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Evaluation of Premature Ejaculation

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Introduction

Since its first description in medical literature in 1887, premature ejaculation (PE) has given rise to various and sometimes highly contrasting theories, approaches, and treatments [1, 2]. Although PE was initially considered as nothing more than a peculiar anomaly, it was believed to be mainly a psychological disorder for the first half of the twentieth century [3]. After the first psychoanalytic publications of Sandor Ferenczi and Karl Abraham in 1908 and 1917, respectively, PE was regarded as a symptom of a neurosis that had to be treated by psychoanalysis in order to solve the unconscious conflicts that were assumed to have caused the neurosis [3]. This purely psychoanalytical theory was later challenged by Bernard Schapiro, an originally German but later American endocrinologist, who in 1943 postulated that PE was not a neurotic but a psychosomatic disorder [4]. Years ahead of his time, Schapiro advocated oral and local anesthetic drug treatment to delay ejaculation [4, 5]. Bernard Schapiro should be regarded as the most important pioneer in the research and treatment of PE [6].

First PE Classification of Schapiro

It has been the great merit of Bernard Schapiro who in 1943 for the first time distinguished two subtypes of PE [4]. Based on his long experience with men with PE, Schapiro distinguished Type B or "*the sexually hypertonic or hypererotic type*" and Type A or the "*hypotonic type*" [4]. Both types were later called lifelong PE and acquired PE, respectively [7]. Schapiro noted that in Type B (lifelong PE) "*premature ejaculation, from the very first act of coitus, was continually present*" [4]. But also that "*careful questioning elicited the information that relatives of the patient (father or brother) with type B suffered from the same disorder*" [4]. Therefore, Schapiro assumed that "*in type B (lifelong PE) heredity may play a part in the etiology"* [4]. In addition, Schapiro noted that in type B "*libido and erection were rather overstrong, and erection was provoked by even mild sexual stimulation",* which phenomenon he called *"erectio praecox*" [4]. Schapiro also noted that in type B men, PE was associated with "*abnormally high sexual tension*", which he called a "*hypertonus of the entire sex apparatus*" [4]. Schapiro emphasized that the characteristics of men with type B or lifelong PE were "*entirely different*" than those of men with "type A" or "acquired PE", who did not have family members with PE and in which erectio praecox and hypertonus was not part of the subtype [4].

Unfortunately, the classification and arguments of Schapiro were completely ignored by clinicians and sexologists for nearly 50 years until Godpodinoff [7] distinguished lifelong and acquired PE, which actually were Type B and Type A of Schapiro, respectively. But erectio praecox remained ignored, and actually completely forgotten, until Waldinger mentioned it again in 2002 [2]. Similarly, Schapiro's terms hypertonic and hypotonic have been completely forgotten, until 2014, when Waldinger reintroduced both terms and explained their clinical importance [8].

Psychoanalytic, Behavioristic, and Drug Treatment Approach of PE

Psychoanalytic treatment, mainly conducted by psychiatrists, prevailed throughout the 1940s and 1950s, but unfortunately, very little information of this treatment has been documented in the literature [6]. In contrast to the psychoanalytic, psychosomatic, and urological approach of PE, William Masters and Virginia Johnson stated in 1970 that PE was the result of self-learned behavior and that behavioral treatment in the form of the so-called squeeze technique could cure PE [9]. Their treatment was a modification to the stop-start technique, a masturbation technique, described in 1956 by James Semans, an English urologist [10]. However, there is a dramatic paucity of evidence-based studies demonstrating its efficacy to delay ejaculation in men who ejaculate within seconds [3]. In the mid-1990s, the introduction of the

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selective serotonin reuptake inhibitors (SSRIs) brought about a revolutionary change in the understanding and treatment of PE [2]. Their efficacy in delaying ejaculation together with the increasing interest of neuroscientists, in investigating sexual behavior in laboratory male rats led to the end of the supremacy of the behavioristic approach of PE that prevailed in the 1970s and 1980s and marked the beginning of the neurobiological view and drug treatment approach of the 1990s [6]. Animal studies and the use of stopwatch assessment of the intravaginal ejaculation latency time (IELT) [11] both during a baseline period and during drug treatment led to a more evidence-based approach of drug treatment trials but also formed the basis of a new classification of PE into four PE subtypes. It should be noted that during the 1990s and around the millennium the evidence-based methodology of investigating drug treatment of PE has been developed by clinical researchers independently of the pharmaceutical industry as in the 1990s SSRI manufacturers have not been interested in official registration of SSRIs for the treatment of PE [6, 12]. However, this very important period in the history of academic interest in PE ended in 2004 when some pharmaceutical companies became interested in PE and an increasing number of clinicians with no previous experience in PE research became involved or participated in PE research of the pharmaceutical industry with its own ideas on how to conduct PE research.

Second PE Classification of Waldinger

In 1994, Waldinger introduced the intravaginal ejaculation latency time (IELT) as a scientific measure of the ejaculation time [11]. The IELT was defined as the time between vaginal intromission and intravaginal ejaculation [11]. Particularly by using a stopwatch—the most accurate tool to measure time—for IELT measurement, it became unambiguously clear that about 85% of men with lifelong PE ejaculate within 1 min after vaginal penetration [13]. In other words, lifelong PE appeared to be a matter of seconds, which was in support of an old psychoanalytic view of PE, whereas later studies provided indications—although less convincing—that acquired PE was a matter of seconds to 3 min [14].

Due to epidemiological stopwatch research of the IELT in the general population in five countries [15, 16], it became no longer tenable to claim that there are only two types of PE. Therefore, Waldinger and Schweitzer postulated the existence of two other PE subtypes: Subjective PE and Variable PE [17–21]. This new classification into four PE subtypes is based on differences in the duration of the IELT, the course of the IELT duration throughout life, the frequency of occurrence of short IELTs, and the cognitive and subjective experience of the IELT [17–21]. Moreover, the etiology and pathogenesis of the four PE subtypes is different [20]. Men with lifelong PE suffer from IELTs that have been consistently less than 1 min since puberty or adolescence [13]. In contrast, acquired PE may be caused by erectile dysfunction, thyroid disorders, acute prostatitis or relationship problems [14, 22–25]. In Subjective PE men have a normal or even long IELT duration but still perceive themselves as having PE. In Variable PE the IELT is only sometimes very short [21]. In other words, according to Waldinger [17–21] there is a natural variation of the IELT in men with Variable PE, and therefore this PE subtype is not based on (psycho)pathology, whereas Subjective PE is mainly related to psychological and cultural factors [17–21]. In contrast, lifelong PE is related to neurobiological and genetic factors, whereas acquired PE is related to mainly medical factors [26, 27]. A clear advantage of this new classification into four subtypes is that any man with a complaint of early ejaculation can be classified into one of the four PE subtypes [21, 28].

Diagnosis of the Four PE Subtypes

Each of the four PE subtypes has its own specific etiology, (patho)genesis and treatment. They are recognizable by taking a brief medical and sexual history with special attention to the duration of the IELT, the frequency of occurrences and the course since the first sexual encounters [6]. In daily clinical practice, diagnosis of the four PE subtypes is not difficult and therefore evaluation with (validated) questionnaires or the use of a stopwatch is not required. However, for drug treatment trials, genetic and epidemiological research, stopwatch assessment of the IELT is a prerequisite [6, 26, 29].

Complaint Versus Disorder

A major misconception in the literature on PE is the idea that PE always represents a male sexual "disorder" [20, 29]. This misconception is blurring an accurate view on diagnosis, classification, epidemiology, genetics, and treatment of PE [6]. In 2006, Waldinger and Schweitzer emphasized the relevance of distinguishing between PE as a "complaint" versus PE as a "syndrome" or "disorder" [17, 18]. PE as a "complaint" may belong to the *normal* variation of ejaculatory performance in a certain number of men, but may also be the manifestation of medically or psychologically determined *pathological* ejaculatory performance [6]. A "syndrome" is defined as a cluster of symptoms and may give rise to a cluster of various complaints that is similar in a large group of men [6]. In contrast, there are also men who complain of PE but lack the whole symptomatology of men with lifelong PE. They report experiencing early ejaculations only occasionally. In other words, the latter men have "complaints" of PE which are not part of an underlying syndrome or disorder. It should be emphasized that a nondistinction between complaint and disorder leads to misunderstanding of for example

the epidemiology of PE [29]. For example, it has become customary to start an article on PE with the following introduction: "PE is the most prevalent male sexual *disorder* affecting some 20-30% of men." This sentence mirrors a general belief that PE always represents a male sexual disorder. However, if one distinguishes PE as a "complaint" versus PE as a "disorder", it appears more appropriate to state "PE is the most prevalent male sexual complaint affecting some 20-30% of men. The prevalence of PE as a sexual disorder, in case of lifelong and acquired PE, in the general male population is 2-3% and 4-5%, respectively" [6].

Lifelong PE

Lifelong PE is a syndrome characterized by the cluster of the following core symptoms: (1) ejaculation occurs too early at nearly every intercourse, (2) with (nearly) every woman, (3) from about the first sexual encounters onwards, (4) in the majority of cases (90%) the male ejaculates intravaginally within 30–60 s, or in a minority of cases (10%) between 1 and 2 min, (5) the early ejaculation remains the same throughout life (70%) or can even aggravate during aging (30%) and, (6) the ability to delay ejaculation, i.e., to withhold ejaculation at the moment of imminent ejaculation may be diminished or lacking [6]. Moreover, as soon as men with lifelong PE get engaged in an erotic or sexual situation they are overwhelmed by an acute hypertonic or hypererotic state that is characterized by an early erection (erectio praecox), an early ejaculation (ejaculatio praecox), and an early penile detumescence (detumescentia praecox) [8]. Some men already get an ejaculation during foreplay, before penetration (ejaculatio ante portas), or as soon as their penis touches the vagina (ejaculatio intra portam). It should be noted that there are no indications that lifelong PE can be cured, neither by drug treatment nor by psychotherapy [6]. In other words, lifelong PE is a chronic ejaculatory dysfunction. However, drug treatment may prolong the IELT as long as the drug is taken [6].

Acquired PE

The complaints of acquired PE differ in relation to the underlying somatic or psychological problem. It is characterized by the following symptoms. (1) Early ejaculation occurs at some point in a man's life, (2) the man has usually had normal ejaculation experiences before the start of complaints, (3) there is either a sudden or gradual onset, (4) men ejaculate within seconds or within 3 min, (5) the ability to delay ejaculation, i.e., to withhold ejaculation at the moment of imminent ejaculation may be diminished or lacking, (5) the dysfunction may be due to urological dysfunctions like erectile dysfunction or acute prostatitis, thyroid dysfunction, and psychological or relationship problems [6]. During sexual activity, there usually is a hypotonic state [8]. Erectio praecox and detumescentia praecox do not occur in acquired PE. In contrast to lifelong PE the acquired form of PE can be cured by treatment of the underlying cause.

Subjective PE

Men with subjective PE experience or complain of early ejaculations while the IELT is in the normal range, i.e., around 3–6 min, and may even be of long duration, i.e., between 5 and 25 min. This type of PE should not be regarded as a symptom or manifestation of true medical pathology [6]. Psychological and/or relationship problems may underlie the complaints. The syndrome is characterized by the following symptoms. (1) Subjective perception of consistent or inconsistent early ejaculation during intercourse. (2) Preoccupation with a perceived early ejaculation or lack of control of ejaculation. (3) The actual IELT is in the normal range or may even be of longer durarion. (4) The ability to delay ejaculation, i.e., to withhold ejaculation at the moment of imminent ejaculation may be diminished or lacking. During sexual activity there is a normal tonic state. Erectio praecox and detumescentia praecox do not occur in subjective PE. In contrast to lifelong PE the subjective form of PE can theoretically be cured by treatment of the underlying cause.

Variable PE

In variable PE, men only coincidentally and situationally experience early ejaculations. This type of PE should not be regarded as a symptom or manifestation of true pathology but of normal variation in sexual performance [6]. Variable PE is characterized by the following symptoms. (1) Early ejaculations are inconsistent and occur irregularly, (2) the ability to delay ejaculation, i.e., to withhold ejaculation at the moment of imminent ejaculation may be diminished or lacking, (3) experiences of diminished ability to delay ejaculation go along with either a short or normal IELT [6]. During sexual activity there is a normal tonic state [8]. Erectio praecox and detumescentia praecox do not occur in variable PE. Similar to lifelong PE there are no indications that the variable form of PE can be cured by drug or psychological treatment.

Epidemiology: Incidence and Prevalence of Four PE Subtypes

Due to a fundamental misunderstanding and disregard of PE in terms of being a complaint or disorder, and therefore also in the responses to questionnaires in epidemiologic studies together with inadequate definitions of PE, large conflicting prevalence rates have been reported in literature. In addition to the lack of a standardized definition and operational criteria, the method of recruitment for study participation and

method of data collection have contributed to the broad range of reported prevalence rates [30]. Waldinger and Schweitzer were the first to postulate that the true prevalence of patients actually seeking treatment for lifelong PE was much less than the previously reported high prevalence rates [17, 18]. They also stated that the prevalence rate of lifelong PE in the general population is very low, whereas the prevalence rate of subjective PE in the general population is probably the highest of the four PE subtypes [17, 18]. Their predictions were confirmed by the epidemiologic studies of Serefoglu [31, 32], Zhang et al. [33] and Gao et al. [34].

Serefoglu et al. [31, 32] were the first to investigate and confirm the existence of the four PE subtypes in a urological clinic in Turkey [31] and in the general Turkish male population [32]. Also Zhang et al. [33] and Gao et al. [34] confirmed the existence of the four PE subtypes in an andrologic clinic in China [33] and in the general male population of a Chinese province [34]. Interestingly, the prevalence rates of the PE subtypes in both countries were remarkably similar. A relatively high proportion of men—20.0% in Turkey and 25.8% in China—reported a concern with ejaculating too early [32, 34], and in line with the classification of Waldinger and Schweitzer [17–21], these men could be distinguished into four PE subtypes. Both studies confirmed the prediction of Waldinger and Schweitzer [17–21] that the percentage of men with lifelong PE in the general male population is small, but relatively high in a clinical sample. In the general male population, it was found by Serefoglu et al. [32] that the prevalence of lifelong PE was 2.3% in Turkey. Gao et al. [34] reported a prevalence of 3% in China. In addition, the prevalence of acquired PE was 3.9% in Turkey [32] and 4.8% in China [34]. Similarly, the prevalence of Variable PE was 8.5% in Turkey and 11% in China, and the prevalence of Subjective PE was 5.1% in Turkey and 7% in China [32, 34]. In other words, among men in the general male population who complain of early ejaculation or are not satisfied with their ejaculation time duration, the percentage of men with Variable PE and Subjective PE is twice as high as the percentage of men with Lifelong PE and Acquired PE.

Mathematical Formula for the Prevalence of Lifelong PE

The similar method and design of two prospective stopwatch studies of the IELT in the general population of five countries [15, 16] and in a cohort of men with lifelong PE [13] enabled the formulation of a mathematical formula to calculate the prevalence of any IELT values in any Western Caucasian male population. This idea has recently been proposed and elaborated by Janssen et al. [35]. Janssen et al. [35] introduced a new method in which the fitness of various well-known mathematical probability distributions are compared with the IELT distribution of two previous stopwatch studies of the Caucasian general male population [15, 16] and a stopwatch study of Dutch Caucasian men with lifelong PE [13]. It appeared that the IELT distribution of the three studies was a gamma distribution. Moreover, it was found that the Lognormal Distribution of the gamma distribution most accurately fitted the IELT distribution of 965 men in the general population, with a GOF of 0.057. The Gumbel Max Distribution most accurately fitted the IELT distribution of 110 men with lifelong PE with a GOF of 0.179. Notably, by the Kolmogorov-Smirnov test the accuracy of fitness is expressed by the Goodness of Fit (GOF). The study of Janssen et al. [35] showed that there are more men with lifelong PE ejaculating within 30 and 60 s than can be extrapolated from the probability density curve of the Lognormal IELT distribution of men in the general population. In other words, it was shown that men with lifelong PE have a separate IELT distribution, e.g., a Gumbel Max IELT distribution, that can only be retrieved from the general male population Lognormal IELT distribution when thousands of men would participate in a IELT stopwatch study. As this will always be difficult to perform, the mathematical formula of the Lognormal IELT distribution, as calculated by Janssen et al. [35] appears to be useful for epidemiological research of the IELT at least when the number of men in a specific population is known. Moreover, the mathematical formula of the Gumbel Max IELT distribution of men with lifelong PE is useful for epidemiological research of the IELT among men with lifelong PE, when the number of men with lifelong PE is known. The study of Janssen et al. [35] provided also indications that the prevalence of lifelong PE in Western countries may be as low as about 1%. Such a low prevalence of lifelong PE is probably a better explanation than the existing taboo to talk about PE for the fact that worldwide a very low number of men are actually seeking medical treatment for lifelong PE.

Neurobiological and Genetic Hypothesis of Lifelong PE

Based on in vivo animal research of the 1980s [36–38], Waldinger et al. [26] postulated in 1998 that lifelong PE in terms of an IELT of less than 1 min is related to genetic factors and to diminished central 5-HT neurotransmission and/or a hyperfunction of 5-HT_{1A} receptors and a hypofunction of 5-HT_{2C} receptors. Notably, due to an absence of selective 5-HT_{1A} and 5-HT_{2C} receptor ligands for safe human usage, Waldinger noted that it currently is impossible to explore and confirm his hypothesis in men with lifelong PE [39].

The hypothesis of Waldinger et al. [26] on genetic and central serotonin neurotransmission and receptor involvement does not mean that lifelong PE is a classical Mendelian inheritable disorder affecting all male members of a family [8, 28]. Also in 1943, Schapiro [4] did not think that lifelong PE was a genetic disorder. Instead he assumed that *"heredity*

may play a part in the etiology" of lifelong PE [4]. In line with this view, Waldinger et al. [40] reported indications of a familial, but not genetic hereditary, occurrence of lifelong PE in first degree relatives of some male patients with lifelong PE.

Genetic Polymorphisms and Lifelong PE

In 2009, Janssen et al. [41] published the first stopwatch study on the influence of 5-HTTLPR polymorphism on IELT duration in 89 Dutch men with lifelong PE. Of these men 83 men ejaculated within 1 min after vaginal penetration, whereas 6 men ejaculated between 1 and 2 min. In this group of men, those with LL genotype ejaculated within 13.2 s, expressed in geometric mean IELT, whereas men with SL and SS genotype ejaculated within 25.3 and 26.0 s, respectively ($p < 0.05$) [41]. In other words, men with LL genotype ejaculated 100% faster than men with SS genotype and 90% faster than men with SL genotype [41]. Notably, there were no significant differences between these men and a control group of 92 Dutch Caucasian men in 5-HTT polymorphism alleles and genotypes [41]. Using the same stopwatch methodology, Janssen et al. [42] investigated 54 men with respect to the role of the C(1019)G polymorphism of the 5-HT_{1A} receptor gene on the IELT duration. It was shown that men with CC genotype ejaculated within 14.5 s, whereas men with CG and GG genotype ejaculated within 27.7 s, and 36.0 s, respectively [42]. Therefore, it was concluded that men with CC genotype ejaculated 250% earlier than men with GG genotype [42]. Similarly, Janssen et al. [43] investigated the role of the Cys23Ser polymorphism of the 5-HT2c receptor on the IELT duration. It was shown that the wild types (CysCys) had an IELT of 22.6 s, whereas the mutants (Ser/Ser) had an IELT of 40.4 s [43]. Thus, the men with CysCys genotype ejaculated 79% faster than the monozygote mutant (Ser/Ser) men [43].

Importance of Hardy Weinberg Equilibrium

Unfortunately, up to now other researchers have not used the stopwatch methodology and exact study design of Janssen et al. [41–43] in the investigation of the relationship between polymorphisms of 5-HTT and 5-HT receptor genes and the duration of the IELT. However, a few clinicians have investigated the relationship between genetic polymorphisms in men with lifelong PE. For example, two questionnaire studies confirmed that there is no association in the 5-HTTLPR polymorphism between men with lifelong PE and a control group [44, 45]. In contrast, there have been three other studies of men with lifelong PE showing they have a higher SS genotype frequency compared with a control group [46–48]. But as the latter three studies were not in Hardy–Weinberg equilibrium (HWE)—most probably due to technical laboratory insufficiencies—their results are not considered to be reliable [49]. Interestingly, an association of the 5-HT_{1A} receptor gene polymorphism had been previously also found by a questionnaire study of the ELT (and not IELT) in a Finnish cohort of twins [50]. The relatively few aforementioned studies might indicate—at least in men with lifelong PE who ejaculate within 1 min—that the duration of the IELT is associated with polymorphism of the 5-HTTLPR gene, the C(1019)G polymorphism of the 5-HT_{1A} receptor, and the (HTR2C)- CysSer polymorphism of the 5-HT_{2C} receptor. However, more studies are needed in a large cohort of men with lifelong PE and a control group with well controlled polymerase chain reaction analysis and which are in Hardy Weinberg equilibrium in order to confirm the robustness of these indications of a possible link between the aforementioned gene polymorphism and the duration of the IELT in men with lifelong PE. Indeed, Genome Wide Association Studies (GWAS) may represent the best available approach to finding candidate genes related to the IELT and lifelong PE. Nevertheless, it is interesting to note that both the studies of Janssen et al. [41–43] and the animal studies [36–38] that formed the basis for the neurobiological-genetic hypothesis of Waldinger et al. [26] provide indications that the short IELT of men with lifelong PE may be associated with central 5-HT neurotransmission, 5-HT_{1A} and 5-HT_{2C} receptor functioning. Although speculative, Waldinger does not exclude the possibility that environmental (maternal and non-maternal) factors that affect gene expression prenatally, shortly after birth or later in life may be associated with the persistent short IELTs in men with lifelong PE [8, 26]. Such epigenetic studies should also be conducted in men with lifelong PE [8, 28].

The IELT in ISSM and DSM-5 Definition of Lifelong and Acquired PE

The aforementioned characteristic features of lifelong PE (see "Lifelong PE" section of this chapter) are not described in such detail in the ISSM definition of lifelong PE [14, 51] nor in the DSM-5 definition of PE [52] as, in general, a definition of a disorder cannot encompass all the detailed features of the disorder (see Table 18-1).

According to the ISSM definition, lifelong PE is defined as "a male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations, which results in negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [14, 51]. In contrast, in DSM 5 lifelong PE is not separately defined but PE is defined as "a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within

Table 18-1. DSM-5 Diagnostic Criteria for Premature Ejaculation 302.75 (F52.4)

A. A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 min following vaginal penetration and before the individual wishes it.
Note: Although the diagnosis of premature (early) ejaculation may be applied to individuals engaged in nonvaginal sexual activities, specific duration criteria have not been established for these activities.

B. The symptom in Criterion A must have been present for at least 6 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 Criterion 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 condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

Mild: Ejaculation occurring within approximately 30 seconds to 1 min of vaginal penetration.

Moderate: Ejaculation occurring within approximately 15–30 s of vaginal penetration.

Severe: Ejaculation occurring prior to sexual activity, at the start of sexual activity, or within approximately 15 s of vaginal penetration.

approximately 1 min following vaginal penetration and before the individual wishes it" [52]. Therefore the DSM-5 definition may perhaps erroneously indicate that also acquired PE occurs within about 1 min.

Erectio Praecox (Premature Erection) and Lifelong PE

Erectio praecox or premature erection is a clinically important and specific clinical feature of lifelong PE [4]. Men with erectio praecox get an erection "too early". This subtle symptom of lifelong PE has never been quoted in sexological literature until 2002, when Waldinger [2] reintroduced the term, thereby noting that many men with lifelong PE report this phenomenon either spontaneously or when asked for it. The phenomenon is so subtle, that men with lifelong PE may not be aware of it. It is not strange that it is noted by their female partner when she has had previous sexual experiences with men who did not have lifelong PE. However, until now there has not been any evidence based research into this remarkable and completely underreported clinical phenomenon, although we are currently investigating its occurrence in men with lifelong PE.

The Hypertonic Type Versus the Hypertonic State and Lifelong PE

Schapiro denoted Type B with erectio praecox as "*the sexually hypertonic or hypererotic type*" [4]. In contrast, he reported that Type A or "*the hypotonic type*" was often accompanied by erectile dysfunction [4].

Recently, Waldinger [8] noted that many men with lifelong PE report a very sudden increased arousal, facilitated erection and facilitated ejaculation as soon as they are engaged in erotic or intimate circumstances. Therefore, Waldinger preferred the word hypertonic "state" for this phenomenon, which is characteristic for the inner mental state of men with lifelong PE [8]. As soon as these men get involved in an erotic intimate situation, they are overwhelmed by an acute hypertonic state that starts with a facilitated erection (erectio praecox) and leads to an early ejaculation (ejaculatio praecox). The hypertonic or hypererotic state should not be confused with hypersexuality [8]. Hypersexuality is not a symptom of lifelong PE. The hypertonic or hypererotic state is a rather acute occurring physical sexual state that only occurs in situations of eroticism or making love.

Detumescentia Praecox (Premature Detumescence) and Lifelong PE

Recently, Waldinger [8] also noted a so far unknown clinical symptom in men with lifelong PE. He reported that a substantial number of men with lifelong PE experience a rather immediate and/or complete detumescence of the penis after an ejaculation [8]. Analogous to "ejaculatio praecox" and "erectio praecox", Waldinger denoted this as "detumescentia praecox" or "premature detumescence" [8]. Notably, he also reported that a substantial number of men with lifelong PE report difficulties in attaining a second erection after a premature ejaculation preventing them from a second intercourse [8]. It is as if they have difficulties becoming sexually aroused for the second time. This may be related to the psychological impact of disappointment and irritation from their early ejaculation, as is often thought by sexologists, but Waldinger suggested that this impairment is probably more related to a so far unknown underlying neurobiological mechanism that is related to the underlying neurobiological cause of the acute hypertonic state [8]. Interestingly, Waldinger also noted that daily use of 20 mg paroxetine in some men delays the penile detumescence in such a way that they are still able to thrust with a gradual

diminishing erection [8]. In other words, in these men with lifelong PE 20 mg paroxetine does not lead to erectile dysfunction but prolongs erection for a very short time.

Classification into Four PE Subtypes According to Genital Tonus

By including the hypertonic state, erectio praecox and detumescentia praecox into the Four PE Subtype Classification, the separate characteristics of the four PE subtypes become more delineated. Lifelong PE is characterized by a hypertonic state. Acquired PE is characterized by a hypotonic state and Variable PE and Subjective PE are characterized by a normotonic state [28, 53]. Figure 18-1 shows the historical development of the classification of PE into four PE subtypes.

Adaptation of the Neurobiological Hypothesis

In 2014, Waldinger [8] noted that the new triad of "ejaculatio praecox", "erectio praecox" and "detumescentia praecox" as part of the acute "hypertonic or hypererotic" state of lifelong PE necessitates an adaptation of his neurobiological hypothesis of 1998 [26]. The hypertonic state indicates that lifelong PE is not only characterized by a diminished serotonergic neurotransmission and a disturbance of 5-HT_{1A} and 5-HT_{2C} receptor functioning causing a disturbed serotonergic modulation of the IELT [8]. Based on currently available neurobiological knowledge on ejaculation, erectile functioning, and sexual arousal, Waldinger speculated that lifelong PE—when characterized by an acute hypertonic phenotype—is mediated by a more complex interaction of the central nervous system, the peripheral nervous system and the endocrinological system [8, 28]. Therefore, it would have to include serotonergic and other neurotransmitter and endocrinological processes—e.g., increased oxytocinergic, and/or increased dopaminergic neurotransmission, decreased prolactinergic functioning and increased activity of gonadotrophic factors [8, 28]. Also involved is the peripheral nervous system, e.g., the sympathetic and parasympathetic nervous system [8, 28]. What needs to be investigated is any interaction between all these factors which may give rise to a very rapidly occurring "overactivated" or "hypertonic" state of the genital area in relation to the sense organs [8]. New neurobiological and pharmacological research is required to unravel the factors mediating this hypertonic state of lifelong PE. The remarkable phenomenon that SSRIs induce much less erectile dysfunction and decreased libido in men with lifelong PE compared to depressed patients without lifelong PE, may well be related to the fact that these drugs diminish the hypertonus state of erection, ejaculation and arousal toward a more "normal" state represented by "normal" sexual functioning [8].

In recent years, research into oxytocinergic, dopaminergic, and endocrinological factors related to PE has been conducted by a number of research groups [25, 54–58]. However, their attention has not been directed to the hypertonic state of lifelong PE. But hopefully, the integration of neurobiological

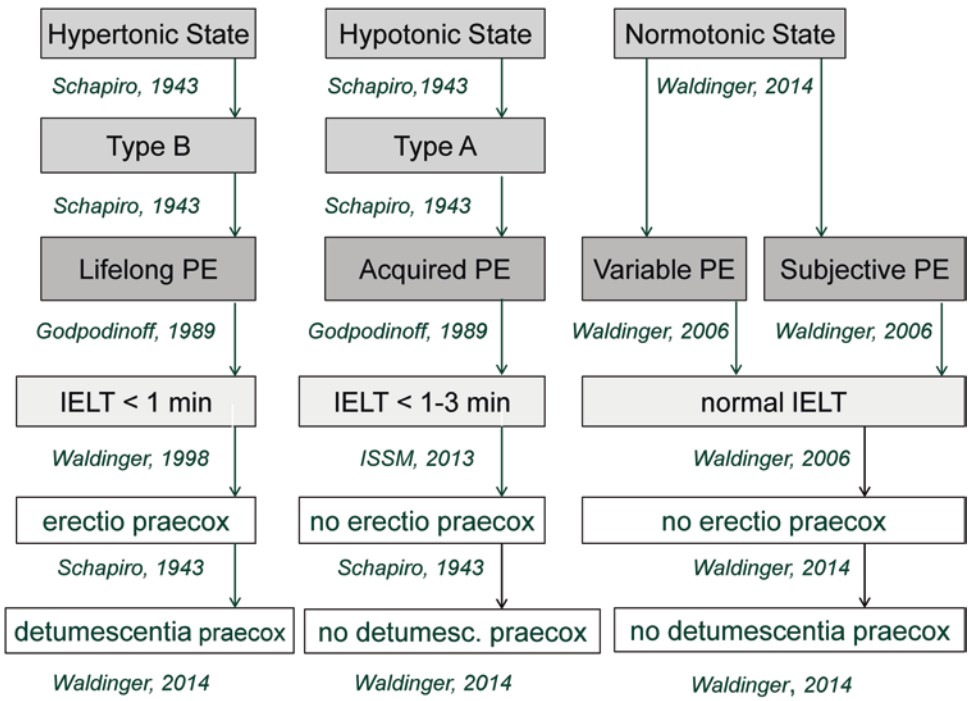

FIGURE 18-1. Classification of Four PE Subtypes. The classification by Waldinger [6, 8] is an extension of the original classification of Schapiro [4] and includes erectio praecox, that was originally reported by Schapiro but has been ignored for many decades. In this classification the hypertonic and hypotonic types of Schapiro have been renamed hypertonic state and hypotonic state. The two new subtypes Variable PE and Subjective PE are examples of a normotonic state with normal IELT values.

and endocrinological knowledge to elucidate the acute co-occurrence of premature ejaculation, premature erection, premature detumescence, and the acute hypererotic state, will become a new focus of research in the current decade [8].

Oxytocin, Erection, Ejaculation and Penile Detumescence

Although other factors may be involved, there are preliminary indications that the rather unknown phenomena of facilitated erection, premature ejaculation, and rapid penile detumescence are associated with an increased release of and/or increased receptor sensitivity to oxytocin [8].

Erection

The release of oxytocin from centrally projecting parvocellular neurons is well known to influence erection and, less clearly, ejaculation (for review see [54]). Increased oxytocinergic neurotransmission in the paraventricular hypothalamic nucleus (PVH) or hippocampus induces either an increase in the number of penile erections or an increase in intracavernous pressure, which is an indication of erection [54, 55].

Detumescence

On the other hand, some evidence indicates that peripherally injected oxytocin might have an inhibiting rather than stimulating effect on erection [54]. For example, systemic oxytocin treatment inhibited the increase in intracavernous pressure elicited by electrical stimulation of the cavernous nerve in rats, which could be prevented by an oxytocin antagonist [57]. It therefore appears that peripheral oxytocin receptors in the corpus cavernosum are involved in penile detumescence [54].

Ejaculation

After ejaculation, oxytocin levels are raised in the blood plasma in rabbits [59] and in the cerebrospinal fluid in rats [60].

Preliminary Pathophysiology of Premature Erection, Ejaculation and Penile Detumescence

In men, plasma oxytocin levels are elevated during sexual arousal, erection, and at the time of orgasm, although the degree of the elevation varies between different studies [61–64]. Taking together animal and human studies, oxytocin appears to play at least a modulating role in erection and ejaculation [65], and in male sexual behavior both peripheral and central oxytocin release seems to be involved [65]. In 2002, Waldinger et al. [2] hypothesized that erectio praecox in the context of lifelong PE may be associated with increased central oxytocin release during coitus as oxytocin facilitates erection and ejaculation. It may further be postulated that an increased peripheral release of oxytocin during ejaculation in men with lifelong PE may be associated with a quick penile detumescence [8].

Rating Scales

The diagnosis of PE and the diagnosis of the four PE subtypes are not difficult as long as one is interested in diagnosing PE and spend time (at least 30 min) to talk with the patient. Questionnaires on PE should never replace the face to face contact of the physician and his PE patient.

So far, five validated questionnaires have been developed and published to date [66]. Currently, there are two questionnaires that have extensive databases meeting most of the criteria for test development and validation: The Premature Ejaculation Profile (PEP) [67] and the Index of Premature Ejaculation (IPE) [68]. A third brief diagnostic measure (PEDT) has also been developed, has a modest database and is available for clinical use [69, 70]. Two other measures, The Arabic Index of Premature Ejaculation and Chinese Index of Premature Ejaculation [71, 72] have minimal validation or clinical trial data available [66]. Importantly, the aforementioned questionnaires are sensitive for complaints of PE, but are inadequate to diagnose any of the four PE subtypes. Therefore, new research for the development of PE Subtype specific questionnaires is warranted.

Premature Ejaculation Profile (PEP)

The PEP is a 4-question patient reported outcome (PRO) that asks a respondent about his subjective sense of control over ejaculation, distress related to PE, interpersonal difficulty and satisfaction with sexual intercourse [66]. Each question is answered on a 5-point Likert-type scale and an index score is derived by averaging the responses to the four questions. A limitation of the PEP is that the original validation of the PEP was based on the DSM-IV-TR PE criterion, which did not have an ejaculation time criterion. The authors of the PEP defined PE in terms of an IELT of less than 2 min [66].

Index of Premature Ejaculation (IPE)

The 10-item IPE was developed as a measure to evaluate sexual satisfaction, control and distress in men with PE [66]. Like the PEP, the initial validation of the IPE used men with a stopwatch assessed IELT of 2 min or less [66].

Premature Ejaculation Diagnostic Tool (PEDT)

The PEDT is a 5-item tool developed to systematically apply the DSM-IV-TR criteria in diagnosing the presence or absence of PE [66]. By employing a three tiered cutoff score it diagnoses PE (score < 8), possible PE (9 or 10), and no PE (>11). The PEDT works best as a screener for PE [66].

Dangers That Threaten Scientific Research of Lifelong PE

Ignoring the PE classification of Bernard Schapiro in lifelong and acquired PE is not solely a tragic phenomenon of the past. Even today the danger exists that long standing hard characteristics of lifelong PE and its accurate research are ignored or become distorted. For example, a cohort of men with lifelong PE usually includes about 90% of males who ejaculate within 1 min and about 10% of males who ejaculate within 1–2 min [13]. A distortion of these percentages will be formed by studies of lifelong PE in which substantially more than 10% of men ejaculate within 1–2 min and less than 90% ejaculate within 1 min. Therefore it is better for scientific research to only include men who ejaculate within about 1 min, on the condition that IELT is measured by a stopwatch. Another danger for scientific research of lifelong PE is formed when one only uses validated or non-validated questionnaires to measure the IELT. For example, recently Ventus et al. [73] argued on the basis of a retrospective questionnaire study among a very small sample of Finnish twins and patients that the term lifelong PE is probably inappropriate as very few participants subjectively reported a bit longer IELT duration on a questionnaire than at baseline questionnaire measurement ignoring the subjective and inaccurate way of their IELT assessment. The consequences of such attempts to ignore or distort the existence of lifelong PE extremely threatens the scientific research of PE in general and will enormously harm the patient with lifelong PE [74].

In an editorial, Waldinger [74] has recently expressed his concern on current research of Lifelong PE, noting that PE research seems more and more to become performed by clinically inexperienced individuals who do not talk to or see patients with PE, do not have clinical experience with PE patients, but who sit behind their PCs, play with statistical programs, try to intimidate clinicians and reviewers with validated questionnaires, selectively choose references, and omit or ignore important information that does not support their view. Particularly, ignoring the necessity of using a stopwatch for accurate IELT research, ignoring the IELT cutoff point of 1 min for inclusion of men with lifelong PE in a study, and with regard to genetic research ignoring the importance of Hardy Weinberg equilibrium endangers the evidence based clinical, pharmacological and genetic research of lifelong PE.

But not only that. Research of lifelong PE that is solely performed by validated questionnairs without face to face contact with a patient with lifelong PE ought to be discouraged [74]. Particularly, studies in which anonymous men are recruited by Internet and are solely investigated by validated questionnaires and become diagnosed as lifelong PE endanger objective research of lifelong PE.

The study of Ventus et al. [73] and the study of Zhu et al. [75] are good examples to which erroneous but catastrophic conclusions such studies can lead. For example, according to the study of Ventus et al. [73] the authors suggest that lifelong PE is an inappropriate diagnosis. And according to Zhu et al. [75] 5-HTTLPR is associated with lifelong PE and L alleles might protect the male against lifelong PE.

Fortunately, the serious limitations and erroneous conclusions of these studies have been reported by other authors [49, 74]. But nevertheless, research of lifelong PE remains endangered by studies that only use validated questionnaires, include anonymous patients, ignore the stopwatch and objective real-time measurement of the IELT.

In order to avoid publication of such potentially harmful articles, Waldinger [74] strongly advised clinicians, reviewers, and editors not to succumb to pressure of technocrats using statistics and questionnaires to understand patients.

Conclusion

For many years it has been thought that lifelong PE is only characterized by complaints of persistent early ejaculations. Both in vivo animal research and neurobiological, genetic, and pharmacological research in men with lifelong PE have much contributed to a better understanding of how the central and peripheral nervous system mediate ejaculation and contribute to persistent early ejaculations. However, our current understanding of the mechanisms behind early ejaculations is far from complete. The new classification of PE into four PE subtypes has much contributed to a better delineation of lifelong PE against acquired PE, subjective PE and variable PE. It has been shown that the symptomatology of lifelong PE strongly differs from the three other PE subtypes. The phenotype of lifelong PE and therefore also the pathophysiology of lifelong PE is much more complex than the phenotype of the three other PE subtypes. A substantial number of men with lifelong PE not only has premature ejaculation, but also premature erection and premature penile detumescence as part of an acute hypertonic or hypererotic

state when engaged in an erotic situation or when making love. As both erectio praecox, ejaculatio praecox, detumescentia praecox, and the hypererotic state are part of the phenotype lifelong PE, it is argued that lifelong PE is not only a disturbance of the timing of ejaculation but also a disturbance of the timing of erection, penile detumescence and arousal. Since 1998, the pathophysiology of lifelong PE was thought to be mainly mediated by the central serotonergic system in line with genetic polymorphisms of certain serotonergic genes. However, by accepting that lifelong PE is not only a matter of a short IELT, but also characterized by a facilitated erection and facilitated penile detumescence as part of an acute but reversible hypertonic state, the hypothesis of mainly serotonergic dysfunction is no longer tenable. Instead, it has been postulated that the pathophysiology of lifelong PE is mediated by a very complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic, and probably also epigenetic factors. The classification of PE into four PE subtypes is relevant for pharmacotherapy and counseling of men with complaints of PE. Progress in research of lifelong PE can only be accomplished when a stopwatch is used to measure the IELT and the cut-off point of 1 min for the definition of lifelong PE is maintained. Current use of validated questionnaires, neglect of stopwatch research, clinically inexperienced investigators, and inclusion of anonymous men in a study performed by the Internet endanger the continuation of objective research of lifelong PE and ought to be discouraged.

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