Sexual Medicine Reviews, 2024, 1–14
https://doi.org/10.1093/sxmrev/qeae048
Review

Possible pathophysiologic roles of neurotransmitter systems in men with lifelong premature ejaculation: a scoping review

Joost J. van Raaij, PharmD[1,2,3], Ege Can Serefoglu, MD, Prof, PhD[4], Thérèse A.M.J. van Amelsvoort, MD, Prof, PhD[3], Paddy K.C. Janssen, PharmD, PhD[1,2,*]

[1]Department of Clinical Pharmacy and Toxicology, VieCuri Medical Center, Venlo, 5912 BL, the Netherlands
[2]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Center +, 6229 HX, Maastricht, the Netherlands
[3]Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, 6226 NB, the Netherlands
[4]Department of Urology, School of Medicine, Biruni University, 34295, Istanbul, Turkey

*Corresponding author: Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Center +, 6229 HX, Maastricht, the Netherlands, Email: paddy.janssen@mumc.nl

Abstract

Introduction: Lifelong premature ejaculation (LPE) is a subtype of premature ejaculation. Genetic research on LPE has primarily focused on neurotransmitters such as serotonin, dopamine, and norepinephrine, whereas LPE treatment studies have focused on drugs such as selective serotonin reuptake inhibitors. However, findings from genetic association and pharmacotherapeutic studies have been inconsistent.
Objectives: To provide a quality overview of neurobiological targets that are potentially associated with LPE by investigating genetic association and pharmacotherapeutic studies.
Methods: This scoping review was conducted per the PRISMA-ScR tool (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews). Five databases were searched in March 2023 without timeline- or language-related restrictions.
Results: After deduplication, 3949 records were obtained for review. Following screening and full-text review with citation tracking, 52 studies were included: 18 genetic and 34 pharmacotherapy studies. Serotonergic targets, such as the serotonin transporter and pre- and postsynaptic serotonergic receptors, were most often associated with LPE in genetic and pharmacotherapeutic studies. Mixed results were found among polymorphisms within genetic studies. This mechanism is in accordance with pharmacotherapeutic studies, as the highest efficacy was found for potent serotonergic antidepressants. Successful treatment was also observed with medication acting on phosphodiesterase-5 enzyme, such as tadalafil and vardenafil. Analyses of other genetic association studies did not yield any further evidence for associated targets.
Conclusions: This review is the first comprehensive scoping review on LPE. We found that serotonergic targets are most often associated with LPE, suggesting that the serotonergic pathway is a predisposing factor in LPE. Furthermore, there is some evidence for phosphodiesterase 5 inhibitors, which should be investigated. Other previously investigated neurobiological targets appear less likely to contribute to LPE. Future studies should focus on multiple targets, ideally in a genome-wide association study design.
This review has been registered with the Open Science Framework (doi:10.17605/OSF.IO/JUQSD).

Keywords: scoping review; lifelong premature ejaculation; genetics; polymorphism; pharmacotherapy.

Introduction

Premature ejaculation (PE) is a common condition with a prevalence of 20%.[1,2] Lifelong PE (LPE) is its subtype that is characterized by (1) ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration; (2) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (3) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.[3]

In 1943, Bernard Schapiro discovered that men affected with LPE have family members with similar ejaculatory complaints.[4] Waldinger et al elaborated on this result, which helped focus the research interest on genetic factors in the etiology of LPE.[5] Furthermore, Jern et al found similar results in a cohort study with Finnish male twins in 2007.[6] The findings suggested a heritable neurobiological component in the pathophysiology of LPE. In addition, neurobiological causes for LPE are supported by findings showing that psychotherapeutic treatments or sex therapy alone is ineffective for a significant remission of symptoms in LPE in contrast to other forms of PE.[7] A major part in the scientific studies of LPE consists of genetic case-control association studies. Another neurobiological approach associates abnormal endogenous blood levels of substances, such as hormones, with LPE.[8,9] Imaging studies on brain structures were recently published that investigated abnormal brain areas as compared with healthy controls.[10-12] Despite several plausible hypotheses and clues for 1 or multiple predisposing factors in the central nervous system causing LPE, no convincing evidence has yet been published. In contrast to these fundamental studies, the treatment of LPE has progressed by scientific research. In particular, pharmacotherapeutic treatment with selective serotonin reuptake inhibitors (SSRIs) such as paroxetine can delay ejaculation and improve clinical symptoms of LPE.[13,14] Other

Received: December 4, 2023. **Revised:** June 13, 2024. **Accepted:** July 3, 2024

studies in the treatment of LPE and PE focus on traditional Chinese medicine or alternative medicine such as acupuncture.[15,16] Surgical interventions in the penis have also been studied; however, they remain controversial because of the risk of postoperative complications with a high impact on quality of life.[17] Local pharmacotherapeutic treatments are well studied with commercial local anesthetics and other locally administered pharmaceuticals.[18,19] Furthermore, psychotherapeutic treatment—such as sex therapy, behavioral therapy (eg, the start-stop technique), or physiotherapy with pelvic floor rehabilitation—has been studied with mixed results in terms of efficacy.[7,20,21]

In 2008, the International Society for Sexual Medicine (ISSM) established clear definitions of LPE and other forms of PE, and the American Psychiatric Association followed in 2013 with a definition for LPE in the *Diagnostic and Statistical Manual of Mental Disorders*.[22,23] Despite the consensus on these definitions, some researchers dispute the distinction among all forms of PE.[24,25] They propose that men may be predisposed to reach ejaculation within a particular time frame; however, the actual timing of ejaculation is likely influenced by a variety of situational and contextual factors that may change in individual sexual experiences and over the lifetime. Consequently, a more prominent role was proposed for nonpharmaceutical treatment such as sex therapy.[24]

LPE research has improved in the last decade, mainly due to standardization in definition and measuring instruments.[3] In 1973, Tanner proposed an objective stopwatch method to measure the intravaginal ejaculation latency time (IELT).[26] This method was reintroduced in the 1990s to standardize research findings and prevent bias. PE research is known to be prone for response bias when the stopwatch method is not used, since men are often bad estimators of their own IELTs.[27,28] Unfortunately, these standardizations are still not used consistently in LPE research, leading to inconsistent and irreproducible findings.

In the field of LPE, mainly genetic and pharmacotherapeutic research has been conducted. Identified targets by pharmacotherapeutic studies or genetic association studies can provide leads for neurotransmitter pathways involved in the pathophysiology of LPE. Therefore, the objective of this scoping review is to provide an overview of genetic association or pharmacotherapeutic studies that evaluated targets that could be involved in the pathophysiology of LPE. Ultimately, a targeted strategy for conducting genome-wide association studies (GWASs) can be developed to identify the cause of LPE.

To our knowledge, this is the first scoping review with such an aim. In addition, strict quality requirements were set for inclusion of studies to guarantee quality evidence.

Materials and methods

Search strategy

For this study, a systematic process for evidence acquisition was set up according to PRISMA-ScR standards (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews).[29] In addition, we complied with guidelines by Levac et al.[30] The protocol for this scoping review was published in detail in March 2023.[31] No timeline- or language-related restrictions were applied.

Selection criteria

Studies eligible for inclusion had to meet a number of criteria. (1) Participants had to be adult men with LPE (age ≥18 years). (2) The type of study was either a genotyping study or a pharmacotherapy study. (3) The control group in the study consisted of men without LPE in genotype studies or patients with LPE who were drug naïve/washed out in pharmacotherapy studies. (4) In genotype studies, a significant or nonsignificant difference between men with LPE and those in the control group could be calculated or was otherwise reported. In pharmacotherapy studies, a fold increase in stopwatch-measured IELTs (sIELTs) pre- and posttreatment could be established. (5) Study designs in pharmacotherapy were randomized clinical trials, crossover drug studies, single-arm trials, or case reports in which a baseline sIELT was reported.

Studies were excluded when they met the following criteria: (1) LPE was not diagnosed by the International Society for Sexual Medicine (2008 or 2014),[3,22] the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition),[23] or a cutoff IELT of approximately 1.5 minutes after vaginal penetration. (2) IELTs were not measured by the stopwatch method. (3) Pharmacotherapy studies with traditional (herbal) medicine or topical anesthetic/locally active agents were excluded.

Study selection occurred in 2 stages. The first exclusion of records was performed according to eligibility by screening the title and abstract. Records that were classified as relevant were included for full-text review and final inclusion in the scoping review. Reports that were unavailable as full text were excluded. Studies were independently selected by 2 authors, and discrepancies were discussed until consensus was reached. The web-based research software Rayyan was used for selection of reports.[32] Studies were imported in the research software Mendeley.[31]

Data extraction

A preliminary data-charting form was drafted in the scoping review protocol.[31] We used this charting form and shaped it to ensure its suitable form for this review as data collection increased. The following were collected in the final charting form for pharmacotherapy studies: agent, country of origin, authors, year of publication, study design, LPE definition, total number of participants, treatment duration, pretreatment sIELT, and posttreatment sIELT. The total number of participants per study was extracted as the total number of participants in the analysis. When IELT measurements were extracted, the geometric mean was the preferred measure for the charting; however, when it was unavailable, the median and arithmetic mean were used. For clarity, IELT measurements were rounded to zero decimals and calculated fold increases to 2 decimals. Fold increases (ΔsIELT) were calculated with the highest posttreatment sIELT measurement within the duration of a study.[33] Single-nucleotide polymorphism (SNP; rs) reference numbers were used to denote polymorphisms. Statistical recalculations for genotype associations (chi-square test) and Hardy-Weinberg equilibrium (HWE) in control groups from genetic studies were performed in R (version 4.2.2). In addition, recalculation of fold increases was performed from pharmacotherapy studies. These were primarily done for uniformity in comparing equal outcome measures among studies. Extraction from studies, conversion of IELTs to seconds, and calculation of fold increases and

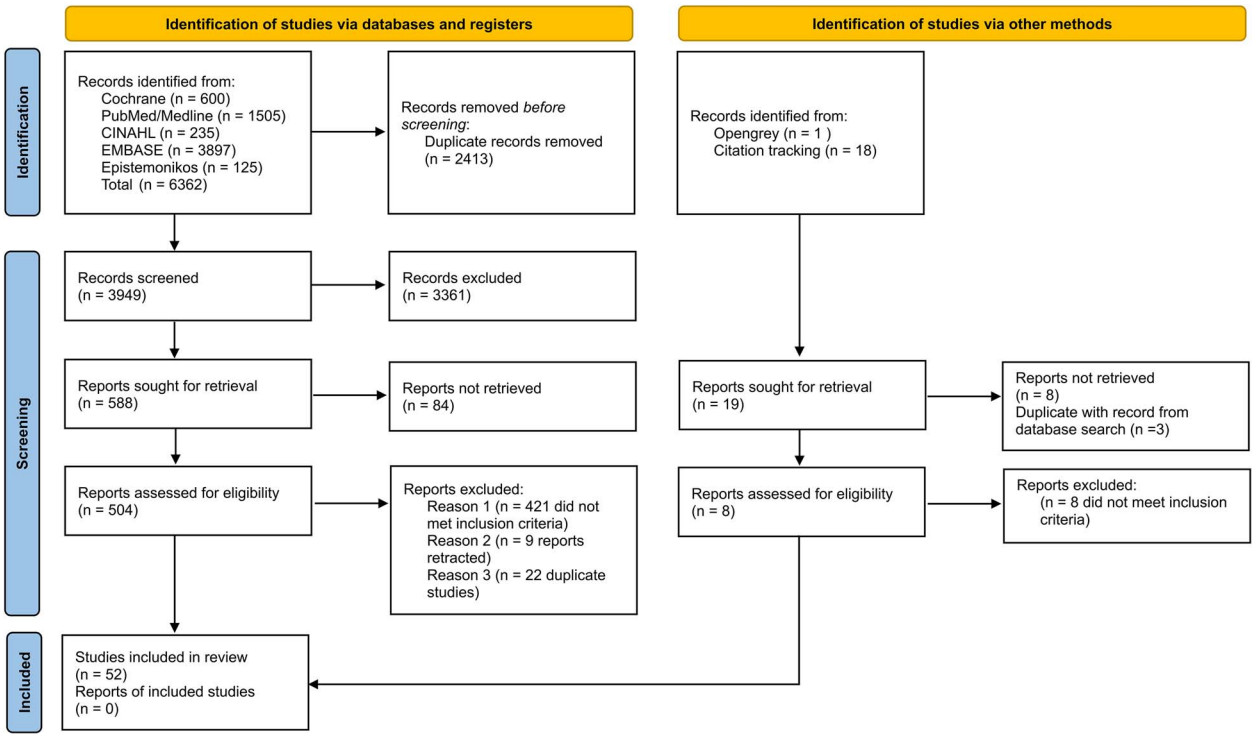

Figure 1. Flow diagram based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

chi-square tests were conducted by 1 author (J.J.v.R.). All extractions and calculations for errors were performed by a second author (P.K.C.J.). All calculations and data extraction details were uploaded onto the Open Science Framework (doi:10.17605/OSF.IO/JUQSD).

Statistics

HWE was determined within the control groups by an exact test.[34] Genotype frequencies between patient and control groups were compared by a chi-square test (R version 4.2.2). $P < .05$ was considered statistically significant. Fold increases >2 were considered therapy-induced and clinically relevant responses.[33] Calculation forms were uploaded onto the Open Science Framework (doi:10.17605/OSF.IO/JUQSD).

Results

The final search was performed in March 2023, and 6362 records were found in 5 scientific databases: Cochrane Database of Systematic Reviews, PubMed/MEDLINE, CINAHL, Embase, and Epistemonikos. After deduplication, 3949 records were obtained for review. After screening and full-text review, 52 studies were included (Figure 1). OpenGrey and citation tracking identified 19 records. Searching for studies via other methods did not result in any inclusions.

Pharmacotherapy studies

In all, 34 studies were identified as pharmacotherapy studies complying with the inclusion criteria for quality assurance.[13,14,16,18,21,35-63] Study characteristics are listed in Table 1. The size of study populations differed from 15 to 221, based on 10 types of similar definitions for LPE. Pharmacotherapy duration ranged from 2 to 52 weeks. Investigation of 17 drugs was done from 8 types of pharmacologic subgroups considering the Anatomical Therapeutic Chemical fifth-level groups.[64] Since epelsiban and cligosiban do not have Anatomical Therapeutic Chemical codes, they could be considered a ninth pharmacologic group.[37,46,47,64] Five studies had a crossover design,[18,35,36,40,54] and 21 studies were designed as parallel studies with ≥2 arms.[13,14,16,21,37,39,42,46-51,53,55,57,58,60-63] The remaining 8 studies were designed as a single-arm trial.[38,41,43-45,52,56,59] In all, 20 studies reported their blinding/nonblinding design.[14,35-37,39-42,46,47,49,51,53,55,57,58,60-63]

The highest fold factor increases ranged approximately from 4 to 8, and they were reported with daily use of paroxetine and sertraline and on-demand use of vardenafil.[14,35,36,41,43,53,59-61] Fluvoxamine, nefazodone, duloxetine, pregabalin, epelsiban, cligosiban, modafinil, and mirtazapine showed no clinically relevant fold increases.[13,14,37,46,47,49,51,53,61] Variable results among studies were seen with on-demand use of paroxetine, tramadol, sertraline, tadalafil, and dapoxetine.[16,18,21,39,40,42,45,48,50,52,54-56,62,63] Daily use of citalopram and tadalafil also resulted in variable fold increases (Table 1).[38,57,58,60]

Genetic studies

In all, 18 studies were identified as genetic studies, and in these studies, 37 polymorphisms on 7 types of genes were analyzed with 28 unique types of polymorphisms: 2 VNTR polymorphisms (variable number tandem repeat), 25 various SNPs, and 1 insertion/deletion polymorphism.[65-82] rs9279036 is thought to be an insertion/deletion polymorphism; however, it was classified as an SNP by Wang et al.[70,83] In addition, 1 GWAS was included (9 SNPs associated). All studies with relevant results are displayed in Table 2. Patient populations differed from 48 to 270 participants based on 8 types of similar definitions for LPE.

Table 1. Characteristics and recalculations of the pharmacotherapy studies included.

Study	LPE definition	Study design	Treatment duration, wk	Agent and dosing	No.	sIELT, s, arithmetic mean		Δ Increase	
						Before therapy	After therapy	Reported	Calculated
Kim (1999)[59]	sIELT ≤1 min in ≥50% of attempted intercourses	Single-arm trial	6	Sertraline 50 mg QD (2 wk) followed by sertraline 50/100 mg PRN (4 wk)	18	23	354	NR	15.39
Waldinger (2001)[60]	sIELT ≤1 min in ≥90% of attempted intercourses	Double-blind RCT	6	Paroxetine 20 mg QD	30	20[a]	170.5[a]	8.9	8.53
				Citalopram 20 mg QD		20[a]	44.21[a]	1.8	2.21
Waldinger (2001)[14]	sIELT ≤1 min in ≥90% of attempted intercourses	Double-blind RCT	6	Paroxetine 20 mg QD	48	17.1[a]	146[a]	9.1	8.54
				Sertraline 50 mg QD		13.9[a]	58.1[a]	3.5	4.18
				Nefazodone 400 mg QD		16.8[a]	28.4[a]	1.4	1.69
				Placebo BID		15.1[a]	23.6[a]	1.43	1.56
Waldinger (2003)[61]	sIELT ≤1 min in ≥90% of attempted intercourses	Double-blind RCT	6	Paroxetine 20 mg QD	24	15.38[a]	119.18[a]	5.7	7.75
				Mirtazapine 30 mg QD		23.86[a]	28.35[a]	0.9	1.19
Waldinger (2004)[62]	sIELT ≤1 min in ≥90% of attempted intercourses	Double-blind RCT	4	Paroxetine 20 mg PRN	30	21.4[a]	54[a]	1.58	2.52
				Clomipramine 25 mg PRN		28.3[a]	266[a]	6.21	9.4
Mattos (2008)[63]	*DSM-IV* criteria + sIELT ≤90 s	Double-blind RCT	12	Fluoxetine 90 mg QW + tadalafil 20 mg PRN	60	49.57	336.13	578%	6.78
				Fluoxetine 90 mg QW + placebo PRN		56.55	233.62	313%	4.13
				Placebo QW + tadalafil 20 mg PRN		49.26	186.53	278%	3.79
				Placebo QW + placebo PRN		49.86	67.82	36%	1.36
Aversa (2009)[35]	ISSM 2008	Double-blind crossover RCT	8 + 4	Vardenafil 10 mg PRN	40	36[a]	270[a]	NR	7.5
				Placebo PRN		42[a]	54[a]	NR	1.29
Mathers (2009)[36]	sIELT ≤90 s	Open-label crossover RCT	6 + 6	Sertraline 50 mg PRN	44	35.4	192	NR	5.42
				Vardenafil 10 mg PRN		35.4	300.6	NR	8.49

(*Continued*)

Table 1. Continued

Study	LPE definition	Study design	Treatment duration, wk	Agent and dosing	No.	sIELT, s, arithmetic mean		Δ Increase	
						Before therapy	After therapy	Reported	Calculated
GlaxoSmithKline (2011)[37]	ISSM (year NR)	Double-blind RCT	8	Placebo PRN	77	37.2[a]	37.2[a]	NA	1
				Epelsiban (GSK557296) 50 mg PRN		37.2[a]	43.2[a]	1.16	1.16
				Epelsiban (GSK557296) 150 mg PRN		37.2[a]	41.4[a]	1.11	1.11
Dadfar (2010)[38]	sIELT ≤1 min	Single-arm trial	4	Citalopram 20 mg QD	16	23.28	258.78	NR	11.12
Hamidi-Madani (2018)[39]	sIELT ≤1 min	Double-blind RCT	12	Paroxetine 20 mg PRN	126	43.2	91.17	NR	2.11
				Tramadol 50 mg PRN		42.42	136.98	NR	3.23
				Placebo PRN		47.71	77.97	NR	1.63
Kaynar (2012)[40]	ISSM (year NR)	Single-blind crossover RCT	8	Tramadol 25 mg PRN	60	38.83	154.67	4	3.98
				Placebo PRN		30.66	55.83	1.65	1.82
Xia (2014)[41]	ISSM 2008	Open-label single-arm trial	8	Sertraline 50 mg QD	58	30.5[b]	193.5[b]	8.1	6.34
Cormio (2015)[42]	ISSM 2014	Open-label RCT	24	Dapoxetine 30 mg PRN	50	85	160	NR	1.88
				Dapoxetine 30 mg PRN + sexual behavioral treatment		92	370.7	NR	4.03
Guo (2015)[43]	ISSM 2014	Single-arm trial	8	Paroxetine 20 mg QD (subgroup baseline IELT <30 s)	125	19.2[a]	727.8[a]	37.9	37.91
				Paroxetine 20 mg QD (subgroup baseline 30 ≤ sIELT <60 s)		46.2[a]	406.8[a]	8.81	8.81
				Paroxetine 20 mg QD (subgroup baseline 60≤ sIELT<120 s)		88.8[a]	271.2[a]	3.05	3.05
Sahin (2016)[16]	ISSM 2014	RCT	4	Dapoxetine 30 mg PRN	55	45.18	103.21	NR	2.28
				Dapoxetine 60 mg PRN		44.78	127.52	NR	2.85
Ozcan (2017)[44]	sIELT ≤1 min in ≥50% of attempted intercourses	Single-arm trial	4	Tadalafil 5 mg QD	30	40.8	190	NR	4.66
Kati (2018)[45]	sIELT ≤1 min	Single-arm trial	NR	Dapoxetine 30 mg PRN	56	39.8[a]	68.2[a]	NR	1.71
McMahon (2019)[46]	sIELT ≤1 min in ≥75% attempted intercourses	Double-blind RCT	8	Cligosiban 400-800 mg PRN	79	29.5[a]	62.3[a]	2.1	2.11
				Placebo PRN		26[a]	29.9[a]	1.1	1.15
Althof (2019)[47]	sIELT ≤1 min in ≥75% attempted intercourses	Double-blind RCT	8	Cligosiban 400 mg PRN	221	33.5[a]	73.1[a]	NR	2.18
				Cligosiban 800 mg PRN		34.2[a]	77.8[a]	NR	2.27
				Cligosiban 1200 mg PRN		30.8[a]	56.9[a]	NR	1.85
				Placebo PRN		36.8[a]	79.9[a]	NR	2.17

(*Continued*)

Table 1. Continued

Study	LPE definition	Study design	Treatment duration, wk	Agent and dosing	No.	sIELT, s, arithmetic mean		Δ Increase	
						Before therapy	After therapy	Reported	Calculated
Sahan (2020)[48]	ISSM 2014	RCT	8	Sertraline 50 mg QD	114	21.2[a]	28.3[a]	NR	1.33
				Sertraline 50 mg PRN		21.2[a]	24.3[a]	NR	1.15
				Sertraline 100 mg PRN		21[a]	27.1[a]	NR	1.29
				Dapoxetine 30 mg PRN		20.5[a]	25.2[a]	NR	1.23
El Najjar (2020)[49]	ISSM 2014	Double-blind RCT	2	Pregabalin 75 mg PRN	116	44[b]	43[b]	1	0.98
				Pregabalin 150 mg PRN		33[b]	65[b]	2	1.97
				Placebo		41.5[b]	40[b]	1	0.96
Ur Rehman (2020)[50]	sIELT ≤1 min	RCT	8	Tramadol 50 mg PRN	106	44.93	136.91	NR	3.05
				Paroxetine 20 mg PRN		43.74	95.42	NR	2.18
Alghobary (2020)[18]	sIELT ≤1 min	Crossover RCT	12	Dapoxetine 60 mg PRN	63	21.87[a]	63.4[a]	3	2.9
				Topical lidocaine		21.87[a]	179.43[a]	9	8.2
Haghighi (2022)[51]	*DSM-5*	Double-blind RCT	4	Modafinil 100 mg PRN	46	36.95	66.95	NR	1.81
				Placebo PRN		31.52	34.34	NR	1.09
Liu (2022)[52]	ISSM 2014	Single-arm trial	12 + 12	Dapoxetine 30 mg PRN (CGIC 1-3)	144	40.8[a]	170.4[a]	NR	4.18
				Dapoxetine 30 mg PRN (CGIC 3-0)		38.4[a]	162.6[a]	NR	4.23
Faddan (2022)[58]	ISSM 2014	Single-blinded RCT	12	Tadalafil 5 mg QD	55	45.7	52.3	NR	1.14
				Placebo		43.2	48.2	NR	1.12
Waldinger (1998)[53]	sIELT ≤1 min in ≥90% of attempted intercourses	Double-blind RCT	6	Fluoxetine 20 mg QD	51	18[a]	135[a]	6.6	7.5
				Fluvoxamine 100 mg QD		10[a]	19[a]	1.9	1.9
				Paroxetine 20 mg QD		13[a]	113[a]	7.8	8.69
				Sertraline 50 mg QD		19[a]	84[a]	4.4	4.42
				Placebo		15[a]	22[a]	1.5	1.47
Hassan (2016)[54]	ISSM 2008	Crossover trial	12 + 12 + 12	Dapoxetine 30 PRN	64	42	144	2.4	3.43
				Dapoxetine 60 mg PRN		42	216	3.8	5.14
				Paroxetine 20 mg PRN		42	108	1.6	2.57
Mokhtari (2014)[55]	sIELT ≤1 min	Double-blind RCT	6	Placebo PRN + sertraline 50 mg QD	108	35.29	87.55	NR	2.48
				Tadalafil 10 mg PRN + 50 mg sertraline QD		40.1	153.63	NR	3.83
Pastore (2012)[21]	ISSM 2008	RCT	12	Dapoxetine 30 PRN	15	31.21[a]	168.2[a]	NR	5.39
				Dapoxetine 60 PRN		37.82[a]	222.57[a]	NR	5.88
				Pelvic floor muscle rehabilitation		NA[a]	NA[a]	NR	NA
Mondaini (2013)[56]	ISSM 2008	Single-arm trial	52	Dapoxetine 30/60 mg PRN	120	54	228	NR	4.22
Ozcan (2015)[13]	sIELT ≤1 min	RCT	4	Duloxetine 40 mg QD	80	60.9	125.8	NR	2.07
				Paroxetine 20 mg QD		59.8	128.1	NR	2.14
Dell'Atti (2017)[57]	ISSM 2008	Double-blind RCT	12	Tadalafil 5 mg QD	78	64.8	204	NR	3.15
				Tadalafil 5 mg QD + lidocaine spray PRN		63	336	NR	5.33
				Lidocaine spray PRN		NA	NA	NR	NA

Abbreviations: BID, twice a day; CGIC, Clinical Global Impression of Change; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); ISSM, International Society for Sexual Medicine; LPE, lifelong premature ejaculations; NA, not applicable; NR, not reported; PRN, as needed; QD, once a day; QW, once every week; RCT, randomized controlled trial; sIELT, stopwatch-measured intravaginal ejaculation latency time. [a] Geometric mean. [b] Median.

Table 2. Characteristics and recalculations of the genetic studies included.

Study	Origin	LPE definition	Target protein	Variant	Polymorphism	Suggested mechanism[a]	Sample size, No.		Genotypes cases vs controls, *P* value		HWE in controls, *P* value	
							Cases	Controls	Reported	Calculated[b]	Reported	Calculated[c]
Safarinejad (2009)[65]	Iran	sIELT ≤1 min	5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	82	82	NR	7.43e-02	.04	3.81e-02
			5-HTT	SNP	rs25531	↓ in G carriers	82	82	NR	4.24e-02	NR	NC
Luo (2011)[82]	Han Chinese	sIELT ≤1 min in ≥90% attempted intercourses	5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	119	90	<.05	1.43e-01	NR	5.23e-03
Huang (2016)[68]	Han Chinese	ISSM 2008	5-HTT	SNP	rs25531	↓ in G carriers	114	101	.091	9.09e-02	NR	NC
			5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	114	101	.494	4.94e-01	.674	6.90e-01
Huang (2016)[67]	Han Chinese	ISSM 2008	5-HTT	VNTR	VNTR	↑ in 12R carriers	114	101	.108	6.77e-02	NR	NC
van Raaij (2021)[69]	Netherlands	ISSM 2014	5-HT2A	SNP	rs6314	↓ in T carriers	65	503	.49	4.88e-01	.77	7.59e-01
Fu (2020)[73]	Han Chinese	sIELT ≤1 min in ≥90% attempted intercourses	THP2	SNP	rs11178998	↓ in G carriers	120	94	.489	5.45e-01	NR	1.00e+00
			THP2	SNP	rs7305115	↑ in A allele carriers	119	94	.366	1.15e-01	NR	5.94e-02
			THP2	SNP	SNV019	U	115	93	.045	NC	NR	1.00e+00
			THP2	SNP	rs1007023	U	117	93	.634	6.52e-01	NR	5.95e-01
			THP2	SNP	rs4290270	↓ in T carriers	121	93	.037	6.83e-01	NR	4.06e-01
			THP2	SNP	rs17110747	No influence	121	94	.983	1.00e+00	NR	4.13e-01
Wang (2022)[70]	Han Chinese	ISSM 2014	LACTBL1	SNP	rs2013948	U	120	366	3.32E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs7864266	U	120	366	3.82E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs10120312	U	120	366	3.82E-06	NC	>5e-6	NC
			FAM53B	SNP	rs11818135	U	120	366	2.82E-06	NC	>5e-6	NC
			FAM53B	SNP	rs73379047	U	120	366	4.65E-06	NC	>5e-6	NC
			LACTBL1	SNP	rs2869051	U	120	366	4.44E-06	NC	>5e-6	NC
			LACTBL1	SNP	rs2903994	U	120	366	4.14E-06	NC	>5e-6	NC
			HCG27-HLA-C	SNP	rs9279036	U	120	366	3.59E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs10114657	U	120	366	1.25E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs10120850	U	120	366	1.25E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs12335994	U	120	366	1.75E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs56742741	U	120	366	3.82E-06	NC	>5e-6	NC
			TNFSF8-TNC	SNP	rs12342713	U	120	366	3.82E-06	NC	>5e-6	NC
Ozbek (2009)[71]	Turkish	sIELT ≤1 min in ≥50% attempted intercourses	5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	69	69	<.002	8.53e-03	NR	6.25e-01
Wang (2020)[72]	Han Chinese	ISSM 2014	5-HTT	SNP	rs1042173	↑ in G carriers	48	NR	NR	NC	.75	NC
			5-HTT	SNP	rs9303628	U	91	362	NR	3.31e-02	.806	8.06e-01
			5-HTT	SNP	rs2054847	U	91	362	NR	6.26e-02	.169	1.69e-01

(*Continued*)

Table 2. Continued

Study	Origin	LPE definition	Target protein	Variant	Polymorphism	Suggested mechanism[a]	Sample size, No.		Genotypes cases vs controls, *P* value		HWE in controls, *P* value	
							Cases	Controls	Reported	Calculated[b]	Reported	Calculated[c]
			5-HTT	SNP	rs140701	Altered expression in T carriers	NR	NR	NR	NC	.560	NC
			5-HTT	SNP	rs8076005	Altered expression in A carriers	NR	NR	NR	NC	.060	NC
			5-HTT	SNP	rs11080122	U	NR	NR	NR	NC	.304	NC
			5-HTT	SNP	rs16965628	Altered expression in C carriers	NR	NR	NR	NC	1	NC
			5-HTT	SNP	rs2020933	U	NR	NR	NR	NC	.882	NC
Sonkurt (2022)[74]	Turkish	*DSM-5*	5-HT2C	SNP	rs518147	↑ in C carriers	87	94	NR	2.38e-02	NR	NC
			5-HT2C	SNP	rs3813929	↑ in T carriers	91	93	NR	1.00e+00	NR	NC
			5-HT1B	SNP	rs11568817	↑ in G carriers	92	94	NR	5.68e-02	NR	5.31e-01
			5-HT1A	SNP	rs6295	↑ Receptor activity in G carriers	93	95	NR	9.15e-01	NR	6.36e-02
Janssen (2009)[66]	Netherlands	ISSM 2008	5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	89	92	.46	7.48e-01	.59	3.02e-01
Luo (2010)[75]	Han Chinese	ISSM 2008	5-HT2C	SNP	rs3813929	↑ in T carriers	106	84	<.05	4.51e-03	NR	NC
			5-HT2C	SNP	rs518147	↑ in C carriers	106	84	<.05	1.16e-02	NR	NC
Safarinejad (2010)[76]	Iran	sIELT ≤1 min in ≥90% attempted intercourses	DAT1	VNTR	VNTR	↑ in 10R carriers ↓ in 9R carriers	270	266	NR	4.01e-01	NR	NC
Zuccarello (2012)[77]	Caucasian	sIELT ≤1 min in ≥90% attempted intercourses	5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	89	100	NS	4.22e-01	NR	6.84e-01
			5-HTT	SNP	rs25531	↓ in G carriers	89	100	NS	6.89e-01	NR	NC
			5-HTT	VNTR	VNTR	↑ in 12R carriers	89	100	NS	NC	NR	NC
Janssen (2014)[78]	Netherlands	ISSM 2008	5-HTT	INS/DEL repeat	rs4795541	↓ in DEL carriers	54	92	.43	5.49e-01	.59	3.02e-01
Eltonsi (2017)[79]	Egypt	ISSM 2008	DAT1	VNTR	VNTR	↑ in 10R carriers ↓ in 9R carriers	60	20	<.001	2.95e-08	NR	3.54e-01
Roaiah (2018)[81]	Egypt	sIELT ≤1 min	5-HT2C	SNP	rs6318	↑ Receptor activity in C carriers	245	105	.146	1.46e-01	NR	1.53e-07
Roaiah (2019)[80]	Egypt	sIELT ≤1 min	5-HT1A	SNP	rs6295	↑ Receptor activity in G carriers	245	105	<.001	3.34e-13	NR	7.10e-11

Abbreviations: DEL, deletion; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); HWE, Hardy-Weinberg equilibrium; INS, insertion; ISSM, International Society for Sexual Medicine; LPE, lifelong premature ejaculation; NC, not calculable; NR, not reported; NS, not significant; sIELT, stopwatch-measured intravaginal ejaculation latency time; SNP, single-nucleotide polymorphism; U, unknown; VNTR, variable number tandem repeat. [a] Suggested mechanism of polymorphism on target protein expression. [b] Chi-square test. [c] Exact test.

In 8 studies, a significant difference in chi-square test result was found between LPE cases and non-LPE genotypes frequencies[67,70,71,73,75,79,80,82]; in 4 studies, this statistic test was not performed.[65,72,74,76] Reanalysis in this review resulted in 7 significant differences between the genotype frequencies of cases and controls: 5-HT transporter–linked promoter region (5-HTTLPR), rs25531,[65] rs4795541,[71] and rs9303628[72] in the dopamine transporter gene (*DAT1*) VNTR[79]; 5-HT1A rs6295[80]; and 5-HT2C rs518147[74,75] and rs3813929[75] ($P < .05$; Table 2).

Original studies associated the following genes with various statistic tests with an increased risk for LPE: promotor mutation of the 5-HTTLPR (S/S genotype),[65,71,82] SNP rs3813929 and rs518147 of 5-HT2C,[74,75] VTNR of 6 and 10 repeat alleles of *DAT1*,[76,79] SNP rs6295 of the 5-HT1A receptor,[80] SNP rs11568817 of the 5-HT1B receptor,[74] and 2 SNPs (SNV019 and rs4290270) in the *THP2* gene.[73]

5-HTTLPR

The most studied SNP, rs4795541, was associated with LPE in 1 study in the reanalysis, as shown in Table 2.[71] In 6 other studies that examined rs4795541, no association with LPE was found.[65,66,68,77,78,82] The second-most studied SNP in the serotonin transporter was rs25531; this SNP differed significantly between cases and controls in 1 study,[65] in contrast to 2 other studies.[68,77] Other nonsignificant or nonrecalculable SNPs studied in this transporter were rs1042173, rs2054847, rs140701, rs8076005, rs11080122, rs16965628, and rs2020933.[72]

Postsynaptic receptors

Three SNPs were studied on the 5-HT2C receptor, rs518147, rs3813929, and rs6318, and 3 were significant in our analysis (Table 2).[74,75] The 5-HT2A receptor was studied on SNP rs6314, and no significant results were found.[69] The 5-HT1B receptor was studied once on SNP rs11568817, with a significant increased risk for T-allele carriers.[74] However, the reanalysis did not find an association between cases and controls per a chi-square test. Roaiah et al found rs6295 on the 5-HT1A receptor to be significantly different between cases and controls, in contrast to Sonkurt et al, and this was confirmed in our reanalysis.[74,80]

Discussion

Serotonergic targets

All SSRIs with the exception of fluvoxamine showed clinically relevant delay in ejaculation when used as a pharmacotherapeutic agent.[14,16,18,21,36,38,39,41-43,50,52-56,59-63] In addition, clomipramine, which is a potent serotonergic antidepressant, corresponded to these results, even with on-demand dosing.[62] Paroxetine daily dosed had the largest effect in delaying ejaculation.[14,43,53,60,61] The exact reason for its superiority has not yet been found.[84] Paroxetine has higher affinity for blocking the 5-HT transporter when compared with other SSRIs; however, all SSRIs have similar potency in 5-HT reuptake inhibition when equipotent dosages are used with regard to their antidepressant efficacy.[60] Therefore, this aspect could not explain the superiority of paroxetine. Nearly all studies using potent serotonergic agents used ≥1× the daily defined dosages.[64] In these studies, increases in IELTs were seen from the beginning of pharmacotherapy,[14,16,18,36,38,39,41-43,45,48,59-63] reinforcing the hypothesis that ejaculation is inhibited by increased synaptic levels of 5-HT rather than desensitization of autoreceptors, which is the likely mechanism of action in depression.[85] Differences in fold increases among SSRIs should be explained by other unique pharmacologic rather than serotonergic action. In addition to potent serotonergic antidepressants, tramadol showed efficacy in the treatment of LPE, with fold increases between 3 and 4.[39,40,50] Like SSRIs, tramadol is hypothesized to delay ejaculation by serotonin reuptake inhibition, although antinociceptive and anesthetic-like effects could contribute.[86]

Genetic research resulted in leads for involved serotonergic targets. SNPs in the 5-HTTLPR have been much studied for its role in LPE. As described in the results, some SNPs in the serotonin transporter gene have been found to be significantly different between cases and controls,[65,71,72] suggesting 5-HTTLPR to be a possible target in the pathophysiology of LPE. The mechanism for these SNPs (rs25531 and rs4795541) suggests downregulation of the serotonin transporter, which fits the hypothesis on decreased synaptic levels of 5-HT in patients with LPE.[65,71] Yet, mixed results among studies have been found in term of these SNPs. Therefore, 5-HTTLPR could not be identified as a convincing contributor to LPE, but it remained suspected.

Pre- and postsynaptic serotonergic receptors have been studied to a lesser extent.[69,74,75,80,81] Three receptors were studied on several SNPs, with only 5-HT1A and 5-HT2C receptors being significantly different between patients with LPE and controls.[74,75,80] 5-HT1A receptors are suggested to be downregulated in G carriers of the rs6295 polymorphism, in contrast to 5-HT2C receptors that could be upregulated in rs518147 C and rs3813929 T carriers.[74,87] A disbalance in 5-HT1A/5-HT2C receptors as a cause for LPE has been suggested.[84] Since only few pre- and postsynaptic serotonin receptors have been studied on limited SNPs, a role for pre- and postsynaptic serotonin receptors in contribution to LPE could not be ruled out.

Nitric oxide synthase

Mixed results were found in IELT delay among studies using phosphodiesterase 5 (PDE5) inhibitors. Nearly all studies revealed clinically relevant fold increases. Several theories for their efficacy in LPE have been suggested—for example, inhibition of central nitric oxide/cyclic guanosine monophosphate transduction next to peripheral inhibition.[88,89] Central inhibition could reduce the sympathetic tonus and therefore delay ejaculation, which is mainly driven sympathetically.[90] Since paroxetine also has blocking properties for nitric oxide synthase (NOS), this theory could support the superiority of paroxetine in LPE treatment.[85] Yet, the success of PDE5 inhibitors in LPE is not elucidated. According to the European Association of Urology 2023 guidelines, PDE5 inhibitors have supported the therapeutic role in PE with inconclusive results.[91] One randomized clinical trial compared a PDE5 inhibitor, sildenafil, with placebo.[92] Sildenafil did not delay ejaculation but enabled those with PE to have sexual intercourse after they ejaculated. Sildenafil reduced the refractory time to achieve a second erection.[92] It is plausible that PDE5 inhibitors are used mainly because of this effect to satisfy one's partner, and efficacy in studies is biased because of this reason. The European Association of Urology 2023 guidelines recommend the use of PDE5 inhibitors, especially when combined with an SSRI. However, based on the results in this review, PDE5/NOS is seen as a potential target in the pathophysiology

of LPE—especially because, to our knowledge, genetic studies regarding NOS in LPE have not yet been conducted.

Noradrenergic targets

Involvement of noradrenergic targets can play a role in the treatment of LPE. Relatively successful agents such as paroxetine, fluoxetine, clomipramine, and tramadol have weak noradrenergic reuptake actions.[85] In contrast to these results, agents with comparable activity, such as duloxetine or nefazodone, yielded different results, with no clinically relevant response.[13,14] No genetic studies on noradrenergic transporters or receptors were conducted. Based on results in this review and because ejaculation is sympathetically driven, noradrenergic targets such as the noradrenalin transporter or α-receptors cannot be ruled out as suspected targets.[86,93]

Dopaminergic targets

Modafinil and sertraline are agents that act as weak dopamine reuptake inhibitors.[85] Inconsistency in results was observed when studies focused on ejaculation delay by dopamine reuptake inhibitors.[14,36,41,48,51,53,55,59] The *DAT1* gene was investigated in 2 genetic studies.[76,79] VNTR on the *DAT1* gene was associated with LPE in 1 study.[79] The 10-repeat allele was associated with upregulation of the dopamine transporter; however, a clear hypothesis for the involvement of dopamine in LPE has not been postulated yet.[76] The *DAT1* gene should be further investigated.

Other targets

One GWAS was included in this review.[70] However, this study did not find any genetic loci significantly associated with LPE ($P < 5.00e-08$), and some targets (*LACTBL1, HCG27;HLA-C, TNFSF8;TNC, FAM53B*) were suggestively significant ($P < 5.00e-06$).[70] Despite these results, a role on these targets cannot be explained by the current hypotheses of LPE. These targets have to be taken in account, although a lack of further evidence exists for these targets. We can exclude several targets based on pharmacotherapy studies without any clinically relevant fold increases. Therefore, targets that are less likely to contribute to LPE are oxytocin (targeted by epelsiban and cligosiban), H1 receptors (targeted by clomipramine, citalopram, and mirtazapine), σ-receptors (targeted by fluoxetine and fluvoxamine), μ-receptor (tramadol), and $a_2\delta$ subunits of voltage-sensitive calcium channels (targeted by pregabalin).[37,38,46,47,49,53,61,62] Finally, 6 SNPs in the *THP2* gene were investigated with nonsignificant results.[73] Although LPE is probably a disorder with multiple targets/pathways involved, we will not focus on these targets in further genetic studies.

Pharmacokinetic influences

Major factors influencing a successful delay of ejaculation seemed to be dosing and duration of therapy. On-demand administration of paroxetine and other SSRIs was less effective than daily dosing.[36,37,94] Furthermore, we noticed that some trials with a short treatment duration, <4 weeks, showed smaller fold increases.[13,16,38,44,49,51,62]

Limitations

Current review

This review has some limitations. First, some studies used factors based on geometric means while others used those based on arithmetic means. Comparing these 2 types of fold increases may lead to overestimation of effects in favor of studies using an arithmetic mean.[33]

Included studies

Several difficulties of pharmacotherapy studies were noticed.

First, in 8 studies, fold factor increases were not reproducible.[14,40,41,53,54,60-62] Data on these studies were requested but not provided. Some genetic studies were nonreproducible in statistical results.[66,67,73,78] Furthermore, essential data for statistical analysis were not always provided (Table 2).[72]

Second, nearly all agents from studies were metabolized by CYP2C19 or CYP2D6. Polymorphisms in these metabolizing enzymes could have led to inconsistencies among the results, especially since none of the studies provided data on CYP status.

Third, since LPE has a relatively low prevalence, all studies had low numbers of cases. In general, in genetic association studies, small groups of inclusion can easily lead to false-positive results. For a proper genetic association study, population sizes should have enough power, and results should ideally be repeated in another independent study population. None of the studies comply with these criteria. In addition, Wang et al raised concerns over the quality of the GWAS.[70] This study was probably underpowered since the LPE prevalence was chosen uncommonly high (25.8%). Signs of underpowering were also visible by deflation in the quantile-quantile plot.[95] If necessary, sample sizes could be increased by using international/multicenter studies. In addition, this study did not comply by conducting all essential steps for a proper GWAS.[96]

Fourth, genetic studies for 5-HTTLPR genotyping may be confounded by laboratory errors, leading to a shift in homozygote frequencies for the short arm of the 5-HTTLPR transporter. At least 3 studies were suspected for the aforementioned error.[65,71,82,97-99]

Fifth, at least 4 studies from Safarinejad et al were retracted due to inappropriate statistical analyses; none were included in this review. However, 2 nonretracted articles from these authors were included. Concerns about validity of results were published before this review.[100]

Sixth, in 5 of 10 genetic studies, control groups were not in HWE, indicating problems in the analyzed data set.[65,75,80-82]

Seventh, Roaiah et al reported hetero- and homozygote genotypes in the rs6318 polymorphism.[81] Since rs6318 is an SNP located on the X chromosome, genotypes in a male population could consist of only hemizygous genotypes. As a consequence, results and analysis in this study are incorrect.[81]

Finally, genetic studies have used different primers for genotyping similar SNPs. By not using a universal standardized method in the polymerase chain reaction, genotyping errors could occur.[97] To overcome major limitations, standardizing LPE research study methods are recommended in terms of setting the indication of patients, measuring IELTs, using universal outcome measures in pharmacotherapy studies, and using standardized methods in genotype association studies.[33,97,101]

Conclusion

Performance of this scoping review led to the selection of the highest-quality studies on genetic and pharmacotherapeutic LPE research. The 5-HTTLPR, all pre- and postsynaptic 5-HT receptors, and NOS have been identified as suspected

targets in the pathophysiology of LPE. These targets should be investigated in future GWASs.

Acknowledgments

We thank Quinten de Bakker, a librarian at the VieCuri Medical Centre who helped shape the final search terms.

Supplementary material

Supplementary material is available at *Sexual Medicine Reviews* online.

Funding

This work was supported by the Prof Dr Marcel Waldinger Foundation (E.20.31.017, 2020).

Conflicts of interest

J.J.v.R., P.K.C.J., and T.A.M.J.v.A. declare no conflicts of interest. E.C.S. reports owning stocks for a premature ejaculation company (in2, Virility Medical; Israel).

References

1. Serefoglu EC, Yaman O, Cayan S, et al. Prevalence of the complaint of ejaculating prematurely and the four premature ejaculation syndromes: results from the Turkish Society of Andrology Sexual Health Survey. *J Sex Med*. 2011;**8**(2):540–548. https://doi.org/10.1111/j.1743-6109.2010.02095.x
2. Gao J, Peng D, Zhang X, et al. Prevalence and associated factors of premature ejaculation in the Anhui male population in China: evidence-based unified definition of lifelong and acquired premature ejaculation. *Sex Med*. 2017;**5**(1):e37–e43. https://doi.org/10.1016/j.esxm.2016.11.002
3. Serefoglu EC, McMahon CG, Waldinger MD, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *J Sex Med*. 2014;**11**(6):1423–1441. https://doi.org/10.1111/jsm.12524
4. Schapiro B. Premature ejaculation: a review of 1130 cases. *J Urol*. 1943;**50**(3):374–379. https://doi.org/10.1016/s0022-5347(17)70462-4
5. Waldinger M, Rietschel M, Nöthen M, et al. Familial occurrence of primary premature ejaculation. *Psychiatr Genet*. 1998;**8**(1):37–40. https://doi.org/10.1097/00041444-199800810-00007
6. Jern P, Santtila P, Witting K, et al. Premature and delayed ejaculation: genetic and environmental effects in a population-based sample of Finnish twins. *J Sex Med*. 2007;**4**(6):1739–1749. https://doi.org/10.1111/j.1743-6109.2007.00599.x
7. Melnik T, Althof S, Atallah AN, et al. Psychosocial interventions for premature ejaculation. *Cochrane Database Syst Rev*. 2011;**10**(8):CD008195. https://doi.org/10.1002/14651858.cd008195.pub2
8. Pazır Y, Guler H, Bulut TB, Ari E, Aktas S, Kadıhasanoglu M. The association of reproductive hormones, thyroid function, and vitamin levels with premature ejaculation: a prospective case-control study. *Investig Clin Urol*. 2024;**65**(2):173–179. https://doi.org/10.4111/icu.20230213
9. Kalkanli A, Gezmis CT, Fikri O, et al. The effect of plasma melatonin levels in the treatment of lifelong premature ejaculation with selective serotonin reuptake inhibitors. *Andrologia*. 2020;**52**(11):e13785. https://doi.org/10.1111/and.13785
10. Geng B, Gao M, Piao R, et al. Multivariate pattern analysis of lifelong premature ejaculation based on multiple kernel support vector machine. *Front Psychiatry*. 2022;**13**:1–9. https://doi.org/10.3389/fpsyt.2022.906404
11. Gao S, Chen J, Liu J, et al. Decreased grey matter volume in dorsolateral prefrontal cortex and thalamus accompanied by compensatory increases in middle cingulate gyrus of premature ejaculation patients. *Andrology*. 2023;**12**(4):841–849. https://doi.org/10.1111/andr.13547
12. Geng B, Gao M, Wu J, et al. Functional connectivity of nucleus accumbens is associated with lifelong premature ejaculation in male adults: a resting-state fMRI study. *Clin Neuroradiol*. 2022;**32**(3):655–663. https://doi.org/10.1007/s00062-021-01105-2
13. Ozcan L, Polat EC, Otunctemur A, Ozbek E. Duloxetine, dual serotonin and norepinephrine reuptake inhibitor, versus paroxetine, selective serotonin reuptake inhibitor, in the treatment for premature ejaculation. *Int Urol Nephrol*. 2015;**47**(2):283–287. https://doi.org/10.1007/s11255-014-0905-9
14. Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomized, placebo-controlled, fixed-dose study with paroxetine, sertraline, and nefazodone. *J Clin Psychopharmacol*. 2001;**21**(3):293–297. https://doi.org/10.1097/00004714-200106000-00007
15. Chubak B, Doctor A. Traditional Chinese medicine for sexual dysfunction: review of the evidence. *Sex Med Rev*. 2018;**6**(3):410–418. https://doi.org/10.1016/j.sxmr.2017.11.007
16. Sahin S, Bicer M, Yenice MG, Seker KG, Yavuzsan AH, Tugcu V. A prospective randomized controlled study to compare acupuncture and dapoxetine for the treatment of premature ejaculation. *Urol Int*. 2016;**97**(1):104–111. https://doi.org/10.1159/000445253
17. Anaissie J, Yafi FA, Hellstrom WJG. Surgery is not indicated for the treatment of premature ejaculation. *Transl Androl Urol*. 2016;**5**(4):607–612. https://doi.org/10.21037/tau.2016.03.10
18. Alghobary M, Gaballah M, El-Kamel MF, et al. Oral dapoxetine versus topical lidocaine as on-demand treatment for lifelong premature ejaculation: a randomised controlled trial. *Andrologia*. 2020;**52**(5):e13558. https://doi.org/10.1111/and.13558
19. Porst H, Burri A. Novel treatment for premature ejaculation in the light of currently used therapies: a review. *Sex Med Rev*. 2019;**7**(1):129–140. https://doi.org/10.1016/j.sxmr.2018.05.001
20. Cooper K, Martyn-St James M, Kaltenthaler E, et al. Behavioral therapies for management of premature ejaculation: a systematic review. *Sex Med*. 2015;**3**(3):174–188. https://doi.org/10.1002/sm2.65
21. Pastore AL, Palleschi G, Leto A, et al. A prospective randomized study to compare pelvic floor rehabilitation and dapoxetine for treatment of lifelong premature ejaculation. *Int J Androl*. 2012;**35**(4):528–533. https://doi.org/10.1111/j.1365-2605.2011.01243.x
22. McMahon CG, Althof S, Waldinger MD, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *BJU Int*. 2008;**102**(3):338–350. https://doi.org/10.1111/j.1464-410X.2008.07755.x
23. American Psychiatric Association ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2014..
24. Ventus D, Ristilä M, Gunst A, et al. A longitudinal analysis of premature ejaculation symptoms raises concern regarding the appropriateness of a "lifelong" subtype. *Eur Urol Focus*. 2017;**3**(2-3):243–245. https://doi.org/10.1016/j.euf.2016.01.015
25. Shindel AW. Does ejaculation latency vary between men with lifelong versus acquired premature ejaculation? *Urology*. 2024;**184**:119–120. https://doi.org/10.1016/j.urology.2023.09.069
26. Tanner BA. Two case reports on the modification of the ejaculatory response with the squeeze technique. *Psychotherapy*. 1973;**10**(4):297–300. https://doi.org/10.1037/h0087604

27. Waldinger MD, Schweitzer DH. Changing paradigms from a historical *DSM-III* and *DSM-IV* view toward an evidence-based definition of premature ejaculation. Part I : validity of *DSM-IV-TR*. *J Sex Med*. 2006;**3**(4):682–692. https://doi.org/10.1111/j.1743-6109.2006.00275.x
28. Janssen PKC. Exciting research in the field of sexual psychopharmacology: treating patients with inside information. In: Schreiber R, ed. *Modern CNS Drug Discovery Reinventing the Treatment of Psychiatric and Neurological Disorders*. Springer Nature; 2021:199–210. https://doi.org/10.1007/978-3-030-62351-7.
29. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;**169**(7):467–473. https://doi.org/10.7326/M18-0850
30. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci*. 2010;**5**(69):1–9. https://doi.org/10.1186/1748-5908-5-69
31. van Raaij JJ, Janssen PKC. Possible pathophysiological roles of neurotransmitter systems in men with lifelong premature ejaculation: protocol for a scoping review. *JMIR Res Protoc*. 2023;**12**:e41301. https://doi.org/10.2196/41301
32. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;**5**(1):1–10. https://doi.org/10.1186/s13643-016-0384-4
33. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Geometric mean IELT and premature ejaculation: appropriate statistics to avoid overestimation of treatment efficacy. *J Sex Med*. 2008;**5**(2):492–499. https://doi.org/10.1111/j.1743-6109.2007.00696.x
34. Wigginton JE, Cutler DJ, Abecasis R. A note on exact tests of Hardy-Weinberg equilibrium. *Am J Hum Genet*. 2005;**76**(5):887–893. https://doi.org/10.1086/429864
35. Aversa A, Pili M, Francomano D, et al. Effects of vardenafil administration on intravaginal ejaculatory latency time in men with lifelong premature ejaculation. *Int J Impot Res*. 2009;**21**(4):221–227. https://doi.org/10.1038/ijir.2009.21
36. Mathers MJ, Klotz T, Roth S, Lümmen G, Sommer F. Safety and efficacy of vardenafil versus sertraline in the treatment of premature ejaculation: a randomised, prospective and crossover study. *Andrologia*. 2009;**41**(3):169–175. https://doi.org/10.1111/j.1439-0272.2008.00910.x
37. GlaxoSmithKline. *A phase III study to evaluate delay in intravaginal ejaculatory latency time (IELT), safety, tolerability, pharmacokinetics and pharmacodynamics of two oral doses of GSK557296 in a randomized, double blind, placebo-controlled, parallel group study in men with premature ejaculation*. Accessed July 2023. https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-011855-40/results
38. Dadfar MR, Baghinia MR. Salvage use of citalopram for treatment of fluoxetine-resistant premature ejaculation in recently married men: a prospective clinical trial. *Urol J*. 2010;**7**(1):40–44.
39. Hamidi-Madani A, Motiee R, Mokhtari G, Nasseh H, Esmaeili S, Kazemnezhad E. The efficacy and safety of on-demand tramadol and paroxetine use in treatment of life long premature ejaculation: a randomized double-blind placebo-controlled clinical trial. *J Reprod Infertil*. 2018;**19**(1):10–15.
40. Kaynar M, Kilic O, Yurdakul T. On-demand tramadol hydrochloride use in premature ejaculation treatment. *Urology*. 2012;**79**(1):145–149. https://doi.org/10.1016/j.urology.2011.09.031
41. Xia J, Chen T, Chen J, et al. The sympathetic skin response located in the penis as a predictor of the response to sertraline treatment in patients with primary premature ejaculation. *J Sex Med*. 2014;**11**(11):2801–2808. https://doi.org/10.1111/jsm.12654
42. Cormio L, Massenio P, La Rocca R, Verze P, Mirone V, Carrieri G. The combination of dapoxetine and behavioral treatment provides better results than dapoxetine alone in the management of patients with lifelong premature ejaculation. *J Sex Med*. 2015;**12**(7):1609–1615. https://doi.org/10.1111/jsm.12925
43. Guo Y, Wang Y, Wang X, Ye G, Jiang Y, Xiong W. Association between changes in serum 5-hydroxy-tryptamine concentrations and improvement in clinical symptoms in primary premature ejaculation with paroxetine treatment. *Med Sci Monit*. 2015;**21**:2521–2527. https://doi.org/10.12659/MSM.894662
44. Ozcan L, Polat EC, Onen E, et al. Effects of tadalafil 5 mg dosed once daily in men with premature ejaculation. *Urol Int*. 2017;**98**(2):210–214. https://doi.org/10.1159/000445839
45. Kati B, Ay H. Evaluation of dapoxetine treatment success in lifelong premature ejaculation patients with penile sympathetic skin response. *Andrologia*. 2018;**50**(9):e13076. https://doi.org/10.1111/and.13076
46. McMahon C, Althof S, Rosen R, et al. The oxytocin antagonist cligosiban prolongs intravaginal ejaculatory latency and improves patient-reported outcomes in men with lifelong premature ejaculation: results of a randomized, double-blind, placebo-controlled proof-of-concept trial (PEPIX). *J Sex Med*. 2019;**16**(8):1178–1187. https://doi.org/10.1016/j.jsxm.2019.05.016
47. Althof S, Osterloh IH, Muirhead GJ, George K, Girard N, PEDRIX Multi-Centre Study Group. The oxytocin antagonist cligosiban fails to prolong intravaginal ejaculatory latency in men with lifelong premature ejaculation: results of a randomized, double-blind, placebo-controlled phase IIb trial (PEDRIX). *J Sex Med*. 2019;**16**(8):1188–1198. https://doi.org/10.1016/j.jsxm.2019.05.015
48. Sahan A, Cubuk A, Ozkaptan O, et al. Comparison of the safety and efficacy of the on-demand use of sertraline, dapoxetine, and daily use of sertraline in the treatment of patients with lifelong premature ejaculation: a prospective randomised study. *Andrologia*. 2020;**52**(11):e13854. https://doi.org/10.1111/and.13854
49. El Najjar MR, El Hariri M, Ramadan A, Hefny Hashem AA. A double blind, placebo controlled, randomized trial to evaluate the efficacy and tolerability of on-demand oral pregablin (150 mg and 75 mg) in treatment of premature ejaculation. *J Sex Med*. 2020;**17**(3):442–446. https://doi.org/10.1016/j.jsxm.2019.12.014
50. Ur Rehman MF, Imran Zaidi A, Ul haq, Rafique, Ali T, S, F. Comparison of the efficacy of tramadol and paroxetine in the management of premature ejaculation. *Cureus*. 2020;**12**(9):e10725. https://doi.org/10.7759/cureus.10725
51. Haghighi M, Jahangard L, Meybodi AM, et al. Influence of modafinil on early ejaculation—results from a double-blind randomized clinical trial. *J Psychiatr Res*. 2022;**146**:264–271. https://doi.org/10.1016/j.jpsychires.2021.11.015
52. Liu G, Yin Y, Zhang L, He D, Yang L. Efficacy of dapoxetine in the treatment of patients with lifelong premature ejaculation as an alternative to sertraline therapy. *Sex Med*. 2022;**10**(1):100473. https://doi.org/10.1016/j.esxm.2021.100473
53. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol*. 1998;**18**(4):274–281. https://doi.org/10.1097/00004714-199808000-00004
54. Hassan M, Hassan MMM. Comparison of paroxetine and dapoxetine regarding intra vaginal ejaculatory latency time and sexual intercourse frequency in patients with lifelong premature ejaculation. *J Sex Med*. 2016;**13**(suppl 2):S224. https://doi.org/10.1016/j.jsxm.2016.03.319
55. Mokhtari G, Damavand RS, Khosropanah I, et al. The efficacy and safety of combination therapy with tadalafil and serteraline in lifelong premature ejaculation: a randomized double blind study using a validated questionnaire. *In J Urol*. 2014;**21**(S2):A274.
56. Mondaini N, Fusco F, Cai T, Benemei S, Mirone V, Bartoletti R. Dapoxetine treatment in patients with lifelong premature ejaculation: the reasons of a "waterloo.". *Urology*. 2013;**82**(3):620–624. https://doi.org/10.1016/j.urology.2013.05.018

57. Dell'Atti L, Galosi AB, Ippolito C. A randomized single-center study to compare the efficacy and tolerability of tadalafil once daily plus lidocaine anesthetic spray on premature ejaculation. *Eur Rev Med Pharmacol Sci*. 2017;**21**(5):1036–1040.
58. Faddan AHA, Gaber H, Oamonov D. Effect of a tadalafil 5-mg single daily dose on lifelong premature ejaculation: a single-blinded placebo-controlled study. *Arab J Urol*. 2022;**20**(2):100–104. https://doi.org/10.1080/2090598X.2021.2007464
59. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5 pm for the treatment of premature ejaculation. *Urology*. 1999;**54**(3):544–547. https://doi.org/10.1016/S0090-4295(99)00187-9
60. Waldinger MD, Zwinderman AH, Olivier B. SSRIs and ejaculation: a double-blind, randomized, fixed-dose study with paroxetine and citalopram. *J Clin Psychopharmacol*. 2001;**21**(6):556–560. https://doi.org/10.1097/00004714-200112000-00003
61. Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomized, fixed-dose study with mirtazapine and paroxetine. *J Clin Psychopharmacol*. 2003;**23**(5):467–470. https://doi.org/10.1097/01.jcp.0000088904.24613.e4
62. Waldinger MD, Zwinderman AH, Olivier B. On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. *Eur Urol*. 2004;**46**(4):510–516. https://doi.org/10.1016/j.eururo.2004.05.005
63. Mattos RM, Marmo Lucon A, Srougi M. Tadalafil and fluoxetine in premature ejaculation: prospective, randomized, double-blind, placebo-controlled study. *Urol Int*. 2008;**80**(2):162–165. https://doi.org/10.1159/000112607
64. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment 2023*. 2022. Accessed July 2023. https://www.whocc.nl/filearchive/publications/2023_guidelines_web.pdf
65. Safarinejad MR. Polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran. *J Urol*. 2009;**181**(6):2656–2661. https://doi.org/10.1016/j.juro.2009.01.105
66. Janssen PKC, Bakker SC, Réthelyi J, et al. Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. *J Sex Med*. 2009;**6**(1):276–284. https://doi.org/10.1111/j.1743-6109.2008.01033.x
67. Huang Y, Zhang X, Gao J, et al. Association of STin2 (VNTR) polymorphism of serotonin transporter gene with lifelong premature ejaculation: a case-control study in Han Chinese subjects. *Med Sci Monit*. 2016;**22**:3588–3594. https://doi.org/10.12659/MSM.897720
68. Huang Y, Zhang X, Gao J, et al. Biallelic and triallelic 5-hydroxytyramine transporter gene-linked polymorphic region (5-HTTLPR) polymorphisms and their relationship with lifelong premature ejaculation: a case-control study in a Chinese population. *Med Sci Monit*. 2016;**22**:2066–2074. https://doi.org/10.12659/MSM.896768
69. van Raaij JJ, Hua KH, de Vries F, Janssen PKC. His452Tyr 5-HT2A polymorphism and intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. *Int J Impot Res*. 2021;**35**(2):103–106. https://doi.org/10.1038/s41443-021-00489-6
70. Wang F, Luo D, Chen J, et al. Genome-wide association analysis to search for new loci associated with lifelong premature ejaculation risk in Chinese male Han population. *World J Mens Health*. 2022;**40**(2):330–339. https://doi.org/10.5534/wjmh.210084
71. Ozbek E, Tasci AI, Tugcu V, et al. Possible association of the 5-HTTLPR serotonin transporter promoter gene polymorphism with premature ejaculation in a Turkish population. *Asian J Androl*. 2009;**11**(3):351–355. https://doi.org/10.1038/aja.2008.3
72. Wang F, Luo D, Chen J, et al. rs9303628 and rs2054847 of SLC6A4 are protective factors for the onset of lifelong premature ejaculation among the Chinese population. *Andrologia*. 2020;**53**(1):e13650. https://doi.org/10.1111/and.13650
73. Fu X, Zhang X, Jiang T, et al. Association between lifelong premature ejaculation and polymorphism of tryptophan hydroxylase 2 gene in the Han population. *Sex Med*. 2020;**8**(2):223–229. https://doi.org/10.1016/j.esxm.2020.02.004
74. Sonkurt MD, Güleç G, Coşan DT, et al. Single nucleotide polymorphisms in 5-HT receptors in the etiology of premature ejaculation. *Rev Int Androl*. 2022;**20**(4):217–224. https://doi.org/10.1016/j.androl.2021.02.009
75. Luo S, Lu Y, Wang F, et al. Association between polymorphisms in the serotonin 2C receptor gene and premature ejaculation in Han Chinese subjects. *Urol Int*. 2010;**85**(2):204–208. https://doi.org/10.1159/000314528
76. Safarinejad MR. Relationship between premature ejaculation and genetic polymorphisms of the dopamine transporter gene (SLC6A3). *BJU Int*. 2010;**108**(2):292–296. https://doi.org/10.1111/j.1464-410X.2010.09809.x
77. Zuccarello D, Ghezzi M, Pengo M, et al. No difference in 5-HTTLPR and Stin2 polymorphisms frequency between premature ejaculation patients and controls. *J Sex Med*. 2012;**9**(6):1659–1668. https://doi.org/10.1111/j.1743-6109.2012.02715.x
78. Janssen PKC, Touw D, Schweitzer DH, Waldinger MD. Nonresponders to daily paroxetine and another SSRI in men with lifelong premature ejaculation: a pharmacokinetic dose-escalation study for a rare phenomenon. *Korean J Urol*. 2014;**55**(9):599–607. https://doi.org/10.4111/kju.2014.55.9.599
79. Eltonsi TK, Tawfik TM, Rashed LA, GamalEl Din SF, Mahmoud MA. Study of the link between dopamine transporter gene polymorphisms and response to paroxetin and escitalopram in patients with lifelong premature ejaculation. *Int J Impot Res*. 2017;**29**(6):235–239. https://doi.org/10.1038/ijir.2017.29
80. Roaiah MF, Elkhayat YI, Rashed LA, et al. 5HT-1A receptor polymorphism effects ejaculatory function in Egyptian patients with lifelong premature ejaculation. *Rev Int Androl*. 2019;**17**(4):138–142. https://doi.org/10.1016/j.androl.2018.07.004
81. Roaiah MF, Elkhayat YI, Rashed LA, GamalEl Din SF, el Guindi AM, Abd El Salam MA. Study of the prevalence of 5 HT-2C receptor gene polymorphisms in Egyptian patients with lifelong premature ejaculation. *Andrologia*. 2018;**50**(2):e12855. https://doi.org/10.1111/and.12855
82. Luo S, Wang F, Xie Z, Huang X, Lu Y. Study on the correlation of the 5HTTLPR polymorphism with premature ejaculation in Han Chinese population. *J Peking Univ Health Sci*. 2011;**43**(4):514–518.
83. Martin FJ, Amode MR, Aneja A, et al. Ensembl 2023. *Nucleic Acids Res*. 2023;**51**(D1):D933–D941. https://doi.org/10.1093/nar/gkac958
84. Waldinger MD, Berendsen HHG, Blok BFM, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res*. 1998;**92**(2):111–118. https://doi.org/10.1016/S0166-4328(97)00183-6
85. Stahl S. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 5th ed. Cambridge University Press; 2021. https://doi.org/10.1017/9781108975292
86. McMahon CG. Current and emerging treatments for premature ejaculation. *Sex Med Rev*. 2015;**3**(3):183–202. https://doi.org/10.1002/smrj.49
87. Yuan X, Yamada K, Ishiyama-Shigemoto S, Koyama W, Nonaka K. Identification of polymorphic loci in the promoter region of the serotonin 5-HT(2c) receptor gene and their association with obesity and type II diabetes. *Diabetologia*. 2000;**43**(3):373–376. https://doi.org/10.1007/s001250050056

88. Schultheiss D, Müller NW, Nager W, et al. Central effects of sildenafil (Viagra) on auditory selective attention and verbal recognition memory in humans: a study with event-related brain potentials. *World J Urol*. 2001;**19**(1):46–50. https://doi.org/10.1007/PL00007092
89. Loughney K, Hill TR, Florio VA, et al. Isolation and characterization of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3′,5′-cyclic nucleotide phosphodiesterase. *Gene*. 1998;**216**(1):139–147. https://doi.org/10.1016/S0378-1119(98)00303-5
90. Mancina R, Filippi S, Marini M, et al. Expression and functional activity of phosphodiesterase type 5 in human and rabbit vas deferens. *Mol Hum Reprod*. 2005;**11**(2):107–115. https://doi.org/10.1093/molehr/gah143
91. European Association of Urology. Guidelines on sexual and reproductive health. Accessed October 2023. https://uroweb.org/guidelines/sexual-and-reproductive-health..
92. McMahon CG, Stuckey BGA, Andersen M, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med*. 2005;**2**(3):368–375. https://doi.org/10.1111/j.1743-6109.2005.20351.x
93. Gul M, Bocu K, Serefoglu EC. Current and emerging treatment options for premature ejaculation. *Nat Rev Urol*. 2022;**19**(11):659–680. https://doi.org/10.1038/s41585-022-00639-5
94. Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res*. 2004;**16**(4):369–381. https://doi.org/10.1038/sj.ijir.3901172.
95. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet*. 2008;**9**(5):356–369. https://doi.org/10.1038/nrg2344
96. Uffelmann E, Huang QQ, Munung NS, et al. Genome-wide association studies. *Nat Rev Methods Prim*. 2021;**1**:59. https://doi.org/10.1038/s43586-021-00056-9
97. Janssen PKC, Olivier B, Zwinderman AH, Waldinger MD. Measurement errors in polymerase chain reaction are a confounding factor for a correct interpretation of 5-HTTLPR polymorphism effects on lifelong premature ejaculation: a critical analysis of a previously published meta-analysis of six studies. *PLoS One*. 2014;**9**(3):9. https://doi.org/10.1371/journal.pone.0088031
98. Waldinger MD, Janssen PKC, Schweitzer DH. Hardy Weinberg equilibrium in genetic PE research remains critical to avoid misinterpretation. *Asian J Androl*. 2009;**11**(4):524. https://doi.org/10.1038/aja.2009.32
99. Waldinger MD, PKC J, Schweitzer DH. Re: polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran. M. R. Safarinejad J Urol 2009; 181: 2656-2661. *J Urol*. 2009;**182**(6):2983–2984. https://doi.org/10.1016/j.juro.2009.08.069
100. Liu S, Singh N, Mol BW. The integrity of seven randomized trials evaluating treatments for premature ejaculation. *Andrologia*. 2022;**54**(11):e14573. https://doi.org/10.1111/and.14573
101. Althof SE, McMahon CG, Waldinger MD, et al. An update of the International Society of Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). *Sex Med*. 2014;**2**(2):60–90. https://doi.org/10.1002/sm2.28