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Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis

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The aim of this systematic review and meta-analysis is to evaluate whether the design and methodology of drug-treatment studies of premature ejaculation affect the efficacy outcome differently. Therefore, methodological, design and efficacy data from 79 studies (3034 males), published between 1943 and 2003, are reviewed. A meta-analysis is performed on 43 selective serotonin reuptake inhibitors (SSRIs) and clomipramine studies (1514 males), published between 1973 and 2003; these studies were pooled to provide a summary variance-weighted effect size. The antidepressant-induced percentage increase of the intravaginal ejaculation latency time (IELT) was calculated and examined against various methodological items. A significant difference in efficacy between SSRIs was observed. Using daily treatment, paroxetine appeared more effective than the other SSRIs. Retrospective use of a questionnaire, subjective reports, single-blind and open study designs generate far greater variability of ejaculation time both at baseline and during active drug treatment than real time assessment by stopwatch. In conclusion, at daily treatment, the overall efficacy of paroxetine, clomipramine, sertraline and fluoxetine is comparable, but paroxetine exerts the strongest ejaculation delay. Only eight (18.5%) studies on antidepressant treatment fulfilled all criteria used in evidence-based medicine, for example, randomised, double-blind studies with prospective real time (stopwatch) assessment of the IELT at each intercourse. Single-blind studies, open designs, retrospective reporting, or the use of a questionnaire to assess ejaculation time should be avoided.
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Introduction

Some selective serotonin reuptake inhibitors (SSRIs) and clomipramine have increasingly become the agents of first choice for the treatment of lifelong premature ejaculation.[1–3] Based on animal[4] and human psychopharmacological studies, Waldinger *et al* have postulated that lifelong premature ejaculation is a neurobiological phenomenon related to decreased central serotonergic neurotransmission, 5-HT_{2C} receptor hyposensitivity and/or 5-HT_{1A} hypersensitivity.[5–7] In addition, Waldinger postulates that lifelong early ejaculation is not an acquired disorder due to learned behavior, as has been suggested by Masters and Johnson, but, instead, belongs to the normal biological variability of the intravaginal ejaculation latency time (IELT) in men, with a possible familial genetic vulnerability.[1,5–9] In this sense, early ejaculation is considered a neurobiological phenomenon, that may become perceived as premature ejaculation and consequently may secondarily lead to psychological distress.[1]

Due to many practical difficulties sexual psychopharmacological research is subjected to, it is questioned whether the methodology of research

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is of relevance for clinical outcome.[10,11] The way to address the issue of methodological bias is to perform a systematic review of the complete literature and to perform a meta-analysis on all data. Such a meta-analysis on methodology and drug treatment has not been performed yet on this issue. Consequently, there is no evidence-based consensus on methodology in research and treatment.[11]

In the current study, a review was performed on all available drug-treatment studies, published between 1943 and 2003, and a meta-analysis was conducted on all studies using serotonergic antidepressants for the daily and as-needed treatment of premature ejaculation.

Method

Literature search

All drug-treatment reports and studies, whether drugs, ointments, creams or solutions, were included in the systematic review. A search by MEDLINE (1966–2002), Web of Science, PICA, and EMBASE (1980–2002), was performed, checking all publications that used the words premature, rapid, ejaculation, praecox in the title, abstract or keywords. The computer search was combined with manual cross-referencing of all papers. Apart from German[12–14] and French[15] articles, the publications in Italian,[16–18] Spanish,[19,20] Portugese,[21] Czech,[22–24] and Hungarian[25] language were translated. Three authors were contacted by e-mail or telephone for further explanation. Of two papers published in a South Korean journal,[26,27] the English abstracts were used and one of the authors was contacted for further information. Abstracts in journals without the full text being published elsewhere or without being in press were not included in the review. Two articles[23,24] of drug treatment combined with behavioral treatment were not included in the meta-analysis.

Data analysis

Only studies reporting quantitative data on the change of the IELT or equivalents of the ejaculation time due to treatment were included in the meta-analysis. Since various scales were used to quantify efficacy (in some papers, a stopwatch was used; in others, a clock, questionnaire or subjective assessment), we decided to bring these different quantifications on the same scale by calculating the percentage change from baseline. Percentage change is defined as 100%* (follow-up IELT−baseline IELT)/baseline IELT. In most papers, no numbers on the percentage change were reported, and we had to calculate it from the average baseline IELT and the average follow-up IELT, which is not complicated. For the meta-analysis, however, we needed the variance of the percentage change. The delta method[28] is a mathematic–statistical technique to calculate the variance of the percentage change from the means and variances of the baseline and follow-up IELT. Standard errors of these average change values were calculated in a similar fashion. The effects of research design characteristics on the change values were assessed in a similar fashion.

A random-effects meta-analysis model was used. Basically, we assumed that each study had its own true percentage change (say, θ_i), which was estimated by the observed/inferred percentage change $\widehat{\theta}_i : \widehat{\theta}_i = \theta_i + e_i$, where e_i is normally distributed with observed variance s_i^2. We further assumed that θ_i followed a normal distribution with mean μ and variance τ^2. The parameters τ^2 and μ were estimated by maximizing the likelihood (using SAS proc mixed). *P*-values were assessed by comparing the loglikelihoods under the null hypothesis to the loglikelihoods under the alternative models.

Results

General results of review

Since the first publication in 1943, there have been 79 publications on drug treatment until 2003. These reports comprised the use of anesthetic ointments,[12,26,27,29–37] neuroleptics,[20,22,38–42] monoamine-oxidase inhibitors,[16,43] sympatholytic drugs,[18,19,44–46] antibiotics,[47,48] and a group of miscellaneous agents[13,14,21,49–51] (Table 1). Between 1973 and 2003, there have been 35 studies[15,17,23–25,60–79,80,81] on daily treatment with clomipramine, a tricyclic antidepressant, and on SSRIs (Table 2). In the same period, on-demand antidepressant treatment results were reported in eight studies[82–89] (Table 3). The current review consists of 3034 males obtained from 79 studies.

Operational definition

A total of 46 (58.2%) studies mentioned an operational definition of premature ejaculation. In all, 41 (51.8%) studies used an exact cutoff point of the ejaculation time as criterion for inclusion: 1 min or less in 19 studies, 2 min or less in 11 studies, 3 min or less in eight studies, 30 s, 4 and 5 min in one study each. Six studies used the DSM classification. With the exception of six publications,[29,90,44,20,21,72] all studies that mentioned a definition of premature ejaculation used the ejaculation time as outcome measure.

Table 1 Drug treatments for premature ejaculation: anesthesia, sympathicolytic drugs, and miscellaneous drugs (daily and as-needed strategies)

	Study	*Year*	*Design*	*Drug*	*Definition*	*Time*	*Measure*	*Instrument*	*Baseline*	*Assessment*	*Duration*	*N*
1	Schapiro	1943	Review	Nupercaine 3% solution	Yes		Control	Subj. report	No	Retrospective		33
2	Aycock	1949	Review	Nupercaine 1% ointment (2–3 h)	No		Ejaculation control					
3	Moser	1953	Case report	Nupercaine cream (20 min)	No		Improvement	Subj. report	No	Retrospective		9
4	Bennet	1961	Case report	Iproniazid, isocarboxazid	No		Ejaculation control	Subj. report	No	Retrospective	8 weeks	6
5	Damrau	1963	Case report	Ethyl-amiNobezoate 3% cream (5 min)	No	1 min	Ejaculation control	Subj. report	No	Retrospective	8 weeks	13
6	Bartova	1965	Double-blind	Thioridazine, placebo	No		Duration coitus	Questionaire	No	Retrospective	2 weeks	20
7	Mellgren	1967	Open design	Thioridazine 25–100 mg (1–3 h)	No		Duration coitus	Subj. report	No	Retrospective	24 weeks	40
8	Boneff	1971	Open design	Hydrocortisone-antibiotic injection	No		Duration coitus	Subj. report	No	Retrospective	12–48 weeks	42
9	Schoning	1972	Open design	Opipramol	No		Improvement	Subj. report	No	Retrospective	2–7 weeks	28
10	Wiederholt	1977	Case report	Cyproteronacetate	No		Improvement	Subj. report	No	Retrospective	8–32 weeks	4
11	Riley	1979	Double-blind	Amitriptyline-perphenazine, placebo	Yes	3 min	Ejaculation control	Subj. report	No	Retrospective	12 weeks	36
12	Nielsen	1981	Open design	Caroxazone	No		Improvement	Subj. report	No	Retrospective	4–30 weeks	13
13	Hurtado	1981	Open design	Guanetidine	No		Improvement	Subj. report	No	Retrospective	16 weeks	35
14	Falaschi	1981	Double-blind	Metoclopramide, placebo	No		Ejaculation score	Subj. report	No	Retrospective	28 weeks	10
15	Falaschi	1981	Double-blind	Metoclopramide 10 mg (2 h), placebo	No		Ejaculation score	Subj. report	No	Retrospective	10 coitus	5
16	Wabrek	1984	Double-blind	Metoclopramide 10 mg (1 h), placebo	Yes	1 min	Ejaculation latency	Subj. report	8 coitus	Retrospective	4 weeks	15
17	Cooper	1984	Double-blind	Propranolol, placebo	Yes	1 min	Ejaculation time	Stopwatch	4 weeks	Prospective	20 weeks	12
18	Shilon	1984	Open design	Phenoxybenzamine	Yes		Satisfaction	Subj. report	No	Retrospective	1–21 weeks	9
19	Beretta	1986	Open design	Phenoxybenzamine	No	2 min	Ejaculation time	Subj. report	No	Retrospective	4 weeks	15
20	Hronek	1986	Open design	Methoclopramide, thioridazine	No	2 min	Ejaculation time	Subj. report	No	Retrospective		142
21	Costero	1986	Open design	Thioridazine	Yes		Improvement	Subj. report	No	Retrospective	4 weeks	29
22	Segraves	1987	Case report	Lorazepam 0.5–1 mg (30 min)	No	30 s	Ejaculation time	Subj. report	No	Retrospective		1
23	Beretta	1988	Open design	Phenoxybenzamine	No		Ejaculation time	Subj. report	No	Retrospective	4 weeks	30
24	Fein	1990	Open design	Papaverine/ phentolamine injection	No		Satisfactory coitus	Subj. report	No	Retrospective	56 weeks	8
25	Choi HK	1993	Single-blind	SS-cream (30 m–1 h)	Yes	3 min	Ejaculation latency	Stopwatch	2 weeks	Prospective	4 weeks	56
26	Xin ZC	1994	Double-blind	SS-cream, placebo (30 m–1 h)	Yes	3 min	Ejaculation latency	Stopwatch	2 weeks	Prospective	4 weeks	43
27	Berkovitch	1995	Open design	Prilocaine–lidocaine cream	No		Ejaculation time	Subj. report	No	Retrospective		11
28	Cavallini	1995	Double-blind	Alphuzosine, terazosine, placebo	No		Satisfaction	Subj. report	No	Retrospective	24 weeks	91

Table 1 *Continued*

	Study	Year	Design	Drug	Definition	Time	Measure	Instrument	Baseline	Assessment	Duration	N
29	Xin ZC	1997	Open design	SS-cream 0.1 g (1 h)	Yes	3 min	Ejaculation latency	Clock	Unclear	Prospective		186
30	Choi HK	1999	Double-blind	SS-cream 0.05–0.20 g (1 h), placebo	Yes	3 min	Ejaculation latency	Stopwatch	Yes	Prospective		50
31	Choi HK	2000	Double-blind	SS-cream 0.2 gm (1 h), placebo	Yes	3 min	Ejaculation latency	Stopwatch	Yes	Prospective		106
32	Slob	2000	Open design	Prilocaine–lidocaine cream 2.5 g (10 min)	Yes	2 min	Ejaculation latency	Questionaire	No	Prospective	4–6 weeks	15
33	Almeida Cl.	2000	Open design	Trazodone	Yes		Improvement	Questionaire	No	Retrospective	13 weeks	317
34	Brown	2000	Case report	Ciprofloxacin	No	2 min	Ejaculation latency	Subj. report	No	Retrospective	4 weeks	1
35	Atikeler	2002	Single-blind	Prilocaine–lidocaine cream 5%, placebo	No	1 min	Ejaculation time	Subj. report	No	Retrospective		40
36	Greco	2002	Double-blind	Levosulpiride, placebo	No		Improvement	Stopwatch	No	Prospective	8 weeks	49

Double-blind vs *single-blind/open design*

Of all 79 studies, 35 (44.3%) used a double-blind, four (5%) a single-blind, and 30 (37.9%) an open design. There were eight case reports and two reviews. From all studies, 34 (43%) were placebo-controlled.

Ejaculation time vs *satisfaction*

In total, 53 (67%) studies used the ejaculation time or equivalents as a clinical outcome, of which 10 mentioned the IELT.[56,62,63,65,70,77–79,81,87] Altogether, 25 studies used qualitative outcome measures: feeling of satisfaction (10),[44,51,46,54,55,59,17,71,72,75] feelings of improvement (10)[12–14,16,19–21,42,15,64] and feelings of control (5).[29,30,43,31,90]

Stopwatch vs *subjective report/questionnaire*

A total of 47 (59.4%) studies used subjective reporting, eight (10.1%) a questionnaire, 19 (24%) a stopwatch and four (5%) a clock or watch to assess the clinical outcome. Of the 23 stopwatch and clock studies, 15 (65.2%) were double-blind,[49,27,34,35,42,57,60,63,65,77–81,87] three (13%) used a single-blind[26,68,86] and five (21.7%) used an open design.[33,69,74,85,89]

Prospective vs *retrospective assessments*

In all, 22 (27.8%) studies used a prospective design to measure the clinical outcome at each intercourse. In 56 (70.8%) studies, the outcome was assessed retrospectively.

Baseline period

Altogether, 23 (29.1%) studies mentioned a baseline assessment. However, in six of these studies, the duration of the baseline period or number of baseline assessments were not mentioned.[33–35,67,76,85] Baseline periods ranged from 1[68,69] or 2[26,27] to mostly 4 weeks.[49,57,65,77–80,89] In some studies, a certain number of intercourses[41,60,74,81] was taken as baseline measurement.

Duration of studies

The majority of studies used a fixed duration period. However, the duration of studies differed considerably, from 1 to 68 weeks. A total of 10 studies (13%) had a variable duration.

Table 2 Drug treatments for premature ejaculation: selective serotonin reuptake inhibitors, clomipramine and modern antidepressants (daily strategy)

	Study	*Year*	*Design*	*Drug*	*Definition*	*Time*	*Measure*	*Instrument*	*Baseline*	*Assessment*	*Duration*	*N*
1	Eaton	1973	Case report	Clomipramine	No		No	Subj. report	No	Retrospective	8 weeks	13
2	Goodman	1980	Double-blind	Clomipramine, placebo	No		Coital rate	Questionnaire	No	Retrospective	4–16 weeks	16
3	Porto	1981	Double-blind	Clomipramine, placebo	No		Improvement	Subj. report	No	Retrospective	5 weeks	20
4	Girgis	1982	Double-blind	Clomipramine, placebo	No		Satisfaction	Questionnaire	No	Retrospective	6 weeks	39
5	Assalian	1988	Case report	Clomipramine	No		Satisfaction	Subj. report	No	Retrospective	1 week	5
6	Waldinger	1994	Double-blind	Paroxetine, placebo	Yes	2 min	IELT	Questionnaire	No	Retrospective	6 weeks	14
7	Althof	1995	Double-blind	Clomipramine, placebo	Yes	4 min	Ejaculatory latency	Stopwatch	1–4 weeks	Prospective	2–7 weeks	15
8	Mendels	1995	Double-blind	Sertraline, placebo	Yes	1 min	Ejaculation time	Subj. report	No	Retrospective	8 weeks	37
9	Montorsi	1995	Double-blind	Clomipramine, placebo	No		Satisfaction	Subj. report	No	Retrospective	8 weeks	33
10	Kery	1995	Open design	Citalopram	Yes		Ejaculation time	Subj. report	No	Retrospective	24 weeks	34
11	Kara	1996	Double-blind	Fluoxetine, placebo	Yes	2 min	Intravag. latency time	Stopwatch	3 coitus	Prospective	4 weeks	14
12	Ludovico	1996	Open design	Paroxetine	Yes		Ejaculation delay	Subj. report	No	Retrospective	2 weeks	31
13	Lee	1996	Open design	Fluoxetine	DSM-III-R		IELT	Subj. report	No	Retrospective	8 weeks	11
14	Waldinger	1997	Double-blind	Paroxetine	Yes	1 min	IELT	Clock	No	Retrospective	8 weeks	34
15	Giammusso	1997	Open design	Paroxetine	No		Satisfaction	Subj. report	No	Retrospective	26 weeks	62
16	Raju GAR	1997	Open design	Fluoxetine	No	1 min	Improvement	Subj. report	No	Retrospective	4 weeks	44
17	Waldinger	1998	Double-blind	Parox., fluox., sertral., fluvox., placebo	Yes	1 min	IELT	Stopwatch	4 weeks	Prospective	6 weeks	51
18	Haensel	1998	Double-blind	Fluoxetine, placebo	DSM-IV		Ejaculation latency	Questionnaire	No	Retrospective	4 weeks	15
19	Biri	1998	Double-blind	Sertraline, placebo	Yes	1 min	Ejaculation latency	Subj. report	Yes	Retrospective	4 weeks	37
20	McMahon	1998	Single-blind	Sertraline, placebo	Yes	1 min	Ejaculat. latency time	Stopwatch	1 week	Prospective	4 weeks	37
21	McMahon	1998	Open design	Sertraline	Yes	5 min	Ejaculat. latency time	Stopwatch	1 week	Prospective	3 weeks	46
22	SC Kim	1998	Double-blind	Fluoxet., sertral., clomipr., placebo	Yes	2 min	IELT	Subj. report	No	Retrospective	4 weeks	36
23	Balbay	1998	Open design	Sertraline	No		Satisfaction	Subj. report	No	Retrospective	2 weeks	16
24	Kolomaznik	1998	Open design	Sertraline, clomipramine	Yes	1 min	Duration coitus	Subj. report	No	Retrospective	2–26 weeks	7
25	Basar	1999	Open design	Sertraline, fluoxetine	Yes	2 min	Satisfaction	Subj. report	No	Retrospective	8 weeks	57
26	Yilmaz	1999	Double-blind	Fluoxetine, placebo	Yes		Intravaginal latency	Subj. report	No	Retrospective	4 weeks	40
27	McMahon	1999	Open design	Paroxetine	Yes	1 min	Ejaculat. latency time	Stopwatch	2 coitus	Prospective	4 weeks	94
28	Atan	2000	Open design	Fluoxetine, fluox. + lidocaine	No		Improvement	Subj. report	No	Retrospective	8 weeks	43
29	Rowland	2001	Open design	Clomipramine	DSM-IV		Ejaculation latency	Questionnaire	Yes	Retrospective	12 weeks	4
30	Waldinger	2001	Double-blind	Parox., sertral.,	Yes	1 min	IELT	Stopwatch	4 weeks	Prospective	6 weeks	48

Table 2 *continued*

	Study	*Year*	*Design*	*Drug*	*Definition*	*Time*	*Measure*	*Instrument*	*Baseline*	*Assessment*	*Duration*	*N*
				nefazod., placebo								
31	Waldinger	2001	Double-blind	Paroxetine, citalopram	Yes	1 min	IELT	Stopwatch	4 weeks	Prospective	6 weeks	30
32	Waldinger	2002	Double-blind	Paroxetine, mirtazapine	Yes	1 min	IELT	Stopwatch	4 weeks	Prospective	6 weeks	24
33	Kolomaznik	2002	Double-blind	Fluoxetine, placebo, stop-start	Yes	3 min	Duration coitus	Subj. report	No	Retrospective	8 weeks	93
34	Novaretti	2002	Double-blind	Fluoxetine, placebo	DSM-IV	3 min	Ejaculation time	Clock	4 weeks	Prospective	8 weeks	55
35	Atmaca	2002	Double-blind	Citalopram, placebo	DSM-III-R		IELT	Stopwatch	3 coitus	Prospective	8 weeks	26

Table 3 Drug treatments for premature ejaculation: selective serotonin reuptake inhibitors, and clomipramine (as-needed strategy)

	Study	*Year*	*Design*	*Drug*	*Definition*	*Time*	*Measure*	*Instrument*	*Baseline*	*Assessment*	*Duration*	*N*
1	Segraves	1993	Double-blind	Clomipr. 25–50 mg (6 h), placebo	Yes	1 min	Ejaculation time	Subj. report	No	Retrospective	3–5 weeks	20
2	Haensel	1996	Double-blind	Clomipr. 25 mg (12–24 h), placebo	DSM-IV		Ejaculation latency	Subj. report	No	Retrospective	6 weeks	24
3	Strassberg	1999	Double-blind	Clomipr. 25 mg (4–6 h), placebo	Yes	2 min	Ejaculation latency	Subj. report	No	Retrospective	4 weeks	34
4	SW Kim	1999	Open design	Sertraline 50–100 mg (5 pm)	Yes	1 min	Ejaculation latency	Stopwatch	Yes	Prospective	8 weeks	24
5	McMahon	1999	Single-blind	Paroxet. 20 mg (3–4 h), placebo	Yes	1 min	Ejaculat. latency time	Stopwatch	3 weeks	Prospective	7 weeks	68
6	Abdel-Hamid	2001	Double-blind	Clom. 25 mg, sertral 50 mg, parox. 20 mg	Yes	2 min	IELT	Watch	No	Retrospective	22 weeks	31
7	SJ Chia	2002	Open design	Sertraline 50 mg (4 h), sertraline 50 mgl (4 h) + sildenafil (1 h)	Yes	2 min	Ejaculation latency	Subj. report	No	Retrospective	68 weeks	52
8	Salonia	2002	Open design	Paroxet. 10 mg daily + paroxet. 20 mg as-needed (3–4 h) + sildenafil 50 mg as needed (1 h)	Yes	1 min	Ejaculat. latency time	Stopwatch	4 weeks	Prospective	27 weeks	80

On average, however, the duration was between 4 and 8 weeks, particularly in the daily treatment studies with SSRIs and clomipramine.

Meta-analysis of 35 daily treatment studies with serotonergic antidepressants. The current meta-analysis was limited to those studies which used either a questionnaire/subjective report of the patient or stopwatches. Reviewing the available literature on this issue, it appeared that this was only feasible in studies reporting on the effects of daily taken serotonergic antidepressants, including 44 treatment groups: 10 with placebo, four with clomipramine, seven with fluoxetine, nine with paroxetine, nine with sertraline, two with citalopram and one each with fluvoxamine, mirtazapine and nefazodone.

Number of subjects in relation to treatment efficacy

With regard to the efficacy, expressed as the percentage of IELT increase of several SSRIs and clomipramine in relation to the number of included individuals per study, no correlation was found between treatment efficacy and patient numbers, indicating a lack of publication bias in our meta-analysis.

Efficacy differences among serotonergic antidepressants (Figure 1)

Regardless of the major differences in design and drug doses of the several studies, it appeared that

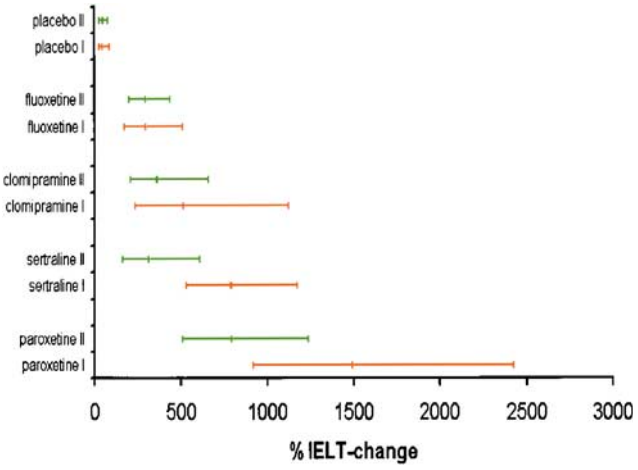

Figure 1 Plot showing the percentage increase of the IELT (95% CI) of serotonergic antidepressant drugs and placebo. The figure shows 35 daily treatment studies (I) (red bars) with heterogenous study designs (eg single blind/open design/double blind) and heterogenous assessments of the IELT (eg subjective report/questionnaire/stopwatch) *vs* eight double-blind, daily treatment studies (II) (green bars) with prospective use of real time stopwatch assessment of the IELT at each intercourse. The small number of studies involving as-needed strategies prevented them from being included in the meta-analysis.

paroxetine, sertraline, fluoxetine and clomipramine were significantly efficacious in delaying ejaculation compared with placebo ($P<0.001$). Moreover, paroxetine induced a stronger ejaculatory delay than fluoxetine ($P<0.001$), clomipramine ($P<0.03$), and sertraline ($P<0.05$). Sertraline-induced delay was significantly stronger than that of fluoxetine ($P<0.006$), whereas clomipramine-induced delay was not significantly different from fluoxetine and sertraline. The rank order of efficacy was therefore: (1) paroxetine (1492% IELT increase, 95% CI: 918–2425%), (2) sertraline (790%, 95% CI: 532–1173%), (3) clomipramine (512%, 95% CI: 234–1122%), (4) fluoxetine (295%, 95% CI: 172–506), (5) placebo (45%, 95% CI: 27–87%), noting that the effect of clomipramine had about the same effect as fluoxetine and sertraline.

Methodological subgroups

In order to investigate the influence of methodology, design and the pharmacological drug properties of the various studies on efficacy, the following items were investigated: dose–response relationship, baseline IELT value *vs* percentage IELT increase, the definition of premature ejaculation (IELT within 1 or 2 min), stopwatch use *vs* questionnaire use or subjective report, prospective *vs* retrospective assessment and double-blind design *vs* single-blind and open design.

Dose–response relationships

Clomipramine was evaluated in doses of 25 mg (one study), 30 mg (one study) or 50 mg (two studies). The doses for the SSRIs were: fluoxetine 10 (one study), 20 (three studies), 40 (two studies), or 60 (one study) mg; paroxetine 20 (seven studies), or 40 (two studies) mg; sertraline 25 (one study), 50 (five studies), 100 (two studies) or 200 (one study) mg daily. There was no significant correlation between dose and response among the various drugs ($P>0.13$).

Relationship between baseline IELT and percentage increase on treatment

The average baseline IELT was (mean $\pm$ s.d.) 41 ± 23 s (range 13–81 s). No relationship was found between baseline IELT and percentage increase on treatment, regardless of which drug was used and of which definition of premature ejaculation was included (1 *vs* 2 min).

Stopwatch vs *questionnaire or subjective reporting*

The IELT or ejaculation time equivalents were measured with a stopwatch in 27 treatment groups, and with a questionnaire or subjective report in 15 groups. On average, the mean percentage IELT change was not significantly different between studies with a stopwatch and with a questionnaire. However, the variability of the outcome measure was far greater in those studies using a questionnaire or subjective report ($P=0.001$).

Prospective vs *retrospective assessment*

Of 24 prospective and 20 retrospective groups, no significant differences were found between the mean percentage of IELT increase. However, retrospective studies showed a significantly higher variability in outcome measure ($P=0.001$) than prospective studies.

Double-blind vs *single-blind and open label studies*

There were 35 double-blind treated groups and nine single-blind or open-treated groups. On average, single-blind and open treatment groups had significantly higher percentage IELT changes ($P=0.004$). The geometric mean IELT change was 864 (95% CI: 447–1667) s in single-blind/open studies and 252 (95% CI: 155–412) s in double-blind design studies. This significant difference was independent of treatment ($P=0.85$).

Prospective, double-blind, real-time-assessed stopwatch studies (Figure 1)

Excluding those studies subjected by greater variability of outcome measure (percentage IELT increase), for example, the use of a questionnaire and subjective report, retrospective and single-blind/open studies, eight prospective, double-blind, real time stopwatch studies[57,60,65,77–81] were left for final analysis. Four of these studies were performed by the same investigators.[65,77–79] In total, these eight studies included four placebo, two clomipramine groups (25/50 mg), three fluoxetine (20/40 mg), four paroxetine groups (20 mg), two sertraline groups (50 mg), two citalopram (20 mg) groups and three groups in which either fluvoxamine (100 mg), mirtazapine (30 mg) or nefazodone (400 mg) were used.

Of all these antidepressants, paroxetine, fluoxetine, sertraline and clomipramine exerted a significant delay of the IELT compared with placebo ($P<0.001$).

Table 4 Efficacy of SSRIs and clomipramine in delaying ejaculation; percentage increase with 95% confidence intervals in all 35 daily treatment groups (meta-analysis I) and in eight selected daily treatment groups (double-blind, prospective, stopwatch studies) (meta-analysis II)

	Mean (I)	*95% CI (I)*	*Mean (II)*	*95% CI (II)*
Placebo	45%	27–87	47%	29–76
Clomipramine	512%	234–1122	360%	201–644
Fluoxetine	295%	172–506	295%	200–435
Paroxetine	1492%	918–2425	783%	499–1228
Sertraline	790%	532–1173	313%	161–608

The percentage IELT increase on paroxetine was significantly greater than on sertraline ($P<0.04$) and fluoxetine ($P<0.08$), but did not differ from clomipramine (<0.06). The effects of clomipramine were not significantly different from those of fluoxetine ($P=0.58$) and sertraline ($P=0.76$). On the basis of data provided by this meta-analysis, the rank order of efficacy to increase the IELT was: (1) paroxetine (783% IELT increase, 95% CI: 499–1228%), (2) clomipramine (360%, 95% CI: 201–644%), (3) sertraline (313%, 95% CI: 161–608%), (4) fluoxetine (295%, 95% CI: 200–435), (5) placebo (47%, 95% CI: 29–76%), noting that clomipramine, sertraline and fluoxetine had about the same effect (Table 4).

Meta-analysis of on-demand treatments

Parrallel to daily treatment, a rather similar rank order of efficacy of paroxetine, sertraline and clomipramine was demonstrated. Although clomipramine only showed a mild increase of the percentage IELT (mean (95% CI); 263 (60–1152)%, $P<0.05$), clear significance was achieved with paroxetine and sertraline. The delay after paroxetine had a mean (95% CI) 929 (398–2166)%, $P<0.001$ and after sertraline 553 (210–1457)%, $P<0.01$. However, caution is needed in interpreting the on-demand treatment data. One should keep in mind that the studies which were included in the meta-analysis greatly differed in methodology (Table 2). The studies were unbalanced for the antidepressants used, baseline IELT values, design (double-blind *vs* open) and assessment techniques (questionnaire *vs* stopwatch). Apart from these arguments, due to the very limited numbers of publications, no final conclusions could be drawn with regard to dose relationships and the influence of baseline IELT on predicting the drug response. Moreover, apart from one double-blind study with a watch,[87] there are as yet no double-blind studies using a stopwatch for on-demand treatment. Similarly, all double-blind

on-demand placebo treatments[82–84] were evaluated without a stopwatch.

Discussion

In the current study, a systematic review was performed on all drug-treatment studies of premature ejaculation, published between 1943 and 2003, with regard to methodology and design. The results of the systematic review have shown that a meta-analysis could not be performed on treatments with anesthetics, miscellaneuous drugs and on-demand treatment of serotonergic antidepressants, due to insufficiently provided data. In contrast, a meta-analysis was feasible on the daily treatment studies with clomipramine and the various SSRIs. The aim of the current study was in the first place to investigate the level and development of methodology in drug-treatment studies, and secondly to investigate whether methodology affected the treatment outcome, as would be expected according to evidence-based medical principles. We have consequently chosen for 'the constant percentage change' of the IELT and have based this choice on the results of the SSRI treatment studies with a stopwatch by our group.[65] This choice was reasoned by the results of a double-blind placebo-controlled study with paroxetine 20 mg/day in men who complained of premature ejaculation.[65] In this study, we compared men with an IELT of less than 1 min and men with an IELT between 1 and 3 min. After baseline measurements of the IELT at home with a stopwatch during 1 month, men with an IELT less than 1 min and those between 1 and 3 min were randomized either to placebo or active treatment with a follow-up of 6 weeks. It appeared that the absolute IELT values in both groups were different, but that the percentage increase of IELT in those men below 1 min (mean IELT 18 s) was identical with those who started with 1 and 3 min (mean IELT 82 s). This finding proves the identical ability of paroxetine to prolong the IELT, regardless of the initial absolute IELT values. The identical percentage increase of paroxetine (and we assume that this is also the case with other SSRIs) forms the basis of the approach to compare men with low and high IELTs at baseline.

Methodological considerations

Review of all studies. The review of all drug-treatment studies illustrates an improvement in methodology from initially published case reports and open label studies towards double-blind, placebo-controlled clinical trials. However, unfortunately, for unknown reasons, in recent years, a gradual increase in single-blind and open label studies has appeared to be again acceptable for peer review, particularly for on-demand treatment,[85,86,88,89] in contrast to the criteria of evidence-based medicine.

Apart from worries regarding the design issues of clinical trials, one of the major issues of premature ejaculation drug-treatment research remains the outcome measure. The review showed that, throughout the years, subjective feelings of 'control', 'satisfaction' and 'improvement' have been used, without clear operational definitions of what is meant by these vague terms. However, particularly since the mid-80s, the majority of studies used the ejaculation time as an outcome measure. A different terminology has been used for ejaculation time, like, for example, the duration of coitus, and an exact definition of ejaculation time is lacking in the majority of studies. An important progress in this methodological issue was made in 1994 by the introduction of the operationally defined IELT.[56] There is a slow increase in the use of this concept.

Another key methodological problem is the instrument of assessment. It is clear that the only instrument to measure time objectively is a stopwatch. An important progress in methodology was made in 1983 by the introduction of a stopwatch[49] and the use of a baseline period. However, in the majority (70%) of studies, a subjective estimate/report or questionnaire is still used. Only in 29% of the studies, a stopwatch, watch or clock was used. Unfortunately, of these 29% studies, 35% were single-blind or had an open design.

Related to the instrument is the moment of assessment. Drug-treatment studies usually have a prospective design. On the other hand, estimation of the ejaculation time either by spontaneous report or by questionnaire always implies retrospective assessment. In contrast, the use of a stopwatch always implies prospective real time assessments of the IELT at each intercourse. A combination of a drug-treatment study with one of the three instruments may erroneously lead to a mix-up of terminology. Caution is therefore warranted, if analysing prospective drug-treatment studies when retrospective IELT estimates have been used.

The use of the IELT and a stopwatch enabled an operational definition or premature ejaculation, which was empirically found in a study[10] of a cohort of Caucasian men with lifelong premature ejaculation, being an ejaculation that takes place within 1 min after vaginal penetration. The current review showed that, in studies using a definition of premature ejaculation, the ejaculation time appeared to range from 30 s to 5 min, with a preference for the 1 min definition. It is of note that the DSM-III-R and DSM-IV definitions do not mention a clear quantifiable ejaculation time, and encompass vague terms.[10] Therefore, these DSM definitions should be avoided as operational

criteria in pharmacological studies. The ICD-10 definition (eg, ejaculation before or within 15 s) has not been mentioned in any of the drug-treatment studies.

The meta-analysis. The meta-analysis was performed on all available studies with serotonergic antidepressants, regardless of methodology and design (mixed-methodology studies). Despite the many confounders in the methodological approach in all of these studies, it appeared that there was a rank order of efficacy for the various antidepressants. Paroxetine exerted the strongest ejaculation-delaying effect compared to the effects of sertraline, clomipramine, fluoxetine and placebo. Clomipramine did not differ from sertraline and fluoxetine.

It has to be emphasised that the meta-analysis of the mixed-methodology studies demonstrated that single-blind and open studies have led to a significantly higher variability of the percentage IELT increase than was found in double-blind studies. This again demonstrates the methodological insufficiency of single-blind and open-design studies. In addition, the meta-analysis also showed that retrospective assessment by subjective report or the use of a questionnaire during prospective drug-treatment studies have led to a significantly higher variability of the percentage increase of the ejaculation time, compared with the prospective use of a stopwatch during each intercourse.

In order to avoid bias of insufficient methodology and design, a final meta-analysis included only those eight (18.6%) studies of proper methodology, for example, randomized, prospective, double-blind clinical trials with a stopwatch. Again, a similar rank order in efficacy was identified, but with far lower values of the percentage IELT increase. The similar outcome of rank order in efficacy supports the superiority of paroxetine as the most effective drug in delaying ejaculation. However, compared to the mixed-methodology meta-analysis, it was now clomipramine instead of sertraline being secondary efficacious. Similarly, clomipramine appeared to be equally efficacious as sertraline and fluoxetine.

Pharmacological considerations

Review of all studies. The review of all drug-treatment studies has shown that, throughout the years, two approaches seem to have become popular to treat premature ejaculation. The initial European approach to use anesthetic ointments is still being used, and research on these methods seems particularly undertaken in the far East with the herbal SS cream. Paroxetine, fluoxetine, clomipramine and sertraline are far more used and investigated in Western countries. This development seems to coincide with a specific interest to perform clinical and basic research on the mechanisms driving premature ejaculation, for example, a tendency to focus on the sensory input of tactile stimuli (eg sensitivity of the glans penis and evoked potentials of peripheral neurons) in the far East,[91,92] in contrast, a tendency to focus on the motoric output (eg serotonergic brain and spinal cord areas) in Western countries.[4,5,93] It is of relevance to note that, in studies on ointments in the Far East, a 3 min criterion seems in use, in contrast to the 1–2 min inclusion criterion in drug treatments in Western countries.

The review illustrated a lack of well-designed studies on α-sympatholytic drugs, dopamine-antagonizing drugs and antibiotics, hampering the application of a meta-analysis. Head-to-head comparisons between anesthetic creams and serotonergic or sympatholytic drugs are currently not available, but need to be initiated.

The meta-analysis. In the mixed-methodology analysis, it was demonstrated that the percentage IELT increase was not related to the baseline IELT, irrespectively of the definition of either 1 or 2 min of baseline IELT and the drug dose that was used. The properly executed eight daily treatment studies did not allow to distinguish differences between 1 and 2 min definitions as well as proper dose–response relationships, due to a lack of data for a statistical valid meta-analysis.

The current meta-analysis showed that paroxetine, clomipramine, sertraline and fluoxetine are effective in delaying ejaculation. Remarkably, in spite of the above-mentioned methodological considerations, the meta-analysis showed that the rank order of efficacy was rather similar in the mixed-methodology analysis and in the final eight daily treatment studies. We assume that the almost similar rank orders could only be the result of the robust pharmacological efficacy of paroxetine, regardless of the many confounding variables related to inappropriate trials. It would be a misinterpretation, however, to conclude that methodology and design are of less relevance for drug-treatment trials in premature ejaculation.

Conclusion

The meta-analysis has shown that the rank order of efficacy of SSRIs, clomipramine and placebo is not extremely distorted by methodology and/or design. We explain this phenomenon to be the result of the strong delaying actions of paroxetine, in particular on ejaculation. However, the meta-analysis also demonstrated that open and single-blind studies

will lead to an exaggerated response and that retrospective assessment of ejaculation time by a questionnaire or subjective report will lead to far more variability in clinical outcomes. Of all 43 serotonergic antidepressant studies, only eight (18.6%)[57,60,65,77–81] have been conducted according to the complete criteria of evidence-based medical research. Of all 79 studies, only 12 (15.1%)[49,27,35,42,57,60,65,77–81] have been performed in this way. Based on this systematic review and meta-analysis, it is recommended that genuine evidence-based research on drug treatment of lifelong premature ejaculation should be performed by randomised, double-blind studies, with the prospective real time use of a stopwatch at each intercourse both during a baseline period and during the active drug-treatment trial. The studies would further gain methodological quality when authors would apply the IELT, and mention an operational definition of premature ejaculation with a clear IELT cutoff point, the duration of the baseline period, and both the absolute IELT values as the percentage increase of the IELTs. The current meta-analysis provided clear empirical evidence that, in order to avoid unacceptable variabilities of outcome measure, open and single-blind studies with a questionnaire or subjective assessment of the IELT should be avoided. Editors and peer reviewers should be aware of the clinical relevance of above-mentioned methodological criteria for the outcome of drug-treatment studies of premature ejaculation.

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