S. men who have sex with men. *The journal of sexual medicine*. 2010;**7**: 3104-14.
[74] Liang CZ, Hao ZY, Li HJ, et al. Prevalence of premature ejaculation and its correlation with chronic prostatitis in Chinese men. *Urology*. 2010;**76**: 962-6.
[75] Shaeer O, Shaeer K. The Global Online Sexuality Survey (GOSS): ejaculatory function, penile anatomy, and contraceptive usage among Arabic-speaking Internet users in the Middle East. *The journal of sexual medicine*. 2012;**9**: 425-33.
[76] Tang WS, Khoo EM. Prevalence and correlates of premature ejaculation in a primary care setting: a preliminary cross-sectional study. *The journal of sexual medicine*. 2011;**8**: 2071-8.
[77] Vakalopoulos I, Dimitriadis G, Varnava C, Herodotou Y, Gkotsos G, Radopoulos D. Prevalence of ejaculatory disorders in urban men: results of a random-sample survey. *Andrologia*. 2011;**43**: 327-33.
[78] McMahon CG, Lee G, Park JK, Adaikan PG. Premature ejaculation and erectile dysfunction prevalence and attitudes in the Asia-Pacific region. *The journal of sexual medicine*. 2012;**9**: 454-65.
[79] Nolazco C, Bellora O, Lopez M, et al. Prevalence of sexual dysfunctions in Argentina. *Int J Impot Res*. 2004;**16**: 69-72.
[80] Shaeer O. The Global Online Sexuality Survey (GOSS): The United States of America in 2011 Chapter III-Premature Ejaculation Among English-Speaking Male Internet Users. *The journal of sexual medicine*. 2013;**10**: 1882-8.
[81] Shindel AW, Vittinghoff E, Breyer BN. Erectile dysfunction and premature ejaculation in men who have sex with men. *The journal of sexual medicine*. 2012;**9**: 576-84.
[82] Stulhofer A, Bajic Z. Prevalence of erectile and ejaculatory difficulties among men in Croatia. *Croatian medical journal*. 2006;**47**: 114-24.
[83] Jannini EA, Lenzi A. Epidemiology of premature ejaculation. *Current opinion in urology*. 2005;**15**: 399-403.
[84] Giuliano F, Clement P. Pharmacology for the Treatment of Premature Ejaculation. *Pharmacological reviews*. 2012.
[85] Simons JS, Carey MP. Prevalence of sexual dysfunctions: results from a decade of research. *Archives of sexual behavior*. 2001;**30**: 177-219.
[86] Vansintejan J, Janssen J, Van De Vijver E, Vandevoorde J, Devroey D. The Gay Men Sex Studies: prevalence of sexual dysfunctions in Belgian HIV(+) gay men. *Hiv/Aids*. 2013;**5**: 89-96.
[87] Waldinger MD. Recent advances in the classification, neurobiology and treatment of premature ejaculation. *Advances in psychosomatic medicine*. 2008;**29**: 50-69.
[88] Lotti F, Corona G, Rastrelli G, Forti G, Jannini EA, Maggi M. Clinical correlates of erectile dysfunction and premature ejaculation in men with couple infertility. *The journal of sexual medicine*. 2012;**9**: 2698-707.
[89] Serefoglu EC, Yaman O, Cayan S, et al. The comparison of premature ejaculation assessment questionnaires and their sensitivity for the four premature ejaculation syndromes: results from the Turkish society of andrology sexual health survey. *The journal of sexual medicine*. 2011;**8**: 1177-85.
[90] Shindel AW, Nelson CJ, Naughton CK, Mulhall JP. Premature ejaculation in infertile couples: prevalence and correlates. *The journal of sexual medicine*. 2008;**5**: 485-91.
[91] Son H, Song SH, Kim SW, Paick JS. Self-reported premature ejaculation prevalence and characteristics in Korean young males: community-based data from an internet survey. *Journal of andrology*. 2010;**31**: 540-6.

[92] Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA*. 1999;**281**: 537-44.
[93] Montorsi F. Prevalence of premature ejaculation: A global and regional perspective. *Journal of Sexual Medicine*. 2005;**Suppl 2**.
[94] Basile Fasolo C, Mirone V, Gentile V, et al. Premature ejaculation: prevalence and associated conditions in a sample of 12,558 men attending the andrology prevention week 2001--a study of the Italian Society of Andrology (SIA). *The journal of sexual medicine*. 2005;**2**: 376-82.
[95] Laumann EO, Nicolosi A, Glasser DB, et al. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res*. 2005;**17**: 39-57.
[96] Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA. Prevalence of chronic prostatitis in men with premature ejaculation. *Urology*. 2001;**58**: 198-202.
[97] Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *The Journal of clinical endocrinology and metabolism*. 2005;**90**: 6472-9.
[98] Adson DE, Kotlyar M. Premature ejaculation associated with citalopram withdrawal. *The Annals of pharmacotherapy*. 2003;**37**: 1804-6.
[99] Peugh J, Belenko S. Alcohol, drugs and sexual function: a review. *J Psychoactive Drugs*. 2001;**33**: 223-32.
[100] Williams W. Secondary premature ejaculation. *The Australian and New Zealand journal of psychiatry*. 1984;**18**: 333-40.
[101] Dogan S, Dogan M. The frequency of sexual dysfunctions in male partners of women with vaginismus in a Turkish sample. *International journal of impotence research*. 2008;**20**: 218-21.
[102] Donatucci CF. Etiology of ejaculation and pathophysiology of premature ejaculation. *The journal of sexual medicine*. 2006;**3 Suppl 4**: 303-8.
[103] Zohdy W. Clinical parameters that predict successful outcome in men with premature ejaculation and inflammatory prostatitis. *The journal of sexual medicine*. 2009;**6**: 3139-46.
[104] Shamloul R, el-Nashaar A. Chronic prostatitis in premature ejaculation: a cohort study in 153 men. *The journal of sexual medicine*. 2006;**3**: 150-4.
[105] Sharlip ID. Guidelines for the diagnosis and management of premature ejaculation. *The journal of sexual medicine*. 2006;**3 Suppl 4**: 309-17.
[106] El-Nashaar A, Shamloul R. Antibiotic treatment can delay ejaculation in patients with premature ejaculation and chronic bacterial prostatitis. *The journal of sexual medicine*. 2007;**4**: 491-6.
[107] Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clinical endocrinology*. 1977;**7**: 481-93.
[108] Atkinson RL, Dahms WT, Fisher DA, Nichols AL. Occult thyroid disease in an elderly hospitalized population. *J Gerontol*. 1978;**33**: 372-6.
[109] McMahon CG, Giuliano F, Dean J, et al. Efficacy and safety of dapoxetine in men with premature ejaculation and concomitant erectile dysfunction treated with a phosphodiesterase type 5 inhibitor: randomized, placebo-controlled, phase III study. *The journal of sexual medicine*. 2013;**10**: 2312-25.
[110] Mamidi P, Gupta K. Efficacy of certain yogic and naturopathic procedures in premature ejaculation: A pilot study. *International journal of yoga*. 2013;**6**: 118-22.
[111] Waldinger M. The neurobiological approach to premature ejaculation. *Journal of Urology*. 1998;**168**: 2359-67.

[112] Jern P, Santtila P, Alanko K, et al. Premature and delayed ejaculation: Genetic and environmental effects in a population-based sample of Finnish twins. *Journal of Sexual Medicine*. 2007;**4**: 1739-49.
[113] Levine L. Evaluation of Withdrawal Effects with Dapoxetine in the Treatment of Premature Ejaculation (PE). *Poster presented at SMSNA* 2006.
[114] Harris SS, Maciag D, Simpson KL, Lin RC, Paul IA. Dose-dependent effects of neonatal SSRI exposure on adult behavior in the rat. *Brain research*. 2012;**1429**: 52-60.
[115] Pryor JL, Broderick GA, Ho KF, Jamieson C, Gagnon D. Comparison of Estimated Versus Measured Intravaginal Ejaculatory Latency Time (IELT) in Men With and Without Premature Ejaculation (PE). *The journal of sexual medicine*. 2005;**3**: 54:abstract 126.
[116] Dunn KM, Croft PR, Hackett GI. Sexual problems: a study of the prevalence and need for health care in the general population. *Family practice*. 1998;**15**: 519-24.
[117] Fugl-Meyer K, Fugl-Meyer AR. Sexual disabilities are not singularities. *Int J Impot Res*. 2002;**14**: 487-93.
[118] Laumann EO, Nicolosi A, Glasser DB, et al. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *International journal of impotence research*. 2005;**17**: 39-57.
[119] Brock GB, Benard F, Casey R, Elliott SL, Gajewski JB, Lee JC. Canadian male sexual health council survey to assess prevalence and treatment of premature ejaculation in Canada. *The journal of sexual medicine*. 2009;**6**: 2115-23.
[120] Traeen B, Stigum H. Sexual problems in 18-67-year-old Norwegians. *Scandinavian journal of public health*. 2010;**38**: 445-56.
[121] Park HJ, Park JK, Park K, et al. Prevalence of premature ejaculation in young and middle-aged men in Korea: a multicenter internet-based survey from the Korean Andrological Society. *Asian journal of andrology*. 2010;**12**: 880-9.
[122] Mialon A, Berchtold A, Michaud PA, Gmel G, Suris JC. Sexual dysfunctions among young men: prevalence and associated factors. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 2012;**51**: 25-31.
[123] Zhang H, Yip AW, Fan S, Yip PS. Sexual dysfunction among Chinese married men aged 30-60 years: a population-based study in Hong Kong. *Urology*. 2013;**81**: 334-9.
[124] Lee SW, Lee JH, Sung HH, et al. The prevalence of premature ejaculation and its clinical characteristics in Korean men according to different definitions. *Int J Impot Res*. 2012.
[125] Jannini E, Lenzi A. Epidemiology of premature ejaculation. *Current opinion in urology*. 2005;**15**: 399-403.