

Review Article

Toward Evidence-Based Genetic Research on Lifelong Premature Ejaculation: A Critical Evaluation of Methodology

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Recently, four premature ejaculation (PE) subtypes have been distinguished on the basis of the duration of the intravaginal ejaculation latency time (IELT). These four PE subtypes have different etiologies and pathogeneses. Genetic research on PE should consider the existence of these PE subtypes and the accurate measurement of the IELT with a stopwatch. Currently, three methods of genetic research on PE have been used. They differ in the investigated population, tool of measurement, study design, and variables of PE. From animal and human research, it is derived that the central serotonergic system “modulates” ejaculation, whereas the ejaculation (reflex) itself is probably not under direct influence of the serotonergic system, but rather under the influence of other neurotransmitter systems in the spinal cord. For genetic research on PE, it is important to take into account that the (serotonergic) modulation of the IELT is variable among men and may even be absent. This means that serotonergic genetic polymorphisms may only be found in men with PE who respond with an ejaculation delay treatment with a selective serotonin reuptake inhibitor.

Key Words: Evidence based research; Genetics; Premature ejaculation; Serotonin

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INTRODUCTION

In 1998, Waldinger et al postulated that there is a continuum of the intravaginal ejaculation latency time (IELT) in the general male population and that this variability in the IELT is influenced by neurobiological and genetic mechanisms [1]. In addition, it was postulated that the persistently short IELTs in men with lifelong premature ejaculation (PE) are associated with diminished serotonin (5-hydroxytryptamine, or 5-HT) neurotransmission, a hyperfunction of 5-HT_{1A} receptors, and/or a hypofunction of 5-HT_{2C} receptors [1]. From the strong ejaculation-delaying effects of selective serotonin reuptake inhibitors (SSRIs) and particularly that of paroxetine [2], it may be derived that serotonin and 5-HT receptors play an important role in the ejaculation process, as was already demonstrated in rodents in the 1980s [3]. However, for about a decade, the details of the neurobiological hypothesis of Waldinger et al could not be confirmed in humans owing to the absence of

specific 5-HT_{1A} and 5-HT_{2C} ligands that were safe for human use. However, recent genetic research on 5-HT gene polymorphisms and the IELT has provided evidence in support of the view that the persistently short IELTs in men with lifelong PE are associated with decreased 5-HT neurotransmission [4]. The idea that PE may have genetic roots was suggested for the first time indirectly in 1943, when Schapiro noted that family members of men with PE also suffered from PE [5]. This remarkable clinical observation was never quoted in sexological literature until 1998 when Waldinger et al published a study in which it was shown that in first-degree male relatives of men with lifelong PE, defined in terms of an IELT of less than 1 minute, a high percentage of men (91%) also suffered from lifelong PE with an IELT of less than 1 minute [6]. However, because only 14 (6%) of 237 men were willing to ask first-degree male relatives about their ejaculation time, this study can only be regarded as an indication that the observation of Schapiro has some validity. At the same time, the study

demonstrated the immense taboo that exists among PE sufferers to openly talk about their PE. Because this taboo still exists today, it may be concluded that family studies on PE are also today practically impossible to perform.

Fortunately, due to new developments in laboratory techniques of the past decade, DNA research has become easier to perform in many laboratory settings nowadays. After the first publication of a DNA study in Dutch men with lifelong PE by Janssen et al [4], a small number of other genetic studies on PE in different countries, in different cohorts of men, and with different methodologies have been published. However, many clinicians, particularly those who have not been educated with current knowledge of genetics, have difficulties in understanding the details of genetic research articles and the often complex associated statistics. The aim of the current article is to clarify and critically review the current methodologies that have been used in genetic research on lifelong PE in the context of recent developments in diagnosis and classification.

COMPLAINT VERSUS DISORDER

In 2006, Waldinger et al emphasized the need to distinguish PE as a “complaint” versus PE as a “disorder” [7,8]. This distinction has important consequences for both epidemiologic research on PE and for the debate on definition and classification. For example, most epidemiologic studies have reported PE to be the most prevalent male sexual “disorder” [9,10]. However, considering the questions that have been asked in these surveys, it appears that these surveys only investigated the prevalence of males who have a “complaint” of PE. Therefore, it has to be concluded that PE is the most prevalent male sexual “complaint” affecting some 20% to 30% of men [7,8]. Until recently, the prevalence of PE as a sexual “disorder” has not been investigated in the general male population. However, the study of

Serefoglu et al showed that in 20% of men with “complaint” of PE, the prevalence of the sexual “disorder” of lifelong PE is rather low in the general male population [11].

FOUR PREMATURE EJACULATION SUBTYPES

The very high percentage of 20% to 30% of men in the general male population who suffer from complaints of PE [8,9,11] contrasts with the rather low percentage of men who visit outpatient clinics for medical treatment of PE [12]. The argument to explain this low percentage by the ever-existing taboo to talk about PE probably only partially explains this remarkable difference. An additional explanation has been put forward by Waldinger et al, who stated that the prevalence of 20% to 30% does not represent the number of men who suffer from lifelong or acquired PE [13-16]. Waldinger et al reported that in contrast with the high percentage of men who have complaints of PE without having a short ejaculation time of less than one minute, the prevalence of the disorders of lifelong and acquired PE with IELTs of less than one minute is rather low (2.5%) in the general male population [13-18]. Presuming that the persistent, very short IELTs of less than one minute are a major disturbing factor for a man’s self-esteem, sexual self-confidence, and feelings of masculinity, the rather low percentage of men who actively seek medical treatment most probably represents the rather low percentage of men with lifelong and acquired PE in the general male population. In 2006, Waldinger et al suggested that apart from the two well-known subtypes of PE (e.g., lifelong PE and acquired PE), there are also two other PE subtypes: natural variable PE and premature-like ejaculatory dysfunction (Table 1) [7,13]. In natural variable PE, men only occasionally suffer from early ejaculations. In premature-like ejaculatory dysfunction, men experience or complain of PE while actually having a normal or even a long IELT duration of, for exam-

TABLE 1. New preliminary classification and characteristics of four premature ejaculation subtypes on the basis of their IELT durations [14-16]

Lifelong premature ejaculation	Acquired premature ejaculation	Natural variable premature ejaculation	Premature-like ejaculatory dysfunction
Ejaculation occurs too early, at (nearly) every intercourse	Early ejaculation occurs at some point in a man’s life	Early ejaculations are inconsistent and occur irregularly	Subjective self-perception of (in)consistent rapid ejaculations
With (nearly) every woman	The man had normal ejaculation experiences before	The ability to delay ejaculation may be diminished or lacking	The ability to delay ejaculation may be diminished or lacking
From about the first sexual encounters onwards	The onset is (usually) at later age	From about the first sexual encounters or onset at later age	From about the first sexual encounters or onset at later age
In 80% within 1 minute (mostly within 30 s)	Ejaculation occurs within 1-2 minutes	Ejaculation time may be short or normal	Ejaculation time is in the normal range or may even be of longer duration
In 20% between 1 and 2 minutes			
Ejaculation remains rapid throughout the lifetime of the subject	Rapid ejaculation is result of urological, thyroid, or psychological problems	This is part of the normal variability of ejaculatory functioning	Rapid ejaculation is a subjective experience independent of actual ejaculation time, which is in the normal range

ple, 5 to 20 minutes [14-16]. The 4 PE subtypes are distinguished on the basis of the IELT duration. In the 1990s, Waldinger et al postulated that lifelong PE is mainly influenced by neurobiological and genetic factors and showed that it is characterized by an IELT of less than 1 minute, usually within about 30 s [19]. Acquired PE is caused by either medical or psychological causes and is also characterized by a short IELT, most probably between 1 and 2 minutes [14]. On the other hand, natural variable PE is considered a normal variation of ejaculatory performance and should not be regarded as an ejaculatory disorder. It has been presumed that the IELT in this subtype is in the normal range. Premature-like ejaculatory dysfunction is considered to be caused by psychological, cultural, or inter-relationship factors and is not considered to be caused by neurobiological or genetic factors [14-16]. Its IELTs are in the normal range or even of longer duration. For a better understanding, premature-like ejaculatory dysfunction may also be denominated as subjective premature ejaculation. Importantly, Waldinger emphasized that the four PE subtypes are characterized by different etiologies and have a different pathogenesis and therefore should be separately defined [14-16]. He assumed that the prevalence of lifelong and acquired PE is probably low in the general male population but high in outpatient clinics of urology [14-16], whereas oppositely he also presumed that the prevalence of natural variable PE and premature-like ejaculatory dysfunction or subjective PE is high in the general male population but rather low in outpatient clinics of urology [14-16]. In addition, Waldinger argued that the sum of the prevalences of these four PE subtypes constitutes the 20% to 30% prevalence of PE as has often been found in epidemiologic studies [14-16].

Interestingly, two studies by Serefoglu et al investigating the prevalence of the 4 PE subtypes in Turkey confirmed the existence of the 4 PE subtypes in both an outpatient clinic of urology and in the general male population (Table 2) [11,20]. Moreover, the self-reported IELT values in their study indeed showed a continuum, with the shortest IELTs in lifelong PE and the longest IELTs in subjective

PE. Also, the prevalence rates of the 4 PE subtypes were in accordance with the hypothesis of Waldinger. The prevalence of lifelong PE was low in the general male population but very high in the outpatient clinic of urology, giving support to the validity of this new PE classification. However, more studies using the methodology of Serefoglu et al in other countries are warranted to further investigate the validity of this classification [11,20].

DEFINITION OF PREMATURE EJACULATION

Until 1980, PE was not officially defined. In the mid of the last century, when many PE sufferers were treated by psychoanalysis, psychoanalysts considered a man to have PE when he ejaculated within about 1 minute [13]. However, Masters and Johnson, two representatives of behaviorism, fiercely rejected this definition in terms of ejaculation time and considered a man to suffer from PE when he was not able to control his ejaculation until the moment that he gave pleasure to his partner [21]. Their opinion influenced the first official definition of PE in the *DSM-III*, in which PE was defined solely in terms of voluntary control [22]. However, in the *DSM-III-R*, *DSM-IV*, and *DSM-IV-TR* versions, control has been deleted and replaced by the criterion of a short ejaculation time, without specification of a cutoff point of this "short" ejaculation time [22]. During the past decade in particular, the *DSM-IV-TR* definition has been criticized for its vagueness [22,23], although some clinicians have also stated that the *DSM-IV-TR* definition of PE is adequate and does not require revision [24]. The debate on this definition came to an end when the International Society for Sexual Medicine (ISSM) organized a meeting of experts in the field to derive an evidence-based definition of PE [25].

DEFINITION OF LIFELONG PREMATURE EJACULATION

During this meeting in Amsterdam, the ISSM decided that there were sufficient data to define a new definition of life-

TABLE 2. Prevalences and self-reported mean and median IELT durations of the four PE subtypes in a turkish outpatient clinic of urology and in the general turkish male population [11,20]

Premature ejaculation subtype	Prevalence of PE in outpatient clinic n=261 males	Self-reported mean IELT (range)	Prevalence in general Turkish male population (n=2,593). Males with PE (n=512; 20%)	Self-reported median IELT
Lifelong premature ejaculation	62.5%	20.47±28.90 s (2 s-2 min)	2.3%	< 1 min
Acquired premature ejaculation	16.1%	57.91±38.72 s (1.5-3 min)	3.9%	1-2 min
Natural variable premature ejaculation	14.5%	144.17±22.47 s (2-3 min)	8.5%	2-3 min
Premature-like ejaculatory dysfunction	6.9%	286.67-69.96 s (3-7 min)	5.1%	> 3 min

IELT: intravaginal ejaculation latency time

long PE but still insufficient data for a new definition of acquired PE [25]. The ISSM defined lifelong PE as an ejaculation that occurs within about 1 minute after penetration in the majority of sexual encounters, with an inability to delay ejaculation and with associated negative personal consequences such as bother and avoidance of sexual activity [25]. Recently, the ISSM also organized a similar meeting in order to derive an evidence-based guideline for the treatment of PE [26]. With both an evidence-based definition of lifelong PE and an evidence-based guideline for the treatment of PE, the ISSM has made an enormous, historical contribution to the research and treatment of PE.

CENTRAL SEROTONERGIC MODULATION OF THE IELT

It has become clear from both human and animal studies that serotonin (5-hydroxytryptamine, or 5-HT) plays a very important role in sexual and particularly ejaculatory activity [27-31]. Animal studies, mainly performed in laboratory rodents, have shown that various brain areas are specifically involved in ejaculatory behavior [32]. Overall, these brain areas are a complex interconnected network that regulates ejaculation. There is also a very important spinal ejaculation generator located lateral to the central canal in lamina X and in the medial portion of lamina VII of L3 and L4 of the lumbar spinal cord. These lumbar spinothalamic (LSt) neurons project to the medial parvocellular subparafascicular nucleus of the posterior thalamus (SPFp) and are specifically activated during ejaculation but not with other components of male rat sexual behavior [33]. Lesions of these neurons cause dramatic disruptions in ejaculatory behavior [33]. Serotonergic fibers have been found in all spinal cord areas containing sensory axons and motor neurons involved in ejaculation. They are present in the dorsal and ventral horns, dorsal commissural grey and thoracolumbar intermediolateral cell column (IML), and sacral parasympathetic nucleus (SPN) of the lumbosacral spinal cord [34]. In addition, serotonergic postsynaptic receptors have been found in the area where LSt cells are located [35]. This suggests a role of serotonin in ejaculation via these possible connections in the spinal cord. However, these serotonergic connections are also found in supraspinal areas. In the nucleus paragigantocellularis (nPGI), an area in the ventrolateral medulla of the brainstem, serotonergic neurons are found to innervate the bulbospongiosus muscles involved in the inhibition of ejaculation [35]. The medial preoptic area (MPOA) might lower the ejaculatory threshold by removing the tonic serotonergic inhibition exerted by the nPGI [36]. Another serotonergic innervation exists in the anterior lateral hypothalamic area (LHA). Lesions of the LHA in male rats strongly affect the occurrence of ejaculations, showing the excitatory role of this brain region in the regulation of ejaculation [37]. This effect is caused by serotonin, because it is released in the LHA at the time of ejaculation [38], and injections of SSRIs into the LHA were shown to increase ejaculation latencies

[38].

The ejaculatory reflex is complex and involves multiple afferent and efferent systems. The afferent stimuli may involve sensory, visceral, proprioceptive, and somatic inputs. It is possible that LSt cells receive stimuli related to the onset of ejaculation and, in turn, trigger the ejaculation reflex. The efferent site of the reflex involves the complex control of sympathetic and parasympathetic systems [33]. Briefly, ejaculation is a spinal reflex controlled by the spinal ejaculation generator that is "modulated" by sensory input from the pelvis and descending input from inhibitory and excitatory centers in the brainstem and the hypothalamus. Allard et al suggested that these supraspinal centers are controlled by cortico-limbic centers, which are responsible for switching on a state of sexual excitement [39]. During sexual intercourse, the cortico-limbic centers inhibit and activate the inhibitory and excitatory centers respectively, shifting the supraspinal tone to the spinal ejaculation generator from overall inhibitory to excitatory.

All together, the data derived from animal research suggest a major role of the central serotonergic system in modulating the spinal ejaculatory reflex. This serotonergic modulation of ejaculation may result in a faster or more delayed ejaculation, whereas the ejaculation itself is probably not under direct influence of the serotonergic system but rather under the influence of other neurotransmitter systems in the spinal cord [33]. This is an important consequence of this central modulation of ejaculation that has hardly been discussed in the literature but may be pivotal for genetic research on PE. For example, it may be assumed that the modulation of ejaculation among men is variable; it can be strong, moderate, weak, or even absent. In the last case, the serotonergic system in the brainstem is unable to modulate the ejaculation reflex in the lower spinal cord. In that case, a male is not able to or hardly able to change the duration of his ejaculation time. Even by using SSRIs, this subject may still not be able to change the duration of his ejaculation time. Although never systematically investigated, it is clinically well known that a subgroup of men with lifelong PE do not respond with ejaculation delay to any SSRI treatment. I therefore suggest that in these men, the serotonergic system is unable to modulate the ejaculation reflex.

The view that serotonin modulates ejaculation may have important implications for genetic research, because it may imply that in a certain cohort of men, an unknown number have no or hardly any ability to modulate ejaculation irrespective of the presence of functional serotonergic polymorphisms. Consequently, irrespective of the presence of these polymorphisms, these men will not show any change in IELT duration when modulation of the IELT is not 100% associated with such serotonergic polymorphisms.

This phenomenon may mask positive outcome data, particularly when the size of the cohort is small. In order to avoid this phenomenon, it may be argued that the odds of finding a positive association between serotonergic polymorphisms and the duration of the IELT is enhanced when

genetic research is performed in men who develop an ejaculation delay in response to daily SSRI, e.g., paroxetine, treatment.

GENETICS OF IELT, LIFELONG PE, AND PE

It is important to distinguish (i) the genetics of the ejaculation time (e.g., the IELT), (ii) the genetics of lifelong PE, and (iii) the genetics of PE.

1. Genetics of the IELT

The aim of genetic research on the ejaculation time (e.g., IELT) is to investigate the genetic factors that influence or “modulate” the duration of the ejaculation time (e.g., the IELT).

2. Genetics of lifelong PE

The aim of genetic research on lifelong PE is to investigate the genetic factors that influence or are involved in the various parameters of lifelong PE.

3. Genetics of PE

The aim of genetic research on PE is to investigate the genetic factors that influence or are involved in men who complain of PE and who have both normal and very short ejaculation times.

GENETICS AND THE FOUR PE SUBTYPES

It should be emphasized that according to Waldinger et al, only a very small percentage of men who “complain” of PE have “genetically” based PE [14-16]. This is explained by the following arguments.

(i) Of the four PE subtypes, it has been argued that only lifelong PE is mainly influenced by genetic and neurobiological factors, because the IELT in these men persistently occurs within 1 minute independent of internal or environmental circumstances. According to this view, the genetics of lifelong PE pertains only to the neurobiological mechanisms that determine the “modulation” of the persistently very short IELTs. In the case of homosexual individuals with lifelong PE, the modulation of ejaculation is better reflected by the duration of the MELT, OELT, or AELT [40].

(ii) The prevalence of men with an IELT of less than 1 minute, irrespective of a complaint of PE, in the general male population is about 2.5% [17,18].

(iii) The prevalence of men with an IELT of less than 1 minute and with a complaint of PE in the general male population is about 2.5% as well [11].

According to Waldinger et al, the duration of the ejaculation time (e.g., the IELT) is influenced by both genetic and nongenetic factors [14-16]. However, it is postulated that the genetic influences on the IELT become most manifest in men who persistently ejaculate within 1 minute, e.g., in men with lifelong PE. In contrast, with increasing genetic and neurobiological ability to delay ejaculation time, it is argued that nongenetic factors increasingly influence the

IELT duration.

The aforementioned view is the basis for the hypothesis of Janssen [4] that the persistently short IELTs in men with lifelong PE are caused by (the sum of) various genetic polymorphisms or other genetic factors that facilitate ejaculation. According to the same view, it is assumed that the genetic profile of genetic polymorphisms in men with lifelong PE is different from the genetic profile of genetic polymorphisms in men with natural variable PE or subjective PE, because the IELT duration in these men is not restricted to less than 1 minute.

THREE DIFFERENT METHODS OF GENETIC RESEARCH ON PREMATURE EJACULATION

So far, three different methods of genetic research on PE have been published.

1. The first method investigates the genetics of the ejaculation time (e.g., the IELT) in men with lifelong PE with IELTs of less than 1 minute [4]. This investigation is based on the hypothesis of Waldinger et al that the skewed distribution of the IELT in the general male population [17,18] in men with lifelong PE [4,19,41] and in any cohort of male Wistar rats [29] is based on genetic factors influencing the central serotonergic system in modulating the duration of the IELT. The methodology of this genetic research consists of real-time, objective stopwatch measurement of the IELT in cohorts of men who actively seek medical treatment for their complaints associated with lifelong PE in terms of lifelong, persistent IELTs of about 1 minute.

2. The second method investigates the genetics of men who complain of PE in the general male twin population [42-45]. This investigation is based on the view of Jern et al that PE consists of various parameters (such as anteportal ejaculation, number of thrusts, ejaculation latency time, and feelings of control) that are potentially genetically interrelated [42-45]. Their methodology of genetic research consists of sending questionnaires to a large cohort of male homosexual and heterosexual twins irrespective of their wish to seek medical treatment for complaints of PE and without objective stopwatch measurements of the IELT.

3. The third method investigates whether the prevalence of genotypes in men with lifelong PE in terms of an IELT of less than 1 minute differs from the prevalence of these genotypes in the general male population [46,47], without investigating potential associations of genetic polymorphism with the IELT (as used in the first method). This investigation is based on the view that men with lifelong PE have a different genotype profile than do men without lifelong PE.

DIFFERENCES BETWEEN THE THREE METHODS

The three methods differ in (i) the investigated population

(men with lifelong PE versus general male twin population), (ii) tool of measurement (stopwatch versus questionnaire), (iii) design (prospective real-time IELT measurement versus retrospective IELT estimation), and (iv) variables (IELT versus feelings of control, ejaculation prior to intercourse, number of thrusts, and ejaculation latency time).

However, the major difference between the three study designs pertains to the investigated population. Whereas Janssen et al investigated a selected cohort of men with lifelong PE who ejaculate within about 1 minute and who present as patients actively seeking treatment [4], Jern et al and Santtilla et al investigated a relatively small group of respondents (40%; 33%) recruited from a large general male twin population who did not present as patients seeking medical treatment [42-45].

Moreover, in the studies of Jern et al and Santtilla et al, most (98%) of the male twins ejaculated after 1 minute [42-45]. Of 1,290 twins, only 26 (2%) twins reported an ejaculation time of less than 1 minute [45]. In contrast, in the study of Janssen et al [4], most (92%) of the men ejaculated within 1 minute, and only 8% ejaculated between 1 and 2 minutes.

The third method of genetic research on PE is different from the method of Janssen et al [4]. In this method, men with lifelong PE are selected but instead of investigating potential associations of genetic polymorphisms with the IELT, the prevalence of genotypes in these men with lifelong PE is compared with the prevalence of these genotypes in a control group. This method has been used by Ozbek et al and Luo et al in Turkey and China [46,47]. The outcome of these studies points to a different genetic profile in men with lifelong PE than in men in the general male population, rather than emphasizing an association between ejaculation time and genetic polymorphism. However, such a difference in genotype profile was not found in the Dutch study of men with lifelong PE by Janssen et al [4]. This discrepancy was explained after re-analysis of the data by Ozbek et al [46], which disclosed that these study populations did not meet Hardy-Weinberg equilibrium, indicating laboratory insufficiencies or patient selection bias [48]. Further studies controlled by Hardy-Weinberg equilibrium are needed to elucidate whether men with lifelong PE indeed have a higher prevalence of certain genotypes than do males in the general male population.

LIMITATIONS OF THE THREE METHODS

Each of the three methods has its own limitations. For example, non-stopwatch assessment of the IELT in the general male population may give rise to about 30% over- and under-estimation of the IELT compared with stopwatch assessment [18]. Therefore, it may be assumed that the non-stopwatch methodology of Jern et al [42-44] and Santtilla et al [45] fails to precisely objectify the IELT duration both in men with an IELT of less than 1 minute and in men with longer IELT durations. Notably, any questionnaire method as has been used by Jern et al and Santtilla

et al is inadequate to investigate the subtle influences of genetic polymorphisms on the IELT in men with lifelong PE who ejaculate within 1 minute [42-45].

On the other hand, the methodology of Janssen et al is inadequate to provide an answer to the question of how genetic factors relating to ejaculation are distributed in the general male population [4]. In addition, the design and method of the study of Janssen et al do not have the precision needed to study associations between subjective feelings of control and genetic polymorphisms [4]. The small number of participants in stopwatch studies in general does not allow sufficient power to analyze subjective feelings and possible polymorphisms. Such studies would require a huge cohort of patients.

THE NEED FOR STOPWATCH MEASUREMENTS IN GENETICS

Interestingly, the current different views on how to perform *genetic* research on PE are strikingly similar to the different views that existed in the 1990s on how to perform *drug treatment* research on PE [49]. Also in that decade, a number of clinicians favored the stopwatch method to precisely assess the IELT, whereas others used questionnaires to measure control, satisfaction, and ejaculation time [49]. However, a final meta-analysis of drug treatments that were mainly performed in the 1990s confirmed that real-time, prospective stopwatch measurement of the IELT is more accurate than retrospective IELT assessments [2]. Similarly, it is my current view that real-time prospective IELT measurement is pivotal for evidence-based genetic research on PE, acknowledging that this requirement may impede large-scale genetic research of the IELT in the general male population.

CONCLUSIONS

A substantial number of men in the general population have complaints of PE. However, only a minority of these men are affected by the disorder of lifelong PE or acquired PE, both of which are characterized by a very short ejaculation time. Notably, particularly men with the latter PE subtypes most frequently seek medical treatment for their complaints of PE. On the other hand, men with natural variable PE and particularly those with premature-like ejaculatory dysfunction or subjective PE complain of PE, whereas their ejaculation time is actually not aberrant from the average ejaculation time in the general male population. For genetic research on PE, it is pivotal to take into account the different etiologies and pathogenesis of the four PE subtypes. For example, if it appears that subjective PE is more associated with social anxiety or specific personality traits than is lifelong PE, then genetic factors associated with social anxiety or these personality traits may more frequently be found in men with subjective PE. By not differentiating the 4 PE subtypes in genetic research, the odds will be increased that genetic outcome data (for example,

a genetic association with personality traits) will incorrectly be generalized to PE subtypes that are not associated with these outcome data. In addition, the odds will be increased that outcome data that have been found in a subtype of PE with a low prevalence (e.g., lifelong PE) are not found in the rest of the investigated cohort and therefore will incorrectly be dismissed. Moreover, the odds that the aforementioned examples may happen is absolutely increased when measurement of the duration of the IELT is not included in the study design or is inadequately assessed, for example, by a questionnaire instead of with a stopwatch.

Currently, three methods are used to perform genetic research on PE. The three methods differ in the investigated population, tool of measurement, study design, and variables of PE. The small number of genetic studies on PE that have so far been published do not yet allow a conclusion as to which of these methods is the most valid. However, as previously mentioned, it is this author's view that prospective stopwatch measurement of the IELT is pivotal for evidence-based genetic research on the IELT in men with lifelong PE and the three other PE subtypes. Moreover, it is emphasized that in finding associations between serotonergic polymorphisms and the IELT duration in men with lifelong PE, the central serotonergic system is mainly involved in the "modulation" of the ejaculation or IELT and not or just minimally in the spinal ejaculation reflex itself. Because this modulation of the IELT is variable among men and may even be absent, serotonergic polymorphisms may only be found in men who respond to SSRI treatment with an ejaculation delay.

Conflicts of Interest

The authors have nothing to disclose.

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