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The mathematical formula of the intravaginal ejaculation latency time (IELT) distribution of lifelong premature ejaculation differs from the IELT distribution formula of men in the general male population

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Purpose: To find the most accurate mathematical description of the intravaginal ejaculation latency time (IELT) distribution in the general male population.

Materials and Methods: We compared the fitness of various well-known mathematical distributions with the IELT distribution of two previously published stopwatch studies of the Caucasian general male population and a stopwatch study of Dutch Caucasian men with lifelong premature ejaculation (PE). The accuracy of fitness is expressed by the Goodness of Fit (GOF). The smaller the GOF, the more accurate is the fitness.

Results: The 3 IELT distributions are gamma distributions, but the IELT distribution of lifelong PE is another gamma distribution than the IELT distribution of men in the general male population. The Lognormal distribution of the gamma distributions most accurately fits the IELT distribution of 965 men in the general population, with a GOF of 0.057. The Gumbel Max distribution most accurately fits the IELT distribution of 110 men with lifelong PE with a GOF of 0.179. There are more men with lifelong PE ejaculating within 30 and 60 seconds than can be extrapolated from the probability density curve of the Lognormal IELT distribution of men in the general population.

Conclusions: Men with lifelong PE have a distinct 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. The mathematical formula of the Lognormal IELT distribution is useful for epidemiological research of the IELT.

Keywords: Goodness of Fit; Gumbel Max distribution; Intravaginal ejaculation latency time; Lognormal distribution; Premature ejaculation

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INTRODUCTION

In 1994, Waldinger et al. [1] introduced the intravaginal ejaculation latency time (IELT) as a measure for the ejaculation time of heterosexual intercourse [1]. The IELT is defined as the time from the moment of vaginal penetration until the moment of intravaginal ejaculation [1]. In case of ejaculation outside the vagina the IELT is zero by definition. The most accurate way to measure the IELT is the use of a stopwatch handled by the female partner. In a stopwatch study in a cohort of Dutch men with lifelong premature ejaculation, it was shown that the IELT had a skewed distribution and that 85% of men ejaculated within 1 minute after penetration [2]. In addition, in a meta-analysis of all drug treatment studies of premature ejaculation from 1943 to 2003, it was shown that prospective real-time stopwatch measurement of the IELT during selective serotonin reuptake inhibitors (SSRI) treatment led to a smaller, and therefore more valid, confidence interval of the IELT compared to retrospective questionnaire studies of the IELT [3]. In 2005, a prospective stopwatch study of 491 men of the general male population in 5 countries (The Netherlands, United Kingdom, Spain, Turkey, and the United States) also showed a skewed distribution to the right with a median IELT of 5.4 minutes (range, 0.55–44.1 minutes) [4]. Using a blinded timer device, a second study was performed in 2009 in a new group of 474 men of the general population in the same countries [5]. This study also showed a remarkable similar skewed distribution to the right, with a median IELT of 6.0 minutes (range, 0.1–52.7 minutes). The precise and similar method of IELT measurement by a stopwatch on various intercourse events in the 3 aforementioned studies facilitates comparison of their IELT distributions. However, a prerequisite for further research of the ejaculation time, is a better knowledge of the type of distribution that is formed by the IELT in different populations of men.

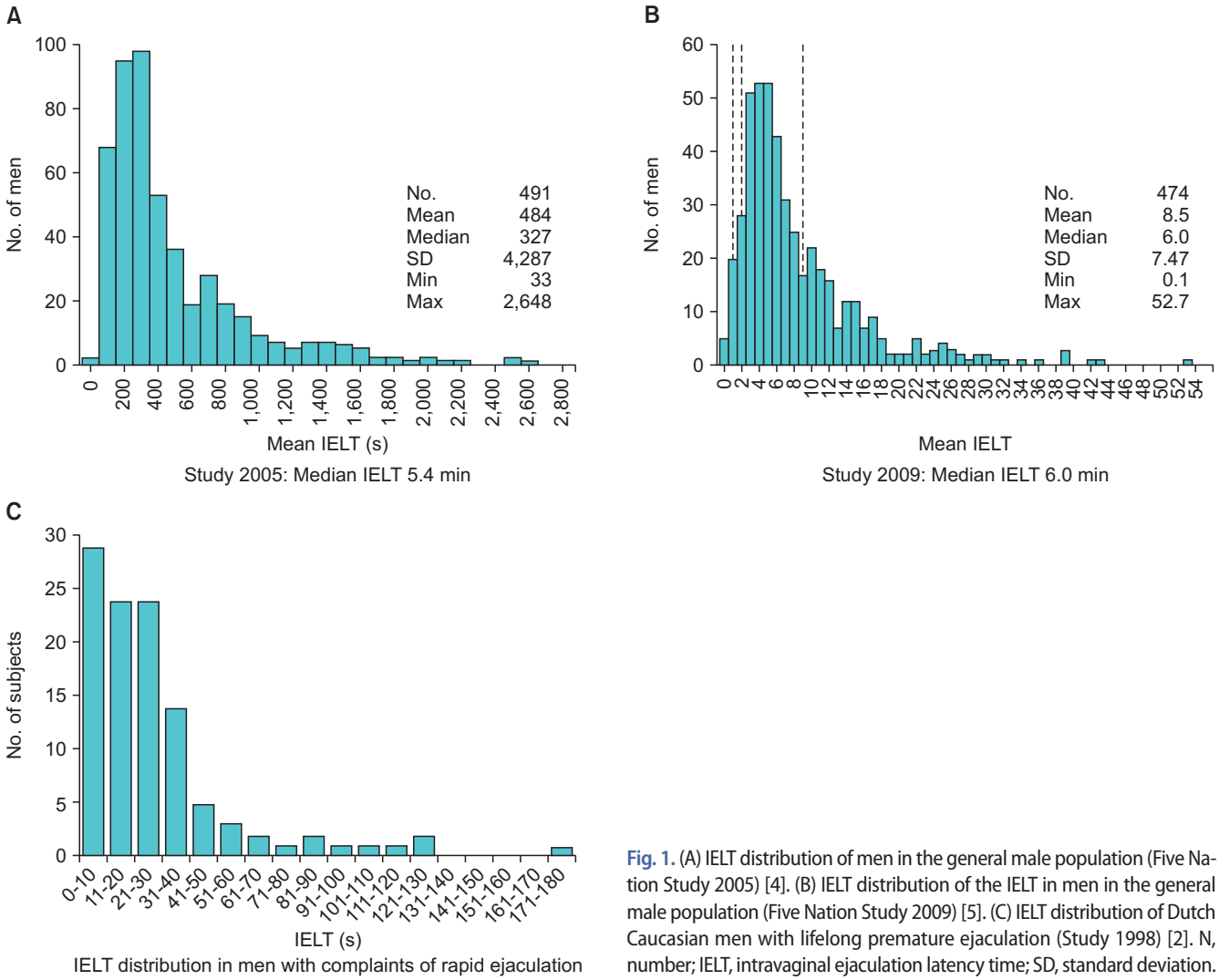

Fig. 1. (A) IELT distribution of men in the general male population (Five Nation Study 2005) [4]. (B) IELT distribution of the IELT in men in the general male population (Five Nation Study 2009) [5]. (C) IELT distribution of Dutch Caucasian men with lifelong premature ejaculation (Study 1998) [2]. N, number; IELT, intravaginal ejaculation latency time; SD, standard deviation.

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The purpose of the current study, was to investigate which type of well-known mathematical distribution fitted to the IELT distribution of men with lifelong PE and of men in the general male population.

MATERIALS AND METHODS

By application of the statistical program Easy Fit Professional ver. 5.6 (Mathwave Technologies Inc.) [6], we analysed the IELT data of 2 previous stopwatch studies of the IELT in the general male population [4,5] (Fig. 1A, B) and of the IELT data of a previous stopwatch study in a clinical cohort of men with lifelong premature ejaculation (Fig. 1C) [2]. In addition, we investigated which of the well-known mathematical probability distributions, fitted most accurately to the curves of the aforementioned IELT distributions. This fitness of the distribution is expressed by the Goodness of Fit (GOF), which is calculated by the Kolmogorov-Smirnov test (KS test) [7,8] The GOF therefore is a measure for the accuracy of the fitness [7,8].

The KS test is a non parametric statistical test of the equality of continuous, one-dimensional probability distributions [7,8].

In the current study it was used to compare the IELT distributions with various well-known theoretical reference probability distributions (one-sample KS test). The difference between the actual measured IELT data (as previously published in the three stopwatch studies) and the theoretical mathematical distribution models is measured with the Kolmogorov Smirnov test. In other words, the KS test measures the GOF. The smaller the difference between the theoretical distribution and the IELT distribution, the more accurate is the fitness of the theoretical distributions on the IELT distributions. Notably, the smaller the GOF, the better is the fitness.

RESULTS

GOF, measured by the KS test showed that the IELT distributions in the 2 studies of the IELT in the general male population (the 2005 study and the 2009 study) [4,5] and in the IELT distribution of Dutch Caucasian men with lifelong PE [2] were a gamma-distribution, which is characterized by (1) a boundary on the left at zero, and therefore excluding negative IELT values, (2) a positively skewed shape, including high IELT values, and (3) a significant flexibility in the shape, allowing the gamma

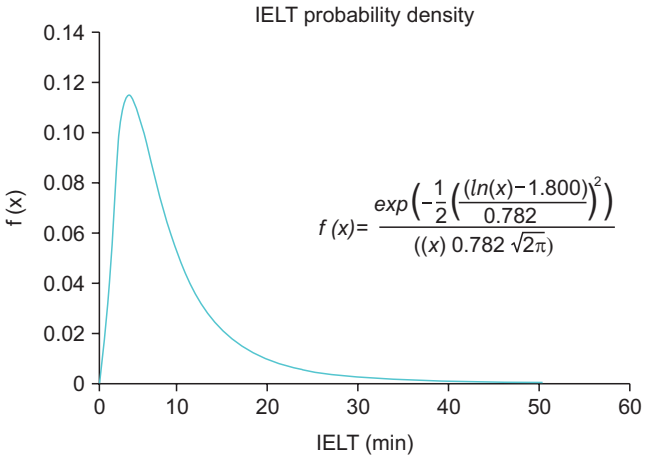

Fig. 2. The combined Log-normal Distribution of men in the general male population (Combination of IELT. Study 2005 and 2009 [4,5]). The form of this gamma-distribution is expressed by the mathematical formula, shown in this Figure. IELT, intravaginal ejaculation latency time.

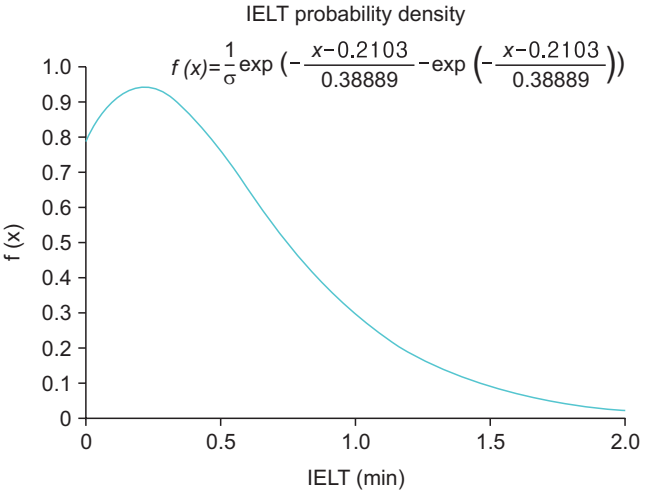

Fig. 4. The Gumbel Max Distribution of the intravaginal ejaculation latency time (IELT) study in men with lifelong premature ejaculation [2]. The form of the gamma-distribution is expressed by the mathematical equation as shown in this Figure.

$$f(x)=\frac{exp\left(-\frac{1}{2}\left(\frac{(ln(x)-1.800)}{0.782}\right)^2\right)}{((x)\ 0.782\ \sqrt{2\pi})}$$

Fig. 3. Mathematical Formula of the intravaginal ejaculation latency time (IELT) of the general Caucasian male population (x=IELT at x-axis; f(x)=relative density of IELT in general male population on y-axis).

$$f(x)=\frac{1}{\sigma}\exp\left(-\frac{x-0.2103}{0.38889}-\exp\left(-\frac{x-0.2103}{0.38889}\right)\right)$$

Fig. 5. Mathematical Formula of the intravaginal ejaculation latency time (IELT) in Dutch Caucasian males with lifelong premature ejaculation (x= IELT at x-axis; f(x)= relative density of IELT in men with lifelong premature ejaculation on y-axis).

distribution any number of IELTs, with reasonable accuracy.

Of the multiple operationalized gamma-distributions, the Lognormal distribution fitted most well on the gamma-IELT distribution in the general male population. The combined Lognormal distribution of men in the general male population (combination of IELT study 2005 and 2009) [4,5] is shown in Fig. 2. The form of this Lognormal distribution is mirrored by the mathematical formula, shown in Fig. 3.

In contrast, the Gumbel Max distribution fitted most well on the gamma-distribution of the IELT in the cohort of men with lifelong premature ejaculation (Fig. 4). The form of this Gumbel Max distribution is mirrored by the mathematical formula, shown in Fig. 5.

This fitness can be visualized by comparing the IELT distributions of Fig. 1A and B with the IELT distribution of Fig. 2.

According to Kolmogorov Smirnov the GOF of the Lognormal distribution for the 2005 study was 0.11708, and for the 2009 study the GOF was 0.06284. The GOF of the combined Lognormal distribution of both the 2005 and 2009 study was 0.057.

According to Kolmogorov Smirnov the GOF of the Gumbel Max distribution of the IELT distribution in the 1998 study of men with lifelong PE was 0.179.

By using the Lognormal distribution, the various IELT values of all men in the general male population of the 2005 study, the 2009 study and their combination were calculated (Table 1).

By using the Gumbel Max distribution, the various IELT values of all men in the 1998 study of Dutch Caucasian men with lifelong PE [2] were calculated (Table 2).

Table 3 shows that in the general male population 1.08% of men ejaculates within 0 to 60 seconds after vaginal penetration (in 2005 study, 1.23%; in 2009 study, 0.99%; in combined study, 1.08%). Moreover, in the general male population 0.077% ejaculates within 0–30 seconds.

In contrast, in the 1998 study of men with lifelong PE, 85.4% ejaculates within 1 minute, and 55.1% ejaculates within 30 seconds.

Notably, in the general male population 7.1% of men ejaculates between 1 and 2 minutes. In contrast in men with lifelong PE, 14% of men ejaculates within 1 and 2 minutes.

Comparison of Figs. 2 and 4 show that the IELT distribution of the cohort of men with lifelong PE is not represented in the IELT distribution of the men in the general male population. This is also shown by the IELT data, as represented in Table 3, which shows that 85.4% of men ejaculates within 1 minute in men with LPE, whereas only 1.08% of men in the general male population ejaculates within 1 minute. This difference is represented by Fig. 6.

DISCUSSION

By investigating which theoretical mathematical distribution fitted most accurately on the IELT distributions of 3 previously published IELT distributions, it appeared that the 3 IELT distributions were gamma distributions, but that the type of gamma distribution of men in the general male population does not fit in the gamma distribution of men with lifelong PE. Therefore this study showed that men with lifelong PE not only differ from men in the general population in their IELT values, e.g., men with lifelong PE have IELTs of less than 1 minute, but also in the mathematical type, e.g., curve of their IELT distribution.

In order to investigate the IELT distributions, we investigated which of the well-known mathematically described distributions fitted most accurately to the IELT distribution of men in the general male population and of men with lifelong PE. For that purpose we summarized the data of 2 prospective real-time stopwatch studies of Caucasian men in the general population, performed in the same five countries (The Netherlands, United Kingdom, Spain, Turkey, and the United States), to one set of IELT data, including 965 males, and compared this IELT distribution with the IELT distribution of a cohort of 117 Dutch Caucasian men with lifelong PE [2,4,5].

In the current study, it was found by application of the KS test on various mathematical distributions that the IELT distribution of the males in the general male population most accurately fitted the Lognormal distribution, which belongs to the family of gamma distributions. However, the IELT distribution of males with lifelong PE did not fit to the Lognormal distribution. Importantly, the IELT distribution of the males with lifelong PE most accurately fitted to the Gumbel Max distribution, which, on its turn, inaccurately fits to the IELT distribution of men in the general male population. This shows that men with lifelong PE have a distinct IELT distribution. For example, whereas only a neglectable minority of men in the general male population ejaculates within 1 minute (e.g., 1.08%) and within 30 seconds after vaginal penetration (e.g., 0.08%), the current study shows that the opposite occurs in men with lifelong PE. In these men, the majority ejaculates within 30 seconds (e.g., 55.1%) and within 30 to 60 seconds (e.g., 30.3%). In other words, there are significantly more men with lifelong PE who ejaculate within 30 seconds than can be extrapolated from the probability density curve of the IELT distribution of men in the general population.

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Table 1. Percentages of men in the general male population with specific IELT values, calculated using the Lognormal distribution of the IELT

IELT (min)	2005 Study (%)	2009 Study (%)	Combined IELT values (%)
0–1	1.2	0.98	1.07
1–2	7.3	6.3	7.9
2–3	11.1	9.9	10.6
3–4	11.7	10.8	11.3
4–5	10.7	10.2	10.5
5–6	9.3	9.0	9.2
6–7	7.8	7.7	7.8
7–8	6.5	6.6	6.6
8–9	5.4	5.5	5.5
9–10	4.4	4.7	4.6
10–11	3.7	3.4	3.8
11–12	3.1	3.3	3.2
12–13	2.5	2.8	2.7
13–14	2.1	2.4	2.2
14–15	1.8	2.0	1.9
15–16	1.5	1.7	1.6
16–17	1.3	1.5	1.4
17–18	1.1	1.3	1.2
18–19	0.93	1.1	1.0
19–20	0.80	0.95	0.9
20–21	0.69	0.83	0.74
21–22	0.59	0.72	0.64
22–23	0.51	0.63	0.55
23–24	0.44	0.55	0.48
24–25	0.39	0.48	0.42
25–26	0.34	0.43	0.37
26–27	0.30	0.38	0.32
27–28	0.26	0.33	0.29
28–29	0.23	0.30	0.25
29–30	0.20	0.26	0.22
30–31	0.18	0.23	0.20
31–32	0.16	0.21	0.16
32–33	0.14	0.19	0.16
33–34	0.13	0.17	0.14
34–35	0.11	0.15	0.12
35–36	0.001	0.14	0.11
36–37	0.0089	0.12	0.10
37–38	0.0080	0.11	0.09
38–39	0.0072	0.099	0.08
39–40	0.0064	0.0090	0.0073
40–41	0.0058	0.0081	0.0066
41–42	0.0052	0.0074	0.0060
42–43	0.0047	0.0067	0.0054
43–44	0.0043	0.0061	0.0049
44–45	0.0039	0.0056	0.0044

IELT, intravaginal ejaculation latency time.

The form of a distribution is expressed by a mathematical formula. An advantage of the formula for the Lognormal distribution, is that it enables the calculation of the number and percentage of men in a specific population with a specific IELT value. Similarly, based on the Gumbel Max distribution, the number and percentage of men with a

specific IELT value can be calculated in a cohort of men with lifelong PE.

Our calculations by means of the formula of the Lognormal distribution (Table 1) showed a striking similarity of the percentages of males with a specific IELT value in the 2 separate studies of men in the general population, supporting the reliability and validity of stopwatch measurement of the IELT in an epidemiological study of the IELT.

Notably, as the 2 general population IELT stopwatch studies, e.g., the 2005 and 2009 studies [4,5], have been conducted in Caucasian men, a limitation of the current study is that the formula may only be valid for Caucasian men in Western Countries, whereas for African, Middle East, and Far East Asian countries our formula remains to be investigated on the condition that similar IELT stopwatch studies in random samples of their general populations have been conducted. So far this has not been done.

One may argue that another limitation of the current study is the number of men with lifelong PE [2]. However, a simple calculation shows that in order to discover the Gumbel Max IELT distribution of men with lifelong PE in the Lognormal IELT distribution in the general male population, one has to multiply the number of men with

Table 2. Percentages of men with lifelong PE with specific IELT values, calculated according to the Gumbel Max Distribution of the IELT

IELT (s)	1998 Study (%)
0–10	9.1
10–20	24.9
20–30	21.1
30–40	14.5
40–50	9.5
50–60	6.3
60–70	4.2
70–80	2.9
80–90	2.0
90–100	1.4
100–110	1.0
110–120	0.74
120–130	0.54
130–140	0.41
140–150	0.31
150–160	0.24
160–170	0.18
170–180	0.14

IELT, intravaginal ejaculation latency time.

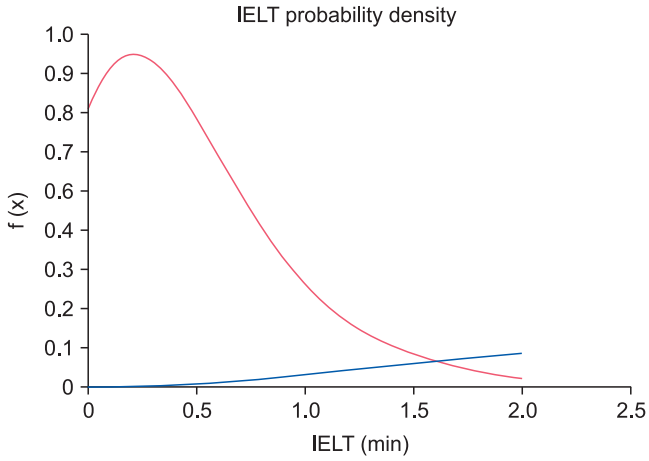

Fig. 6. The Gumbel Max Distribution of the intravaginal ejaculation latency time (IELT) in men with lifelong premature ejaculation (PE) (red curve) in relation to the Lognormal Distribution of the IELT in men of the general male population (blue curve). In the general male population, 99% of men of the IELT distribution is represented after an IELT of 1 minute, whereas only 14.6% of men with lifelong PE is represented after an IELT of 1 minute [2,4,5].

Table 3. Percentages of men in the general male population and of men with lifelong PE with specific IELT values less than 1 minute, and with IELT values of 1–2 minutes, calculated according to the Kolmogorov Smirnov formula for Lognormal distribution (e.g., 2005 Study, 2009 Study, and combined IELT Study [4,5]) and Gumbel Max distribution (e.g., 1998 Study [2]) of the gamma distribution of the IELT

IELT (s)	2005 General population study (%)	2009 General population study (%)	Combined IELT general population (%)	1998 Lifelong premature ejaculation study (%)
0–10	0.0003	0.0025	0.0022	9.1
10–20	0.013	0.011	0.013	24.9
20–30	0.069	0.056	0.062	21.1
30–40	0.20	0.16	0.17	14.5
40–50	0.37	0.31	0.32	9.5
50–60	0.58	0.45	0.51	6.3
Total	1.23	0.99	1.08	85.4
60– 90	2.9	2.4	2.7	9.0
90–120	4.4	3.8	4.4	5.0
Total	7.3	6.2	7.1	14.0

IELT, intravaginal ejaculation latency time.

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lifelong PE by 100. For example, the men with lifelong PE (n=110) shown in Fig. 1C could be extracted out of a general male population of 11.000 men (1% = 1/100 of the population). As it is impossible to perform a stopwatch study of the IELT in 11.000 males, it may be argued that such stopwatch studies will never be performed. Still, with a few hundreds of men with lifelong PE who have measured their IELT prospectively with a stopwatch it is argued that the current formula of the Gumbel Max IELT distribution can be become more accurate for application in a cohort of men with lifelong PE.

Interestingly, based on the formula of the Lognormal distribution that most accurately describes the IELT data of men in the general male population, it is possible to answer certain questions regarding the IELT of men in the general male population without the necessity of conducting real-time stopwatch measurements in very large samples of men.

For example, according to the Statistics Netherlands (Centraal Bureau voor de Statistiek or CBS), the Netherlands currently has 16.982.433 inhibitants and 8.372.858 of them are males [9]. Of these males, 5.912.984 are aged between 18 and 70 years. Application of our Lognormal formula shows that in the Netherlands there are 70.305 men (1.19%) who ejaculate within 1 minute, and 48.546 (0.82%) men who ejaculate within 30 seconds. In addition, using this formula, 502.012 (8.5%) men ejaculate between 0 and 2 minutes, 2.419.002 men (40.9%) who ejaculate between 1 and 5 minutes, and 1.971.330 (33.3%) men who ejaculate between 5 and 10 minutes. In addition, there are 1.112.291 men (18.8%) who ejaculate between 10 and 20 minutes. Notably, after 20 minutes, the number and percentages decrease: 233.208 men (3.9%) ejaculate between 20 and 30 minutes and 66.225 men (1.12%) ejaculate between 30 and 40 minutes. Briefly, in the Netherlands 99.3% of men ejaculates between 0 and 40 minutes. A minority of 40.633 (0.687%) ejaculates with an IELT of more than 40 minutes.

The application of the formula, which describes the probability density of the IELT, shows that it may provide answers to questions that cannot be measured by a stopwatch, due to the extremely large number of men that otherwise ought to be included in an epidemiological study, or just cannot be measured as the IELT duration is too long and potentially painful for the female partner of a subject participating in a scientific study.

Notably, it is questioned why the IELT distribution of the men with lifelong PE is so completely different from the IELT distribution of men in the general male population. Further research into this question is warranted and is presumably associated with genetic and epi-genetic factors [10-13].

According to the recent classification by Waldinger and Schweitzer [14,15], there are 4 PE subtypes, e.g., lifelong PE, acquired PE, subjective PE, and variable PE. Their prevalence in the general population differs significantly, as has been shown by Serefoglu et al. [16] and Gao et al. [17], with the lowest prevalence of lifelong PE. Notably, lifelong PE is characterized by a hypertonic state, consisting of premature ejaculation (ejaculatio praecox), a facilitated erection (erectio praecox) and a facilitated penile detumescence (detumescentia praecox), when the male is becoming involved in an erotic situation [18]. The current study shows that lifelong PE not only differs from the 3 other PE subtypes with regard to this triad of symptoms, but that lifelong PE has a different IELT and a different IELT distribution than males in the general population, of which men with variable and subjective PE are part of. The separate state of lifelong PE among the 3 other PE subtypes with regard to the IELT and its IELT distribution has consequences for the methodology and design of drug treatment studies. As has recently been argued by Waldinger [19], the method and design for drug treatment studies of men with lifelong PE who ejaculate within seconds, are not required for drug treatment studies of men with variable and subjective PE with normal IELT values.

CONCLUSIONS

The IELT distribution of men in the general population is most accurately fitted by the Lognormal distribution, whereas the IELT distribution of men with lifelong PE is most accurately fitted by the Gumbel Max distribution. As there are significantly more men with lifelong PE who ejaculate within 30 and 60 seconds than can be extrapolated from the probability density curve of the IELT distribution of men in the general population it is concluded that men with lifelong PE have a distinct IELT distribution that can only be retrieved from the general male population IELT distribution when thousands of men would participate in a stopwatch study of the IELT. The cause of the difference in IELT distribution should be further investigated and may be due to genetic and epigenetic factors. Application of the mathematical formula of the Lognormal IELT distribution is useful for epidemiological research of the IELT in large populations of men.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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EDITORIAL COMMENT

In the present issue of Investigative and Clinical Urology, Janssen and Waldinger [1] publish an important mathematical contribution on the intravaginal ejaculatory latency time (IELT) distributions of men in the general adult population compared to the IELT distribution of men with lifelong premature ejaculation (PE). Data used to study these distributions were derived from earlier studies on Caucasian males in Europe and North America. Although both populations (normal and lifelong PE) are small due to the experimental design with stopwatch methodology, the authors have convincing and valid arguments that both populations have distinct mathematical IELT distributions. This leads to interesting consequences, hypotheses and research possibilities.

Lifelong PE has convincingly been shown to be a very

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stable putative endophenotype within the range of all IELT's measured all over the world in different populations and cultures [2]. This stability strongly suggests that this endophenotype is caused by underlying biological mechanisms, presumably anchored in the central nervous system. The mathematical different distribution models of the IELT in the general population and lifelong PE males furthermore strongly supports biological differences underlying these IELT distributions and argues against psychological or behavioral interventions aimed at elongation of the IELTs in PE males. Whether such biological and fundamental different processes in the IELT of lifelong PE can be considered as 'pathological' remains a tricky question. As long as men present their PE as an unwished phenomenon from which they and their partner suffer and look for help, PE can be considered as pathological and deserves treatment if possible.

Further studies into the underlying mechanisms of life long PE is urgently needed as the only efficient treatment of PE so far are the SSRI. Apart from their side effects, SSRIs have to be taken daily and life long, i.e., as long as a wish for a 'normal' sex life exists. Ideally, an 'on demand' treatment should be used, but the existing SSRI's, including dapoxetine as an approved 'on-demand' prescription drug for PE, hardly fulfill such claims [3]. Much more fundamental insight into the brain and spinal cord mechanisms involved in sexual behavior and ejaculatory processes are needed to possibly develop new pharmacological approaches to better treatment of lifelong PE.

Several strategies have to be developed and applied, in particular genetic, genomic and epigenetic approaches and techniques have to be implemented. The biological hardware differences in IELT between the normal and abnormal (lifelong PE) populations and the high familiar occurrence of PE [4] suggest that genetic technology (e.g., GWAS and expression studies) might help to identify factors (e.g., functional SNPs) that are involved. Moreover, central nervous system (CNS) functional magnetic resonance imaging studies (including spinal cord imaging) comparing normal IELT with lifelong PE men, where males are challenged with various sexual stimuli (visual, tactile) might unravel or differentiate activity (or lack of) in brain/spinal cord areas that generate new ideas and hypotheses on brain mechanisms involved.

Similarly, comparison of SSRI-treated (by preference chronically treated) males with normal IELT and lifelong PE males using brain/spinal cord imaging might further contribute to understanding of the mechanisms and brain localizations of the SSRI-induced changes in focal areas. Fundamental results from such brain studies in untreated and SSRI-treated populations might also generate hypotheses that can be used in a translational way in animal models of sexual behavior and sexual dysfunctions.

The serotonergic (5-HT) system seems an extremely important neurotransmitter system in the modulation of sexual behavior including ejaculatory processes [5]. Most research into this topic derives from animal studies, but the translational prediction of rat models of ejaculatory speed for human ejaculation latencies (IELT) appears rather high [6]. In general, increased 5-HT levels in the CNS elevate ejaculatory thresholds probably via activation of 5-HT_{1B} and 5-HT_{2C} receptors, whereas 5-HT depletion decreases the ejaculatory threshold. 5-HT_{1A} receptor activation strongly facilitates ejaculatory processes, either mediated by lowering 5-HT levels via activation of presynaptic (somatodendritic) 5-HT_{1A} autoreceptors and/or stimulation of postsynaptic 5-HT_{1A} heteroreceptors. We found that concurrent treatment of SSRIs and a silent 5-HT_{1A} receptor antagonist, strongly facilitated the inhibiting effects of SSRIs on male ejaculation [6], both after acute and chronic dosing. This suggests a new approach to an 'on-demand' treatment of PE; acute SSRI administration (e.g., paroxetine or escitalopram) plus a 5-HT_{1A} receptor antagonist (e.g., pindolol, a relative weak 5-HT_{1A} receptor antagonist and a ß-adrenoceptor antagonist-with the intrinsic risk of cardiovascular side effects). Safarinejad [7] used a high dose of pindolol (7.5 mg/d) for 6 weeks to men with PE who were refractory to paroxetine (20 mg/d) treatment for at least 2 months. Pindolol had a slight facilitating effect on PE in these paroxetine-treated men over the 6 weeks treatment. Although in this case pindolol appears a mild augmentation strategy in paroxetine-refractory patients, the data suggest that pindolol exerts its effects via blockade of 5-HT_{1A} receptors interfering with the SSRI-induced enhancement of overall 5-HT neurotransmission. Further support for an important role of the 5-HT_{1A} receptor in the inhibitory action of SSRIs on sexual behavior and ejaculation, in depression treatment considered as unwanted side effect, comes from findings with vilazodone in sexual behavior. Vilazodone exerts blockade of the serotonin transporter (SERT) concomitant with 5-HT_{1A} receptor agonistic activity. In a rat model of measuring sexual side effects, vilazodone has no inhibitory effects on male sexual behaviors after acute or chronic treatment, whereas paroxetine or citalopram, SSRI, had strong inhibitory effects [8]. This suggests that vilazodone is probably not very (or not at all) effective in lifelong PE, but a potential attractive antidepressant/anxiolytic with no or less sexual side effects.

The serotonergic system in the brain is a complex, extremely ramified system emerging in the raphé nuclei in the midbrain and projecting to practically all areas of the brain and spinal cord [3]. The 5-HT complex (in)directly interacts with all neurotransmitter systems in the CNS via 14 different postsynaptic (hetero) receptors and presynaptic autoreceptors; the serotonin transporter (SERT or 5-HTT) is the main regulatory mechanism in the modulation of the serotonergic tone via uptake of released 5-HT, thereby terminating 5-HT-ergic stimulation [3]. The SERT is the target of SSRI's that are known to delay ejaculation. Having a high affinity for 5-HT, the SERT controls the duration, availability and signaling capacity of synaptic 5-HT and therefore might determine the speed of ejaculation. If SERT activity is high, serotonergic neurotransmission is low(er) and this seems associated with a short IELT (5-HT functions as a brake on ejaculation). The 5-HTT functioning is moderated by a polymorphism in the 5-HTT promoter region of the *SERT* gene (SCL6A4) which encodes for the SERT protein (5-HT transporter-linked promoter region: 5-HTTLPR). The latter has a short (S) and a long (L) variant allele associated with low (S) and high (L) transcriptional activity. Thus, SS genotypes have much lower SERT activity than LL genotypes (SL are intermediate) and it has been postulated that men with SS genotype have longer IELT durations than men with LL genotypes. This was confirmed in a population of men with life long PE [9]. This is indeed a remarkable finding because in a population with already extremely short ejaculation latencies, a functional polymorphism (LL) was associated with a reduction of IELT of 50%. Data in the normal population are lacking, but a comparable pattern might be expected. An important remark, however, is that the promoter length polymorphism in the SERT gene cannot be the genetic base for lifelong PE but only a modulatory factor [9]. Moreover, the ejaculatory process itself is not critically dependent on the serotonergic system; it seems logical to postulate that many other neurotransmitter systems in the CNS contribute to the complex ejaculatory process although much research is needed to unravel the complex processes involved [3].

In conclusion: the finding by Janssen and Waldinger [1] that the ejaculatory process in lifelong PE essentially differs from that in normal ejaculating males, strongly indicates that PE can be considered as a dysfunction of the ejaculatory process. Future studies have to support this finding and might lead to new ideas about PE and possibly new treatments.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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