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Selective serotonin re-uptake inhibitors for premature ejaculation in adult men (Review)

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[Intervention Review]

Selective serotonin re-uptake inhibitors for premature ejaculation in adult men

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ABSTRACT

Background

Premature ejaculation (PE) is a common problem among men that occurs when ejaculation happens sooner than a man or his partner would like during sex; it may cause unhappiness and relationship problems. Selective serotonin re-uptake inhibitors (SSRIs), which are most commonly used as antidepressants are being used to treat this condition.

Objectives

To assess the effects of SSRIs in the treatment of PE in adult men.

Search methods

We performed a comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, CINAHL), clinical trial registries, conference proceedings, and other sources of grey literature, up to 1 May 2020. We applied no restrictions on publication language or status.

Selection criteria

We included only randomized controlled clinical trials (parallel group and cross-over trials) in which men with PE were administered SSRIs or placebo. We also considered 'no treatment' to be an eligible comparator but did not find any relevant studies.

Data collection and analysis

Two review authors independently classified and abstracted data from the included studies. Primary outcomes were participant-perceived change with treatment, satisfaction with intercourse and study withdrawal due to adverse events. Secondary outcomes included self-perceived control over ejaculation, participant distress about PE, adverse events and intravaginal ejaculatory latency time (IELT). We performed statistical analyses using a random-effects model. We rated the certainty of evidence according to GRADE.

Main results

We identified 31 studies in which 8254 participants were randomized to receiving either SSRIs or placebo.

Primary outcomes: SSRI treatment probably improves self-perceived PE symptoms (defined as a rating of 'better' or 'much better') compared to placebo (risk ratio (RR) 1.92, 95% confidence interval (CI) 1.66 to 2.23; moderate-certainty evidence). Based on 220 participants per 1000 reporting improvement with placebo, this corresponds to 202 more men per 1000 (95% CI 145 more to 270 more) with improved symptoms with SSRIs.

SSRI treatment probably improves satisfaction with intercourse compared to placebo (defined as a rating of 'good' or 'very good'; RR 1.63, 95% CI 1.42 to 1.87; moderate-certainty evidence). Based on 278 participants per 1000 reporting improved satisfaction with placebo, this corresponds to 175 more (117 more to 242 more) per 1000 men with greater satisfaction with intercourse with SSRIs.

SSRI treatment may increase treatment cessations due to adverse events compared to placebo (RR 3.80, 95% CI 2.61 to 5.51; low-certainty evidence). Based 11 study withdrawals per 1000 participants with placebo, this corresponds to 30 more men per 1000 (95% CI 17 more to 49 more) ceasing treatment due to adverse events with SSRIs.

Secondary outcomes: SSRI treatment likely improve participants' self-perceived control over ejaculation (defined as rating of 'good' or 'very good') compared to placebo (RR 2.29, 95% CI 1.72 to 3.05; moderate-certainty evidence). Assuming 132 per 1000 participants perceived at least good control, this corresponds to 170 more (95 more to 270 more) reporting at least good control with SSRIs.

SSRI probably lessens distress (defined as rating of 'a little bit' or 'not at all') about PE (RR 1.54, 95% CI 1.26 to 1.88; moderate-certainty evidence). Based on 353 per 1000 participants reporting low levels of distress, this corresponds to 191 more men (92 more to 311 more) per 1000 reporting low levels of distress with SSRIs.

SSRI treatment probably increases adverse events compared to placebo (RR 1.71, 95% CI 1.48 to 1.99; moderate-certainty evidence). Based on 243 adverse events per 1000 among men receiving placebo, this corresponds to 173 more (117 more to 241 more) men having an adverse event with SSRIs.

SSRI treatment may increase IELT compared to placebo (mean difference (MD) 3.09 minutes longer, 95% CI 1.94 longer to 4.25 longer; low-certainty evidence).

Authors' conclusions

SSRI treatment for PE appears to substantially improve a number of outcomes of direct patient importance such as symptom improvement, satisfaction with intercourse and perceived control over ejaculation when compared to placebo. Undesirable effects are a small increase in treatment withdrawals due to adverse events as well as substantially increased adverse event rates. Issues affecting the certainty of evidence of outcomes were study limitations and imprecision.

PLAIN LANGUAGE SUMMARY

Selective serotonin re-uptake inhibitors for premature ejaculation

Review question

We wanted to find out if medicines called selective serotonin re-uptake inhibitors (SSRIs), which are used mostly to treat depression, can help men that ejaculate faster than they want, to slow down.

Background

Premature ejaculation is a common problem among men, that occurs when ejaculation happens sooner than a man or his partner would like during sex; it may cause unhappiness and relationship problems. SSRIs are medicines that are often given to help treat premature ejaculation, but we do not understand how well they actually work and what unwanted effects they might cause.

Study characteristics

We studied the evidence up to 1 May 2020. We found 31 studies with 8254 men. The studies compared SSRIs to placebo (a pill with inactive ingredients).

Key results

SSRIs probably improve sexual satisfaction for men with premature ejaculation compared to placebo. They probably also improve the sense of control over ejaculation and decrease unhappiness and relationship problems. However, they likely increase side effects.

Quality of evidence

We judged the quality of evidence to be moderate for SSRIs, helping men’s sense of change with treatment, happiness with intercourse, and feeling of control over ejaculation. The quality of evidence was also moderate for medicine side effects. These results mean that our evaluation is likely to be close to the truth. However, the evidence on improving relationship problems and the time to ejaculation is of

low certainty. This means that the true effect of treatment on those two concerns could be different from the results of this review. That may be caused by weaknesses and variations in the studies we examined.

Summary of findings 1. SSRI compared to placebo for premature ejaculation

SSRI compared to placebo for premature ejaculation in adult men

Patient or population: adult men with premature ejaculation
Setting: outpatient
Intervention: SSRI
Comparison: placebo

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		What happens
				Risk with placebo	Risk difference with SSRI	
Participant perception of change with treatment assessed with: Clinical Global Impression of Change questionnaire (event is good as it represents improvement in symptoms)	3260 (6 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	**RR 1.92** (1.66 to 2.23)	**Study population** 220 per 1000	202 more per 1000 (145 more to 270 more)	SSRI probably results in perceived improvement compared to placebo.
Participant satisfaction with intercourse assessed with: Premature Ejaculation Profile questionnaire (event is good as it represents increased satisfaction)	4273 (3 RCTs)	⊕⊕⊕⊖ **Moderate** [a,b]	**RR 1.63** (1.42 to 1.87)	**Study population** 278 per 1000	175 more per 1000 (117 more to 242 more)	SSRI probably results in improved satisfaction with intercourse compared to placebo.
Study withdrawal due to adverse events	7367 (20 RCTs)	⊕⊕⊖⊖ **Low** [a,c]	**RR 3.80** (2.61 to 5.51)	**Study population** 11 per 1000	30 more per 1000 (17 more to 49 more)	SSRI may result in more withdrawals due to adverse events compared to placebo.
Perceived control over ejaculation assessed with: Premature Ejaculation Profile questionnaire (event is good as it represents increased control over ejaculation)	4273 (3 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	**RR 2.29** (1.72 to 3.05)	**Study population** 132 per 1000	170 more per 1000 (95 more to 270 more)	SSRI probably results in improved perceived control over ejaculation compared to placebo.
Participant distress about PE assessed with: Premature Ejaculation Profile questionnaire (event is good as it represents less distress)	652 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	**RR 1.54** (1.26 to 1.88)	**Study population** 353 per 1000	191 more per 1000	SSRI probably results in increased numbers of men not distressed about PE compared to placebo.

					(92 more to 311 more)	
Adverse events	4624 (17 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	**RR 1.71** (1.48 to 1.99)	**Study population**		SSRI probably results in increased adverse events compared to placebo.
				243 per 1000	173 more per 1000 (117 more to 241 more)	
IELT	5872 (20 RCTs)	⊕⊕⊖⊖ **Low** [a,d]	—	The mean IELT was 1.41 minutes	**MD 3.09 minutes** higher (1.94 higher to 4.25 higher)	SSRI probably results in extended IELT compared to placebo.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IELT:** intravaginal ejaculatory latency time; **MD:** mean difference; **PE:** premature ejaculate; **RCT:** randomized controlled trial; **RR:** risk ratio; **SSRI:** selective serotonin reuptake inhibitor.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations: most studies had an unclear or high risk of selection, performance and detection bias.
[b]Not downgraded for high I^2 statistic since observed inconsistency did not appear clinically relevant.
[c]Downgraded one level due to serious concerns regarding attrition bias.
[d]Downgraded one level for serious inconsistency.

BACKGROUND

Description of the condition

Premature ejaculation (PE) is broadly defined as a male sexual disorder in which ejaculation occurs at a time earlier than desired by the patient or his partner, or both, usually with minimal sexual stimulation before, or shortly after penetration. Other names for this condition are early ejaculation, rapid ejaculation, rapid climax, premature climax and (historically) ejaculatio praecox. The International Society of Sexual Medicine's guideline for PE provides a more specific definition: "a male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within one minute of vaginal penetration, either present from the first sexual experience or following a new bothersome change in ejaculatory latency, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy" (Serefoglu 2014). It should be noted that other definitions of PE have been proposed but these have not been widely adopted or have not been evidence-based (McMahon 2004). However, all these definitions were based around time to ejaculation, the inability to control ejaculation and the negative impact on an individual.

There are several classification systems for subtypes of PE, but the commonly used Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) and International Classification of Diseases 11th Revision (ICD-11) define four broad subtypes: lifelong, acquired, natural variable and premature-like ejaculatory dysfunction (Waldinger 2006; Waldinger 2007). This classification likely encompasses most types of patients encountered in clinical practice. A clinical differentiation has been made between primary or lifelong versus secondary or acquired PE. With lifelong (primary) PE, the patient has experienced PE since the beginning of sexual life and it occurs in the absence of organic illnesses. Men with acquired PE encounter ejaculatory problems later in their lifetime after normal encounters in adolescence. There is generally a somatic or psychological dysfunction that is underpinning the ejaculatory problems, such as, urogenital disease, thyroid abnormalities or relationship problems. The treatment of acquired PE is based on addressing the underlying issue.

PE has a significant negative impact on a man's quality of life. Rowlands 2007 reported that men with PE have lower satisfaction with intercourse, increased personal distress and more interpersonal difficulty. These issues are also reflected in the female partners of men with PE. There are reports that the adverse effects of PE extend into a man's overall quality of life with lower 36-item Short Form (SF-36) scores in the following domains: general health, vitality, social function, emotional, mental health, role-physical and the mental health component score (Rowlands 2007). Thus, successful treatment of PE has the potential to markedly improve quality of life.

Pathophysiology of premature ejaculation

The pathophysiology of PE is not completely understood. Ejaculation represents the last phase of the sexual response cycle. It is a reflex requiring interaction of somatic, sympathetic and parasympathetic nerve functions of mostly central dopaminergic and serotonergic neurons (Buvat 2011; McMahon 2004). The somatic system with the pudendal nerve enables the expulsion phase of ejaculation. Based on experimental studies in animals, serotonin has an important regulatory role in ejaculation. Different types of serotonin receptors exist in the brain, spine and peripheral autonomic ganglia, where they either have a stimulatory or inhibitory effect on ejaculation (Waldinger 2002). One of the underlying issues in PE appears to be a diminished sensitivity of one type of receptor versus the increased sensitivity of another type of receptor to serotonin. The exact cause of this problem remains unclear. Genetic, neurobiologic, pharmacologic, psychological, urologic and endocrine factors have been implicated (Buvat 2011). Genetic factors include variations in the serotonin-transporter-linked promoter region (5-HTTLPR) on chromosome 17 where the short allele has been shown to be more prevalent in men with PE compared to controls (Ozbek 2011). It is likely that PE is multifactorial and that psychological and somatic factors and psychological stress contribute (Buvat 2011). Developmental factors such as history of sexual abuse, negative attitudes towards sex or individual psychological factors such as a negative body image, depression and performance anxiety may also play a role at times (Althof 2014).

Epidemiology

There have been largely variable estimates of PE prevalence because of the contention in the exact definition. Historical data from The USA National Health and Social Life Survey estimated that nearly one-third of all adult males under 60 years of age in 1992 had PE (Laumann 1999). However, it is thought this is a gross overestimate given the number of men that present for medical attention. Contemporary data estimates the prevalence of lifelong and acquired PE as 5% of the general population (Althof 2014).

Diagnosis

Diagnosis of PE is predominantly based on the medical and sexual history of the man (Shabsigh 2006). Specifically, clinicians should ask patients how long they have had PE; how often it occurs; whether it happens during all sexual encounters and with all partners; whether the degree of sexual stimulation matters and how often they engage in sexual activity including masturbation, foreplay and intercourse. Clinicians should also ask the patient to estimate their intravaginal ejaculatory latency time (IELT), ideally with corroboration of this information by a partner if present. While assessing IELT with a stopwatch is widely used in clinical trials, it is not routinely used in clinical practice due to the intrusive nature of this measurement method and because it has been shown to be relatively comparable to self-estimated IELT (Althof 2014; Rosen 2007a).

It is also helpful to ask the patient to define his perceived control over ejaculation, the perceived degree of bother related to PE and the impact it has on his relationship(s). Kempeneers 2013 reported that sexual satisfaction and distress better reflected the feeling of control than self-estimated IELT. There are several questionnaires that have been developed to diagnose PE and characterize its effect on quality of life. These include the Premature Ejaculation Diagnostic Tool (PEDT) (Symonds 2007), Arabic Index of Premature Ejaculation (Arafa 2007), Premature Ejaculation Profile (PEP) (Patrick 2009), and Male Sexual Health Questionnaire Ejaculatory Dysfunction (Rosen 2007b).

It is important to distinguish between PE and erectile dysfunction (ED), recognizing that some men with ED may develop secondary PE. Vice versa, men with lifelong PE may develop ED as they age.

Furthermore, possible acquired (secondary) causes of PE should be explored in an attempt to define the relevant subtype. Although physical examination is an essential part of the patient evaluation, it is unusual to find anything that explains the etiology of the patient's PE (Shabsigh 2006).

Treatment

Treatment approaches to PE, other than selective serotonin re-uptake inhibitors (SSRIs), can be broadly categorized into behavioral therapy, oral agents and topical agents (Althof 2014; Castiglione 2016). We have introduced the most widely used treatment options below.

Behavioral therapy

Behavioral psychosexual therapies predate the use of pharmacologic agents by decades (Cooper 2015).

- One early approach was referred to as the 'stop-start' technique (Semans 1956). It involves partner stimulation of the man's penis until the sensation of near climaxing at which time stimulation is abruptly stopped until the sensation of imminent orgasm disappears. This exercise is repeated until the patient learns to voluntarily control his ejaculations.
- Masters and Johnson reported a similar maneuver in which the partner squeezes the penis and stops penile stimulation (Melnik 2011). After a short interval, the female partner restarts the stimulation. This is referred to as the 'squeeze' technique.

The common feature of both approaches is distraction and the reduction of sexual excitement. It is intended to help men recognize the early signs for ejaculation/orgasm and work with their partner in improving self-control.

Oral agents

- Clomipramine: a tricyclic antidepressant that inhibits the uptake of norepinephrine and serotonin. Findings of several randomized controlled trials (RCTs) summarized in systematic reviews and meta-analyses indicate that the daily use of clomipramine increases IELT (Choi 2019; Cooper 2015; Kim 2018; McMahon 2011).
- Tramadol: a synthetic opiate analgesic that is primarily used for pain control. Its mechanism of action in PE is not fully understood. Several RCTs and reviews suggest that it results in an increase in IELT (Kirby 2015; Martyn-St James 2015; Safarinejad 2006a; Salem 2008).
- Phosphodiesterase-5 inhibitors: the primary role of this therapy is in treating ED. However, ED is also common among men with PE and there appears to be a benefit with sildenafil or tadalafil treatment (El-Hamd 2018; Martyn-St James 2017)
- Alfa-adrenoreceptor antagonists: this drug class is primarily used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia, but there are studies that have shown that it can improve PE (Cavallini 1995).

Topical agents

Topical agents decrease the sensitivity of the penis to sexual stimulation. Perceived advantages of these agents are the absence of systemic adverse effects.

- Lidocaine-prilocaine (marketed as EMLA) is a local anesthetic cream for topical use that can anesthetize intact skin. Several trials indicate an increase in IELT (Martyn-St James 2016; Pu 2013; Xia 2013). Adverse effects include some loss of penile sensitivity, ED and female genital anesthesia.

Description of the intervention

SSRIs are oral drugs primarily used to treat depression. Their effect on delaying ejaculation was first identified as an adverse effect in this setting (Althof 2014; Buvat 2009). Depending on the type of agent and its half-life, these drugs are used either daily or on-demand.

Adverse effects of the intervention

The adverse effects of SSRIs are fairly well understood through their widespread and long-term use in people with depression.

- The most common short-term adverse effects are reported to be drowsiness, weight gain, dry mouth, insomnia, fatigue and nausea (Cascade 2009).
- Sexual adverse effects such as reduced libido and new-onset or worsening ED have been reported (Cascade 2009).
- Stopping long-term treatment of SSRIs may lead to 'SSRI discontinuation syndrome,' beginning one to three days after drug cessation and possibly continuing for more than one week. Symptoms include nausea, vomiting, dizziness, headache, ataxia, drowsiness, anxiety and insomnia. Therefore, it is recommended that SSRIs be gradually withdrawn over several weeks (Mulhall 2012).
- Multiple drug interactions exist and can potentially lead to 'serotonin syndrome,' a group of serious, persistent symptoms including myoclonus, hyper-reflexia, sweating, shivering, and motor co-ordination and mental status changes (Iqbal 2012).
- Studies of depressed people treated with SSRIs have indicated a small increase in the risk of suicide ideation or suicide attempts, especially in younger age groups, but the evidence remains weak (Pompili 2010). Nonetheless, caution is urged in younger people with PE and concomitant depression or suicidal ideation, or both. Based on current guidelines, patients should also be advised to avoid sudden cessation or rapid dose reduction of daily dose SSRIs.

How the intervention might work

The role of 5-hydroxytryptamine (5-HT) (also known as serotonin) in the process of ejaculation appears to be inhibitory. SSRIs work by the blockage of serotonin transporters at the level of the synapse resulting in increased concentrations (Fuller 1994; Giuliano 2006; Waldinger 2005a). Based on a study of monkeys, administration of sertraline 20 mg/kg (an SSRI) resulted in the serotonin concentration in cerebrospinal fluid increasing by nearly 300% within hours of administration (Anderson 2005). Due to increased serotonin levels in the synapse, 5-HT1A and 5-HT1B receptors on the postsynaptic and presynaptic membranes become activated, causing a reduction in secretion of serotonin into the synapse (Waldinger 2005a). These receptors ultimately become desensitized, resulting in the serotonin release into the synapse, but this time because of transport inhibition by the SSRI, the synaptic serotonin levels remain high, causing persistent activation of postsynaptic receptors, which is thought to mediate the clinical effects of SSRI including the prolongation of IELT (Sprouse 2001).

Why it is important to do this review

SSRIs are among the most widely used drugs for PE (Althof 2014), but others have also argued that PE is not a disease at all (Puppo 2014), or have raised the notion that the fairly recent availability of pharmacologic treatment of PE, including SSRIs, has reinforced stereotypes of 'normal' sexual conduct and thereby reinforced social norms that cause men distress (Soderfeldt 2017). While most use of these agents is off-label, dapoxetine, a short-acting SSRI, is also approved for the treatment of PE in many countries outside the USA. Therefore, it is important for clinicians to fully understand both the benefits and potential harms associated with these agents as Feys 2014 raised the concern that dapoxetine may be a costly and dangerous placebo. Although multiple systematic reviews have been conducted on the treatment of PE, including the use of SSRIs (Castiglione 2016; Cooper 2015; Feys 2014; Russo 2016; Waldinger 2004; Yue 2015), these have not been performed in a methodologically rigorous manner. This review distinguishes itself by virtue of a published, a priori protocol governing all aspects of this study (New Reference), a comprehensive search of the literature not limited by publication status or language and its focus on patient-important outcomes with rating of the certainty of evidence using the GRADE approach on a per-outcome basis. Cochrane Reviews such as ours are also governed by a strict conflict of interest policy. Therefore, we expect this review to provide important, evidence-based information for patients, clinicians, guideline developers and health policy makers.

OBJECTIVES

To assess the effects of SSRIs in the treatment of PE in adult men.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs in which participants were allocated to receive either SSRI or placebo/no treatment. We also included cross-over clinical trials because we believed that this would be a suitable design to test interventions in PE as this is a relatively stable condition and SSRIs have a short half-life (Elbourne 2002). We did not consider cluster-RCTs as they did not appear applicable to this particular clinical question.

Types of participants

We included studies of men aged ≥ 18 years with lifelong PE only (from first sexual experience). We excluded men with PE secondary to other known conditions such as prostatitis or PE as a medication side effect (acquired PE).

Diagnostic criteria for premature ejaculation

Since a standardized definition was developed by the International Society of Sexual Medicine in 2014 (see Description of the condition), we included studies whether they used this definition or not (but recorded all definitions used).

Types of interventions

We investigated the following comparisons of intervention versus control/comparator.

Intervention

- SSRI.

Comparator

- Placebo.
- No treatment (but we found no trials with no treatment as the comparator).

Concomitant interventions were the same in both the intervention and comparator groups to establish fair comparisons.

For trials with multiple arms, we included any arm that met the inclusion criteria in the review and listed all arms in the Characteristics of included studies table).

We did not consider agents classified as serotonin-norepinephrine re-uptake inhibitors such as duloxetine.

Minimum duration of intervention and follow-up

- Four weeks.

We defined the trial duration according to the number of weeks over which the interventions and comparators were conducted and only included trials in the analyses with treatments that lasted at least four weeks.

Exclusion criteria

- Males aged less than 18 years.
- Men with known conditions thought to cause PE or in whom PE was thought to be secondary to other medications.

Types of outcome measures

We did not exclude trials because one or several of our primary or secondary outcome measures were not reported in the publication. In case none of our primary or secondary outcomes were reported, we were unable to include such trials in the analysis but provided information for these trials in Table 1 and Table 2.

Primary outcomes

We focused on outcomes of direct patient importance that are directly applicable to routine clinical practice using instruments that have undergone validation.

- Participant perception of change with treatment.
- Participant satisfaction with intercourse.
- Study withdrawal due to adverse events.

We assessed participant perception of change using the Clinical Global Impression of Change (CGIC) questionnaire, which is a validated instrument that is administered after treatment (Althof 2010). We recorded the number of participants describing the change as 'better' or 'much better' after treatment in a dichotomous manner. An event was considered 'good' as it represented 'better' or 'much better' symptoms after treatment. No minimal clinically important difference (MCID) has been reported; we considered a 10% difference between groups as clinically meaningful. This was a participant self-reported outcome.

We assessed participant satisfaction with intercourse using the PEP questionnaire (Patrick 2009), a validated instrument that addresses

four domains. We recorded the number of participants describing their satisfaction as 'good' or 'very good' before and after treatment (for satisfaction and control) in a dichotomous manner. An event was considered 'good' as it represented 'good' or 'very good' satisfaction after treatment.

We recorded the number of participants withdrawing from the trial due to adverse events in a dichotomous manner. We considered a 5% difference between groups as clinically meaningful. This was an investigator-assessed outcome.

For study withdrawals due to adverse events, we considered a 2% absolute difference as clinically meaningful.

In the absence of any reported MCIDs for these three outcomes, all thresholds were informed by the clinical expertise and experience of the clinical authors. We did not formally involve any external stakeholders (such as men with PE) in this process. This also applies to the secondary outcomes (listed below).

Secondary outcomes

- Perceived control over ejaculation.
- Participant distress about PE.
- Relationship difficulties.
- Adverse events.
- IELT.
- Depression.

We also used the PEP questionnaire to assess participant satisfaction with control over ejaculation, distress about PE and relationship difficulties (Patrick 2009). We recorded the number of participants describing their satisfaction as 'good' or 'very good' before and after treatment (for satisfaction and control). An event was good as it represented 'good' or 'very good' control after treatment. This was measured in a dichotomous manner. For distress and relationship difficulties, we recorded the number of participants describing their distress 'a little bit' or 'not at all.' An event was considered good as it represented 'a little bit' or 'not at all' relationship difficulties/distress after treatment. This was also measured in a dichotomous manner. No MCID has been reported; we considered a 10% difference between groups as clinically meaningful. All of these were participant self-reported outcomes.

We further assessed the cumulative number of adverse events in a dichotomous manner. We considered a 5% difference between groups as clinically meaningful. This was an investigator-assessed outcome. We also provided descriptive information on the most common adverse events contributing to this analysis.

We assessed IELT as measured using a stopwatch in minutes (Waldinger 2005b). Although this method of measurement is not routinely used in clinical practice, it represents the best current method for assessing the fundamental issue that defines PE. This was measured as a continuous outcome. No MCID has been reported in the literature. Therefore, we assumed a one-minute difference as the smallest difference between groups to be clinically meaningful. This was based on the mean IELT; we did not use the geometric mean IELT, which has been proposed as an alternative measure more robust to non-normal distributions (Waldinger 2008).

We recorded the incidence of new symptoms of depression in participants in a dichotomous manner. We looked for information using validated instruments such as the Beck Depression Inventory questionnaire (Novaretti 2002), but also recorded other types of information as collected by the investigators. No MCID has been reported; we considered a 10% difference between groups as clinically meaningful. This may have been a participant self-reported or investigator-assessed outcome.

Search methods for identification of studies

A dedicated information specialist (JL) conducted all systematic searches. We applied no restrictions regarding language or publication status.

Electronic searches

We searched the following sources from the inception of each database. Complete search strategies for each resource are available in the Appendices.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library (2020, Issue 4) (Appendix 1).
- PubMed MEDLINE (from 1946) (Appendix 2).
- Embase via Elsevier (from 1947) (Appendix 3).
- Cumulative Index of Nursing and Allied Health Literature (CINAHL) via EBSCOhost (from 1981) (Appendix 4)
- Latin American and Caribbean Health Sciences Literature (LILACS) via BIREME-PAHO-WHO (from 1982) (Appendix 5).
- Scopus via Elsevier (from 1970) (Appendix 6).
- US National Institutes of Health ClinicalTrials.gov Registry (clinicaltrials.gov) (Appendix 7).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) (Appendix 8).
- ProQuest Dissertations & Theses (PQDT; from 1861) (Appendix 9).
- OCLC WorldCat Dissertations and Theses (Appendix 10).

We applied publication type filters as follows. For CENTRAL, we selected only clinical trials via the Cochrane Library results interface. For PubMed, we applied the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format from the *Cochrane Handbook for Systematic Reviews of Interventions* (accessed 16 June 2017). For Embase, we translated the RCT filter from SIGN (Scottish Intercollegiate Guidelines Network) (accessed from www.sign.ac.uk/search-filters.html on 19 June 2017) to appropriate syntax for Embase-Elsevier. For CINAHL, we used the RCT filter from SIGN (accessed from www.sign.ac.uk/search-filters.html on 19 June 2017). We applied no filter for LILACS due to a low yield. For Scopus, as a published or validated filter was not available, the Cochrane Urology Assistant Information Specialist developed one based loosely on the CINAHL filter. No filter was needed for PQDT. For WorldCat, we selected Content Type: Thesis/Dissertation. We applied no other filters or limits to the searches. The search strategies were peer reviewed by a second Cochrane Urology Assistant Information Specialist, and recommendations were incorporated into the final strategies.

We applied a PubMed (MEDLINE) email alert through 1 May 2020 to identify newly published trials using the same search strategy

as described for MEDLINE (see Appendix 2 for search strategy). After we submitted the final review draft for editorial approval, the Information Specialist on our review team performed a complete search update (1 May 2020) on all databases and sent the results to the review authors. New trials were evaluated and we incorporated the findings from the new trials into our review for all included trials.

If we detected additional relevant keywords during any electronic or other searches, we modified the electronic search strategies to incorporate these terms and documented the changes.

Searching other resources

We identified other potentially eligible trials or ancillary publications by searching the reference lists of included trials, as well as related systematic reviews, meta-analyses and health technology assessment reports. We also contacted authors of included trials to identify additional information on the retrieved trials and any trials that we might have missed.

We included studies presented in abstract form only as well, focusing on these relevant meetings from 2017 to 2020. For these years, abstract proceedings from can be searched and identified through electronic searches of the journals identified and captured through our electronic MEDLINE search. This included the following meetings:

- American Urological Association (AUA); Journal of Urology;
- European Urology Association (EAU); European Urology Supplements;
- International Society of Sexual Medicine (ISSM); Journal of Sexual Medicine;
- World Association for Sexual Health (WASH); Journal of Sexual Medicine;
- European Society for Sexual Medicine (ESSM); Journal of Sexual Medicine;
- World Meeting on Sexual Medicine (WMSM); Journal of Sexual Medicine;
- Sexual Medicine Society of North America (SMSNA); Journal of Sexual Medicine.

Data collection and analysis

Selection of studies

At least two of four review authors (RM, AS, JB, SS) independently scanned the abstract, title, or both of every record we retrieved in the literature searches, to determine which trials we should assess further. We obtained the full text of all potentially relevant records. We resolved any disagreements through consensus or by recourse to a third review author (PD). If we could not resolve a disagreement, we categorized the trial as a 'study awaiting classification' and contacted the trial authors for clarification. We presented an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009).

Data extraction and management

For trials that fulfilled our inclusion criteria, at least two of four review authors (RM, AS, JB, SS) independently extracted key participant and intervention characteristics. We reported data on efficacy outcomes and adverse events using standardized data extraction sheets from the Cochrane Metabolic and Endocrine Disorders Group. We resolved any disagreements by discussion or, if required, by consultation with a third review author (PD).

We provided information about potentially relevant ongoing trials, including the trial identifier, in the Characteristics of ongoing studies table. We attempted to find the protocol for each included trial and reported primary, secondary and other outcomes.

We emailed all authors of included trials to ask if they were willing to answer questions regarding their trials. Thereafter we requested relevant missing information on the trial from the primary trial author(s).

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we maximized the information yielded by collating all available data and used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a primary trial and trial documents of included trials (such as trial registry information) as secondary references under the study ID of included trials. Furthermore, we listed duplicate publications, companion documents, multiple reports of a trial and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of excluded trials.

Data from clinical trial registers

If data of included trials were available as study results in clinical trial registers such as ClinicalTrials.gov, we made full use of this information and extracted the data. If there is also a full publication of the trial, we collated and critically appraised all available data. If an included trial was marked as a completed study in a clinical trial register but no additional information was available, we added this trial to the Characteristics of studies awaiting classification table.

Assessment of risk of bias in included studies

Two review authors (RM, SS) independently assessed the risk of bias of each included trial. We resolved any disagreements by consensus or by consulting a third review author (PD). In case of disagreement, we consulted the rest of the group and made a judgment based on consensus. If adequate information was not available from trial authors, trial protocols, or both, we contacted the trial authors for missing data on 'Risk of bias' items.

We used the Cochrane 'Risk of bias' assessment tool and judged 'Risk of bias' criteria as low, high or unclear risk (Higgins 2011a; Higgins 2011b). We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorizations contained therein (Higgins 2011a).

Random sequence generation (selection bias due to inadequate generation of a randomized sequence) – assessment at trial level

For each included trial, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or

envelopes, and throwing dice were adequate if an independent person performed this who was not otherwise involved in the trial. We considered the use of the minimization technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment) – assessment at trial level

We described for each included trial the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We also evaluated trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias (Corbett 2014). Chance imbalances may also affect judgments on the risk of attrition bias. In case of unadjusted analyses, we distinguished between studies we rated at low risk of bias on the basis of both randomization methods and baseline similarity, and studies we rated at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We reclassified judgments of unclear, low or high risk of selection bias.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial) – assessment at outcome level

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judged that the outcome was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to have been influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessors) – assessment at outcome level

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judged that the outcome measurement was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature, or handling of incomplete outcome data) – assessment at outcome level

For each included trial for each outcome, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the trial reported attrition and exclusions, and the number of participants included in the analysis at each stage (compared with the number of randomized participants per intervention/comparator groups). We also noted if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We considered the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference (MD) or standardized mean difference (SMD)) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods such as multiple imputation were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle

missing data were likely to introduce bias; the trial did not address this outcome.

- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (MD or SMD) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting) – assessment at trial level

We assessed outcome reporting bias by comparing the published data to the study protocol (if available).

- Low risk of bias: the trial protocol was available and all of the trial's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (Outcome Reporting Bias in Trials (ORBIT) classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all of the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we could not enter them in a meta-analysis; the trial report failed to include results for a key outcome that would have been expected to have been reported for such a trial (ORBIT classification).

Other bias (bias due to problems not covered elsewhere) – assessment at trial level

- Low risk of bias: the trial appeared free of other sources of bias.
- Unclear risk of bias: insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to have been fraudulent; or the trial had some other serious problem.

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We distinguished between self-reported, investigator assessed, objective and adjudicated outcome measures.

We accepted the following outcomes as self-reported.

- Participant perception of change with treatment.
- Participant satisfaction with intercourse.
- Perceived control over ejaculation.
- Participant distress about PE.
- Relationship difficulties.
- Depression.

We required the following outcomes to be investigator assessed.

- Study withdrawal due to adverse events.
- Adverse events.

We classified the following outcome as objective.

- IELT.

We did not anticipate encountering any adjudicated outcome measures.

Summary assessment of risk of bias

Risk of bias for a trial across outcomes

Some 'Risk of bias' domains such as selection bias (sequence generation and allocation sequence concealment) affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we marked all endpoints investigated in the associated trial as high risk. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains; unclear risk to denote an unclear risk of bias for one or more key domains; and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These are our main summary assessments, which we incorporated into our judgments about the certainty of evidence in a 'Summary of findings' table. We defined outcomes as low risk of bias when most information came from trials at low risk of bias; unclear risk when most information came from trials at low or unclear risk of bias; and high risk when a sufficient proportion of information came from trials at high risk of bias.

Measures of treatment effect

When at least two included trials were available for a comparison and a given outcome, we expressed dichotomous data as a risk ratio (RR) with 95% confidence interval (CI) for ease of interpretation rather than using odds ratios (ORs). For continuous outcomes measured on the same scale (e.g. weight loss in kilograms), we estimated the intervention effect using the MD with 95% CI. For continuous outcomes measuring the same underlying concept (e.g. health-related quality of life) but using different measurement scales, we calculated the SMD with 95% CI.

Unit of analysis issues

We took into account the level at which randomization occurred, such as cross-over trials, and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we

either combined groups to create a single pair-wise comparison or appropriately reduced the sample size so that the same participants did not contribute multiple times (e.g. by splitting the 'shared' group into two or more groups). While the latter approach offers some solutions to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2011a). When we included cross-over trials, we only included data from the first period to mitigate any confounding effect from carry-over.

Dealing with missing data

We obtained missing data from the authors of the included trials. We carefully evaluated important numerical data such as screened, randomly assigned participants as well as intention-to-treat, as-treated and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals) and critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

In trials where the standard deviation of the outcome was not available at follow-up or could not be re-created, we standardized by the mean of the pooled baseline standard deviation from those trials in which this information was reported.

Where included trials did not report means and standard deviations for outcomes and we were unable to obtain the required information from trial authors, we imputed these values by estimating the mean and variance from the median, range and the size of the sample (Hozo 2005). We investigated the impact of imputation on meta-analyses by performing sensitivity analyses and reported per outcome which trials were included with imputed standard deviations.

Assessment of heterogeneity

In the event of excessive clinical or methodologic heterogeneity, we would not have reported trial results as the pooled effect estimate in a meta-analysis.

We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis.

We interpreted the I^2 statistic as follows (Higgins 2002; Higgins 2003; Higgins 2011a).

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

When we found heterogeneity, we attempted to determine the possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

If we included 10 or more trials that investigated a particular outcome, we used funnel plots to assess small-trial effects. Several explanations can account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodologic design (and hence bias of small trials) and publication bias. Therefore, we carefully interpreted the results (Sterne 2011).

Data synthesis

We undertook (or displayed) a meta-analysis only if we judged participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across trials, we primarily summarized data at low risk of bias using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration to the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we planned to use the Peto's OR method, provided that there was no substantial imbalance between intervention and comparator group sizes, and intervention effects were not exceptionally large. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and carried out the following subgroup analyses including investigation of interactions.

- Long-acting SSRIs (e.g. paroxetine, fluoxetine, sertraline, citalopram and fluvoxamine) versus short-acting (on-demand type) SSRIs (e.g. dapoxetine). We compared the long- versus short-acting SSRIs because not only may there be a difference in efficacy, but the incidence of adverse effects may vary by taking SSRIs daily rather than on-demand.
- Among the long-acting SSRIs, comparison of individual agents (e.g. paroxetine versus fluoxetine versus sertraline versus citalopram versus fluvoxamine). We compared these agents because although they are from the same class, there is evidence to suggest that they have varying efficacy and adverse effect profile (Sanchez 2014)
- If applicable, different dose levels (e.g. dapoxetine 30 mg versus 60 mg). Dose levels are compared because the use of SSRIs in PE is an off-label indication and there is no clear evidence on the optimal dosage for the best trade-off of benefit versus risk.

Sensitivity analysis

We performed a sensitivity analysis to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Taking into account risk of bias, as specified in the Assessment of risk of bias in included studies section, by removing studies judged at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity, such as directness of results. Two review authors (RM, PD)

independently rated the certainty of the evidence for each outcome.

We presented a summary of the evidence in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* by means of the table editor in Review Manager 5 (Review Manager 2014). We used GRADEpro GDT software and present evidence profile tables as an appendix (GRADEpro GDT 2015). We presented results for the outcomes as described in the Types of outcome measures section. If meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the certainty of studies using footnotes, and made comments to aid the reader's understanding of the Cochrane Review where necessary.

The 'Summary of findings' table includes following outcomes, listed according to priority.

1. Participant perception of change with treatment.
2. Participant satisfaction with intercourse.
3. Study withdrawal due to adverse events.
4. Perceived control over ejaculation.
5. Participant distress about PE.
6. Adverse events.
7. IELT.

Although we did not include relationship difficulties and depression as outcomes in the 'Summary of findings' table (due to a limit of seven outcomes), we provided the same type of analysis in the Results section and also rated the certainty of the evidence using GRADE for these outcomes.

RESULTS

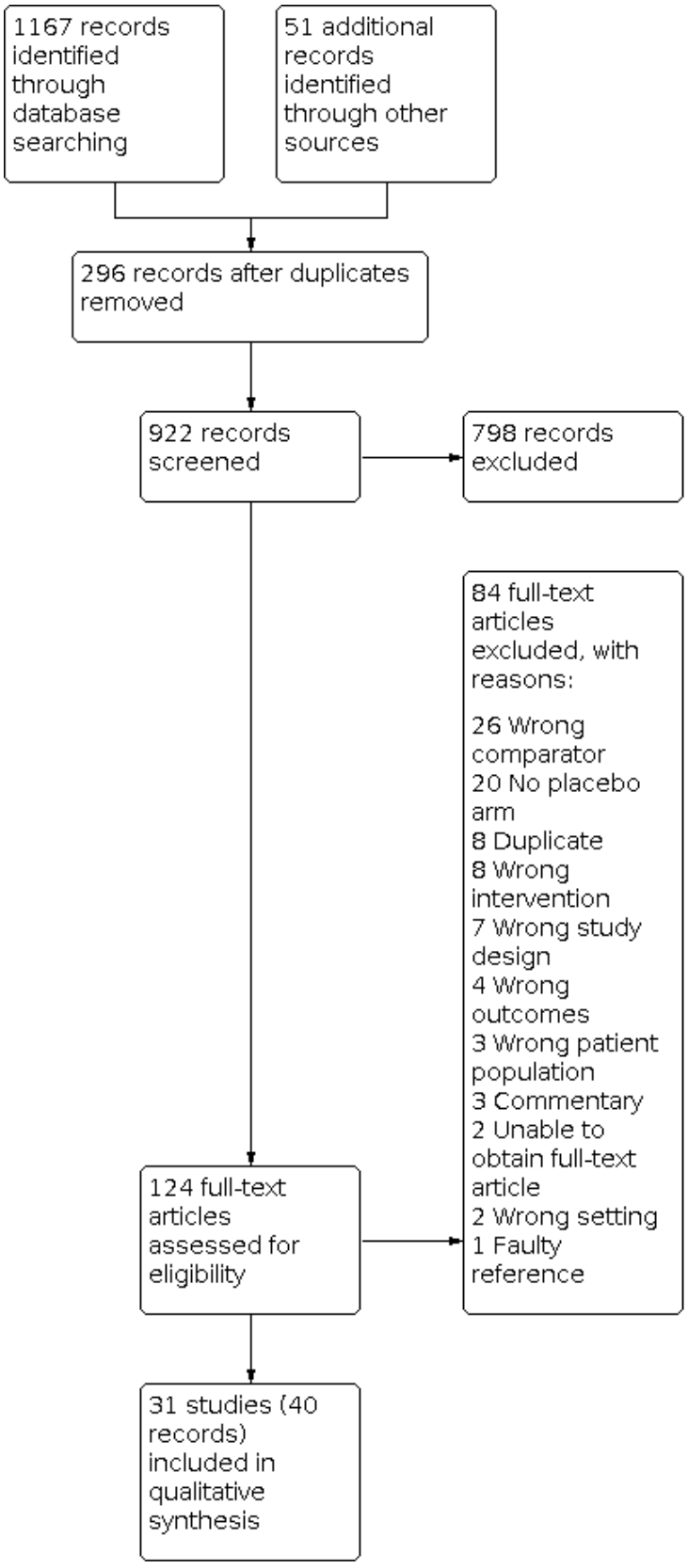
Description of studies

We presented details of included studies in the Characteristics of included studies and Table 1 and Table 2.

Results of the search

Our search of multiple electronic databases up to May 2020 yielded 1218 references (Figure 1). After exclusion of duplicates, we screened 922 references at the title/abstract stage. Subsequently after screening titles/abstracts, 124 unique studies entered the full-text screening stage. We included 31 studies (40 records) in the quantitative analyses. We summarized reasons for exclusion at the full-text stage in the PRISMA flow diagram (Figure 1), and we provided further details Characteristics of excluded studies table.

Figure 1. Study flow diagram.



Included studies

Source of data

We included 29 studies published in full-text and two additional studies only available as abstract proceedings (Hamidi Madani 2016; Khelaia 2012), for a total of 31 unique studies. Two studies were published in Korean (Ahn 1996; Na 1996), and two studies were published in Chinese (Gong 2011; Shang 2012). One review author (ECH) translated the Korean studies into English and Dr Yu Xie translated the Chinese studies into English. The remaining 27 studies were published in English.

Study design and settings

Four studies were cross-over trials (Kim 1998; McMahon 1998; McMahon 1999; Novaretti 2002), and remaining studies were parallel, RCTs. All studies were likely conducted in an outpatient clinic setting.

Participants

We included 8254 randomized participants (SSRI 4990, placebo 2928, other drug 131). Two studies did not report the number of participants in each arm (Hamidi Madani 2016; Novaretti 2002). All studies included sexually active men aged over 18 years with PE.

Interventions and comparators

Studies used a range of SSRIs with different doses. Seven studies used fluoxetine (Ahn 1996; Kara 1996; Kim 1998; Mattos 2008; Novaretti 2002; Waldinger 1998; Yilmaz 1999), one used duloxetine (Athanasios 2007), three used citalopram (Atmaca 2002; Farnia 2009; Shang 2012), seven used sertraline (Biri 1998; Kim 1998; McMahon 1998; Mendels 1995; Na 1996; Tuncel 2008; Waldinger 1998), seven used dapoxetine (Buvat 2009; Kaufman 2009; McMahon 2010; McMahon 2013; Pryor 2006; Safarinejad 2006b; Safarinejad 2008), eight used paroxetine (Gameel 2013; Gong 2011; Hamidi Madani 2016; Khelaia 2012; McMahon 1999; Safarinejad 2006c; Waldinger 1994; Waldinger 1998), one used escitalopram (Safarinejad 2007), and one used fluvoxamine (Waldinger 1998).

All studies used placebo as the comparator.

Outcomes

For our predefined primary outcomes, six studies reported participant perception of change with treatment (Athanasios 2007; Atmaca 2002; Buvat 2009; Kaufman 2009; McMahon 2010; McMahon 2013), three reported participant satisfaction with intercourse (Kaufman 2009; McMahon 2010; Pryor 2006), and 20 studies reported study withdrawal due to adverse events (Athanasios 2007; Atmaca 2002; Biri 1998; Buvat 2009; Gameel 2013; Gong 2011; Kara 1996; Kaufman 2009; McMahon 2010; McMahon 2013; Mendels 1995; Pryor 2006; Safarinejad 2006b; Safarinejad 2006c; Safarinejad 2007; Safarinejad 2008; Shang 2012; Waldinger 1994; Waldinger 1998; Yilmaz 1999).

In terms of predefined secondary outcomes, three studies reported perceived control over ejaculation (Kaufman 2009; McMahon 2010; Pryor 2006), 17 reported adverse events (Ahn 1996; Athanasios 2007; Atmaca 2002; Biri 1998; Buvat 2009; Kara 1996; Kaufman 2009; Mattos 2008; McMahon 2010; McMahon 2013; Mendels 1995; Safarinejad 2006b; Safarinejad 2007; Safarinejad 2008; Shang 2012; Tuncel 2008; Yilmaz 1999), 20 reported IELT (Ahn 1996; Athanasios 2007; Atmaca 2002; Biri 1998; Buvat 2009; Gameel 2013; Gong 2011; Kara 1996; Mattos 2008; McMahon 1998; McMahon 1999; McMahon 2010; McMahon 2013; Mendels 1995; Pryor 2006; Safarinejad 2006c; Shang 2012; Waldinger 1994; Waldinger 1998; Yilmaz 1999), and one reported depression (Kara 1996). One study reported participant distress about PE and relationship difficulties (Kaufman 2009)

Please refer to Analysis 1.1 through Analysis 1.9.

Funding sources and conflicts of interest

Four studies reported no funding source (Gameel 2013; Mattos 2008; Safarinejad 2007; Safarinejad 2008), and pharmaceutical companies supported seven studies (Buvat 2009; Kaufman 2009; McMahon 2010; McMahon 2013; Novaretti 2002; Pryor 2006; Waldinger 1998). The remaining studies did not address their funding source.

Two studies reported no conflicts of interest (Gameel 2013; Safarinejad 2008), and six studies reported investigators having relationships with pharmaceutical companies (Buvat 2009; Kaufman 2009; McMahon 2010; McMahon 2013; Mendels 1995; Pryor 2006). The remaining studies did not address conflicts of interest.

Excluded studies

We excluded 84 records after evaluation of the full-text publications for which we presented details in the Characteristics of excluded studies table.

Studies awaiting classification

We found one study awaiting classification that has not provided usable outcome data at this time (Kolomazník 2002; see Characteristics of studies awaiting classification table).

Ongoing trials

We identified no ongoing studies.

Risk of bias in included studies

A summary of the risk of bias in included studies are provided graphically in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

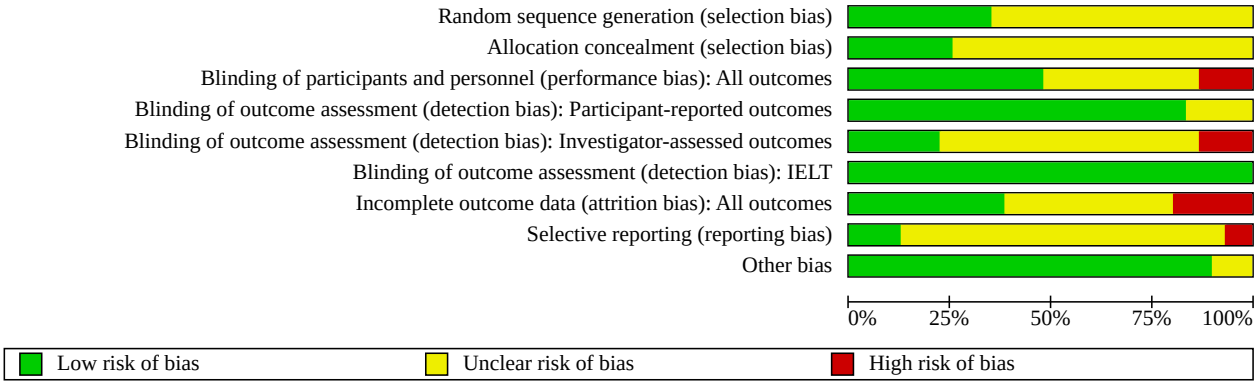


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

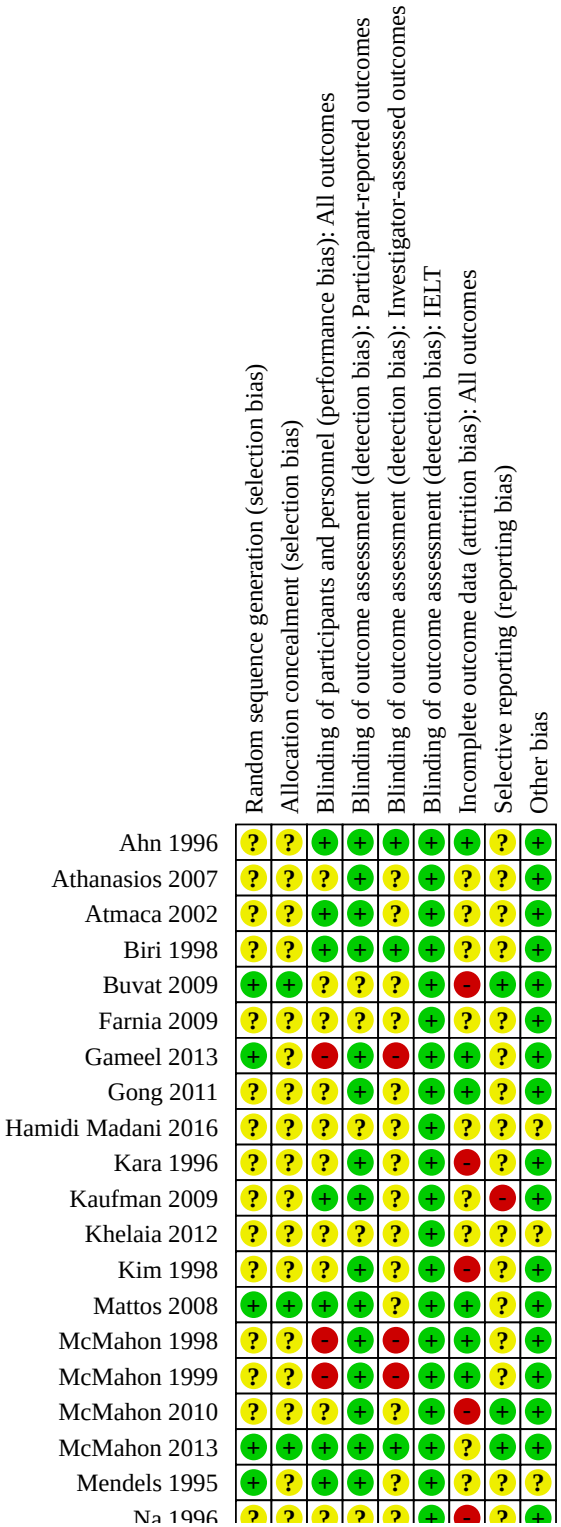
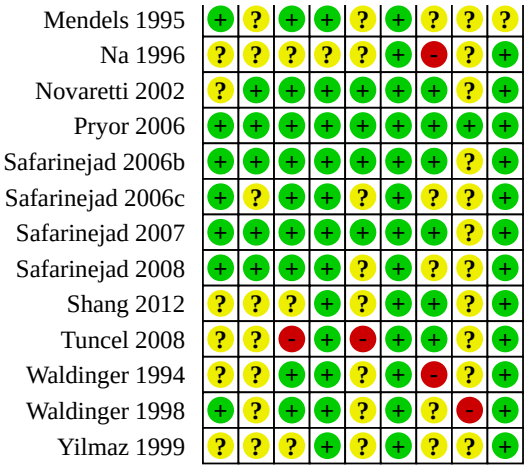


Figure 3. (Continued)



Allocation

Random sequence generation

Eleven of 31 studies were at low risk of bias because they employed an appropriate method of generating a random sequence (Buvat 2009; Gameel 2013; Mattos 2008; McMahon 2013; Mendels 1995; Pryor 2006; Safarinejad 2006b; Safarinejad 2006c; Safarinejad 2007; Safarinejad 2008; Waldinger 1998). The remaining 20 studies were at unclear risk because they did not explicitly describe the method of random sequence generation (Figure 2; Figure 3).

Allocation concealment

Eight of 31 studies were at low risk of bias because they implemented appropriate mechanisms to ensure that individuals enrolling participants were unaware of the upcoming group assignment for that participant (Buvat 2009; Mattos 2008; McMahon 2013; Novaretti 2002; Pryor 2006; Safarinejad 2006b; Safarinejad 2007; Safarinejad 2008). The 23 remaining studies were at unclear risk because they did not explicitly describe the methods utilized to ensure allocation concealment (Figure 2; Figure 3).

Blinding

Blinding of participants and personnel

Fifteen of 31 studies appropriately blinded both participants and personnel and were at low risk of bias (Ahn 1996; Atmaca 2002; Biri 1998; Kaufman 2009; Mattos 2008; McMahon 2013; Mendels 1995; Novaretti 2002; Pryor 2006; Safarinejad 2006b; Safarinejad 2006c; Safarinejad 2007; Safarinejad 2008; Waldinger 1994; Waldinger 1998). Twelve studies were at unclear risk of bias because they did not clearly describe which party was blinded (Athanasios 2007; Buvat 2009; Farnia 2009; Gong 2011; Hamidi Madani 2016; Kara 1996; Khelaia 2012; Kim 1998; McMahon 2010; Na 1996; Shang 2012; Yilmaz 1999). Four studies were at high risk of bias because they were single-blind in which personnel were not blinded (Gameel 2013; McMahon 1998; McMahon 1999; Tuncel 2008). (Figure 2; Figure 3).

Blinding of outcome assessment

For participant-reported outcomes, 26 studies were at low risk of bias because participants appeared to adequately blinded and five studies were at unclear risk of bias (Buvat 2009; Farnia 2009; Hamidi Madani 2016; Khelaia 2012; Na 1996). No study was at high risk (Figure 2; Figure 3).

For investigator-assessed outcomes, seven studies were at low risk of bias because the outcome assessors were adequately blinded (Ahn 1996; Biri 1998; McMahon 2013; Novaretti 2002; Pryor 2006; Safarinejad 2006b; Safarinejad 2007). Twenty studies were at unclear risk because it was not clearly described whether outcome assessors were blinded (Athanasios 2007; Atmaca 2002; Buvat 2009; Farnia 2009; Gong 2011; Hamidi Madani 2016; Kara 1996; Kaufman 2009; Khelaia 2012; Kim 1998; Mattos 2008; McMahon 2010; Mendels 1995; Na 1996; Safarinejad 2006c; Safarinejad 2008; Shang 2012; Waldinger 1994; Waldinger 1998; Yilmaz 1999) Four studies were at high risk of bias because the investigators were not blinded (Gameel 2013; McMahon 1998; McMahon 1999; Tuncel 2008). (Figure 2; Figure 3).

All studies were at low risk of bias for the IELT outcome because this is an objectively assessed measure that would have been expected to be affected by blinding or lack thereof in terms of detection bias (Figure 2; Figure 3).

Incomplete outcome data

We assessed the risk of attrition bias on a per-outcome basis but then collapsed these rating into one group since all judgments were identical. Twelve studies were at low risk of bias (Ahn 1996; Gameel 2013; Gong 2011; Mattos 2008; McMahon 1998; McMahon 1999; Novaretti 2002; Pryor 2006; Safarinejad 2006b; Safarinejad 2007; Shang 2012; Tuncel 2008). Thirteen studies were at unclear risk of bias as the proportion of randomized participants not included in the analyses was not clearly reported and the risk of attrition bias could not be estimated (Athanasios 2007; Atmaca 2002; Biri 1998; Farnia 2009; Hamidi Madani 2016; Kaufman 2009; Khelaia 2012; McMahon 2013; Mendels 1995; Safarinejad 2006c; Safarinejad 2008; Waldinger 1998; Yilmaz 1999). Six studies were at high risk of bias because large proportions of participants were excluded from the final analysis (Buvat 2009; Kara 1996; Kim 1998; McMahon 2010; Na 1996; Waldinger 1994).

Selective reporting

Four studies were at low risk of bias as they reported all outcomes according to their protocol and conducted their analyses according to their a priori plans (Buvat 2009; McMahon 2010; McMahon 2013; Pryor 2006). Twenty-five studies were at unclear risk of bias because the no study protocols were available (Ahn 1996; Athanasios 2007; Atmaca 2002; Biri 1998; Farnia 2009; Gameel 2013; Gong 2011; Hamidi Madani 2016; Kara 1996; Khelaia 2012; Kim 1998; Mattos 2008; McMahon 1998; McMahon 1999; Mendels 1995; Na 1996; Novaretti 2002 Safarinejad 2006b; Safarinejad 2006c; Safarinejad 2007; Safarinejad 2008; Shang 2012; Tuncel 2008; Waldinger 1994; Yilmaz 1999). Two studies were at high risk of bias because one did not complete report outcomes on one of their group (Kaufman 2009), and another did not completely report on side effects (Waldinger 1998) (Figure 2; Figure 3).

Other potential sources of bias

Twenty-seven studies were at low risk of bias (Ahn 1996; Athanasios 2007; Atmaca 2002; Biri 1998; Buvat 2009; Farnia 2009; Gameel 2013; Gong 2011; Kara 1996; Kaufman 2009; Kim 1998; McMahon 1998; McMahon 1999; McMahon 2010; McMahon 2013; Na 1996; Novaretti 2002; Pryor 2006; Safarinejad 2006b; Safarinejad 2006c; Safarinejad 2007; Safarinejad 2008; Shang 2012; Tuncel 2008; Waldinger 1994; Waldinger 1998; Yilmaz 1999). Three studies were at unclear risk of bias because there was imbalance in the baseline characteristics (Mendels 1995), or they were only reported in abstract form and there was insufficient information to make a judgment (Hamidi Madani 2016; Khelaia 2012). One study was at high risk of bias because it only evaluated specific adverse effects (Mattos 2008) (Figure 2; Figure 3).

Effects of interventions

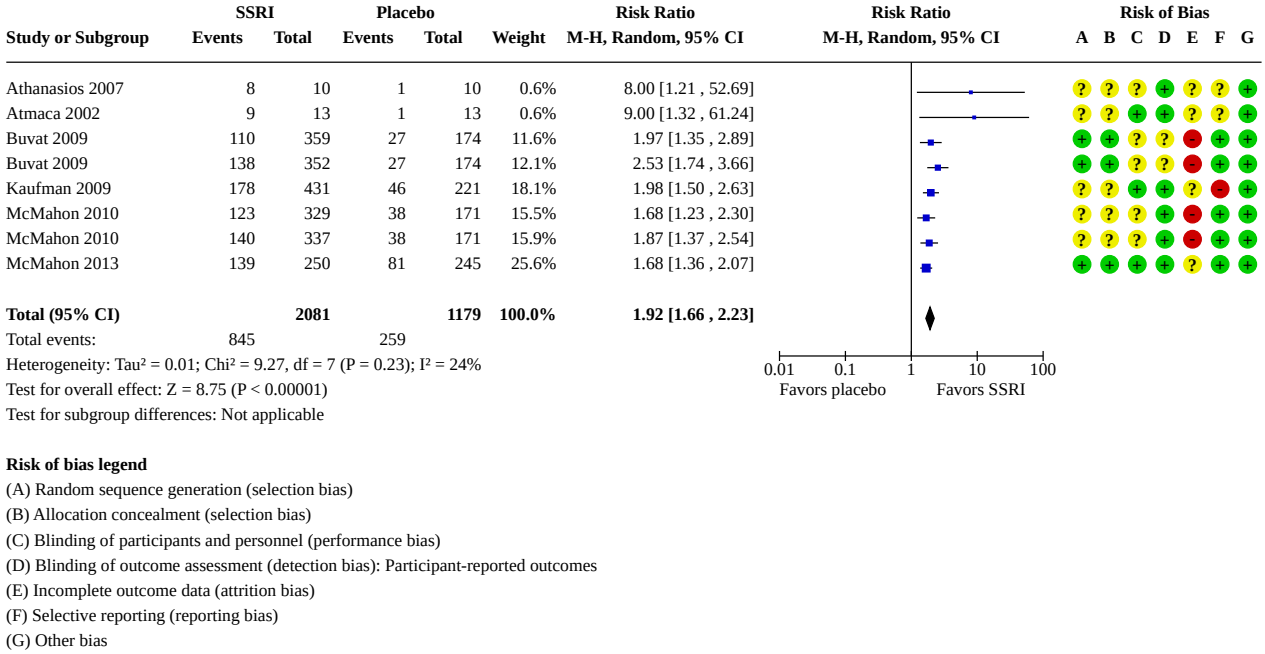
See: **Summary of findings 1** SSRI compared to placebo for premature ejaculation

Primary outcomes

1.1 Participant perception of change with treatment

SSRI treatment probably results in an improvement in PE-related symptoms defined as a rating of 'better' or 'much better' using the CGIC questionnaire compared to placebo (RR 1.92, 95% CI 1.66 to 2.23; I^2 = 24%; studies = 6, participants = 3260; Analysis 1.1; Figure 4). Compared to placebo and a baseline risk of 220 per 1000 men, this corresponds to 202 more men per 1000 (95% CI 145 more to 270 more) perceiving that their condition as 'better' or 'much better' with SSRIs.

Figure 4. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.1 Participant perception of change with treatment.



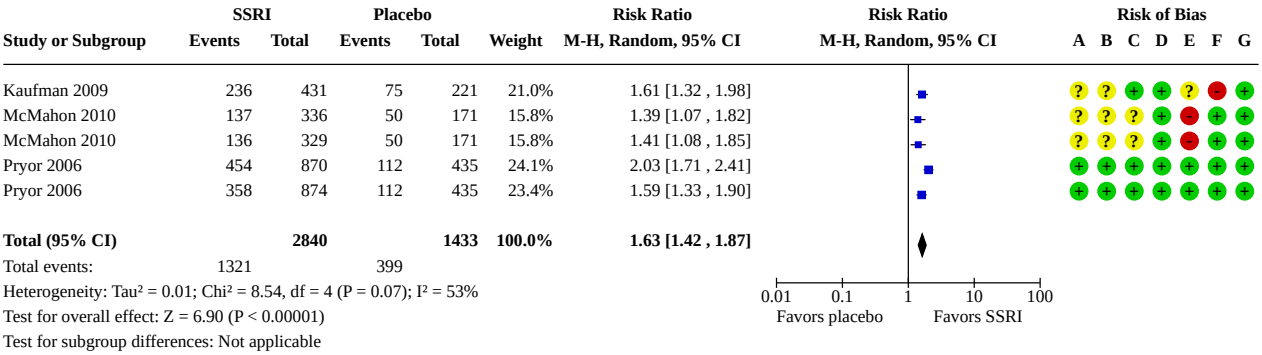
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Participant-reported outcomes
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

We rated the certainty of evidence as moderate, downgrading one level due to serious study limitations given that of the six studies included in this analysis, four had an unclear risk of selection bias, three had an unclear risk of performance bias and one had an unclear risk of detection bias. In addition, two were at high risk for attrition bias.

1.2 Participant satisfaction with intercourse

SSRI treatment probably improves satisfaction with intercourse defined as a rating of 'good' or 'very good' using the CGIC questionnaire compared to placebo (RR 1.63, 95% CI 1.42 to 1.87; I^2 = 53%; studies = 3, participants = 4273; Analysis 1.2; Figure 5). Compared to placebo and a baseline risk of 278 per 1000 men, this corresponds to 175 more men per 1000 (95% CI 117 more to 242 more) describing their satisfaction with intercourse as being 'good' or 'very good' with SSRIs.

Figure 5. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.2 Participant satisfaction with intercourse.



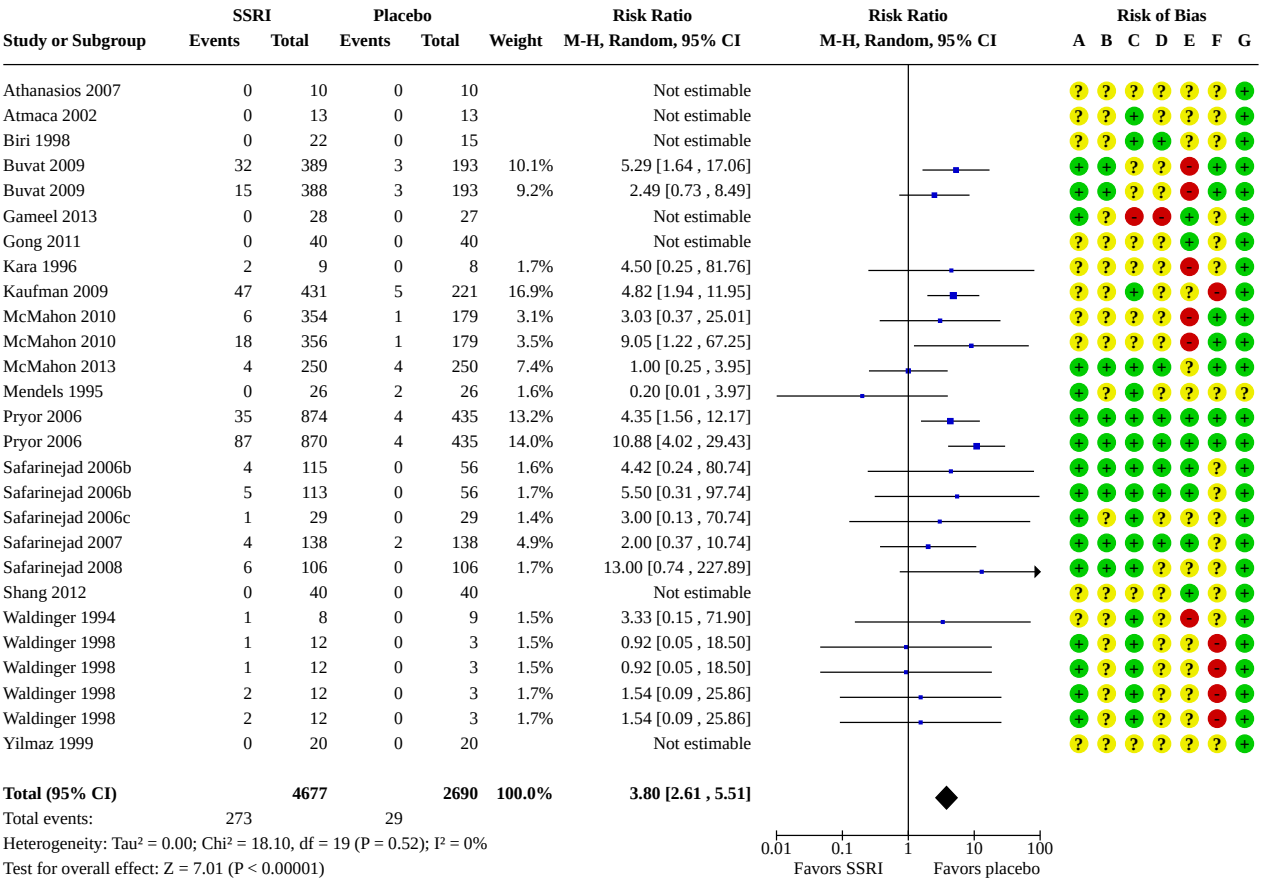
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Participant-reported outcomes
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

We rated the certainty of evidence as moderate, downgrading one level due to serious study limitations. Two of three included studies were at unclear risk of selection bias, one was at unclear risk of performance bias and one study that contributed a weight of 61.6% to the analysis was at high risk of attrition bias. However, we did not downgrade for the I^2 statistic of 53% since we did not judge the observed inconsistency to be clinically relevant.

1.3 Study withdrawal due to adverse events

SSRI treatment may result in an increase in the number of treatment cessations due to adverse events compared to placebo (RR 3.80, 95% CI 2.61 to 5.51; I^2 = 0%; studies = 20, participants = 7367; Analysis 1.3; Figure 6). Compared to placebo and a baseline risk of 11 per 1000 men, this corresponds to 30 more men per 1000 (95% CI 17 more to 49 more) stopping treatment due to adverse events due to SSRI treatment.

Figure 6. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.3 Study withdrawal due to adverse events.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Investigator-assessed outcomes
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

We rated the certainty of evidence as low, downgrading two levels due to very serious study limitations because more than half the included studies were at unclear risk of selection bias or performance bias, or both. Four studies were at high risk of attrition bias for this outcome and two studies were at high risk of selective reporting bias.

Secondary outcomes

1.4 Perceived control over ejaculation

SSRI treatment probably improves participants' control over ejaculation defined as a rating of 'good' or 'very good' based on the PEP questionnaire compared to placebo (RR 2.29, 95% CI 1.72 to 3.05; I^2 = 75%; studies = 3, participants = 4273; Analysis 1.4). Compared to placebo and a baseline risk of 132 per 1000 men, this corresponds to 170 more men per 1000 (95% CI 95 more to 270 more) describing their control over ejaculation as being 'good' or 'very good' with SSRIs.

We rated the certainty of evidence as moderate, downgrading one level due to serious study limitations. Two of three studies had an unclear risk of selection bias, one had an unclear risk of performance bias and one had a high risk of attrition bias.

1.5 Participant distress about premature ejaculation

SSRI treatment probably decreases PE-related distress defined as 'a little bit' or 'not at all' distressing based on the PEP questionnaire compared to placebo (RR 1.54, 95% CI 1.26 to 1.88; studies = 1, participants = 652; Analysis 1.5). Compared to placebo and a baseline risk of 353 per 1000 men, this corresponds to 191 men more per 1000 (95% CI 92 more to 311 more) reporting their distress about PE as being only 'a little bit' or 'not at all' with SSRIs.

We rated the certainty of evidence as moderate, downgrading one level due to serious study limitations because the only included study had unclear risk of selection bias, an unclear risk of attrition bias and a high risk of selective reporting bias.

1.6 Relationship difficulties

SSRI treatment may reduce relationship difficulties to only 'a little bit' or 'not at all' based on the PEP questionnaire compared to placebo (RR 1.20, 95% CI 1.07 to 1.34; studies = 1, participants = 652; Analysis 1.6). Compared to placebo, this corresponds to 129 men more per 1000 (95% CI 45 more to 218 more) reporting their relationship difficulties as being only 'a little bit' or 'not at all' with SSRIs.

We rated the certainty of evidence as low, downgrading one level each for serious study limitations and imprecision. The only included study had an unclear risk of selection bias, an unclear risk of attrition bias and a high risk of selective reporting bias. We perceived the absolute effect size to cross the threshold for a clinically important difference of 10% and, therefore, downgraded a further level for imprecision.

1.7 Adverse events

SSRI treatment probably increases adverse events substantially compared to placebo (RR 1.71, 95% CI 1.48 to 1.99; I^2 = 41%; studies = 17, participants = 4624; Analysis 1.7). Compared to placebo and a baseline risk of 243 per 1000, this corresponds to 173 more adverse events per 1000 men (95% CI 117 more to 241 more).

We rated the certainty of evidence as moderate, downgrading one level due to serious study limitations because more than half the included studies were rated as unclear risk for selection bias or performance bias, or both. Two studies had a high risk of attrition bias and over half had an unclear risk of selective reporting bias.

1.8 Intravaginal ejaculatory latency time

SSRI treatment may increase IELT compared to placebo (MD 3.09 minutes longer, 95% CI 1.94 longer to 4.25 longer; I^2 = 99%; studies = 20, participants = 5872; Analysis 1.8).

We rated the certainty of evidence as low, downgrading one level due to serious study limitations; most studies had an unclear or high risk of selection, performance, attrition and reporting bias. We also downgraded one level for serious concerns about inconsistency. These may in part be attributable to the duration of action (long versus short acting; Analysis 3.4) and type of SSRI (Analysis 3.4).

1.9 Depression

We are very uncertain whether SSRI treatment compared to placebo increases depression (RR 2.00, 95% CI 0.23 to 17.34; studies = 1, participants = 14; Analysis 1.9). We rated the certainty of evidence as very low, downgrading due to serious study limitations (unclear risk of selection and performance bias, high risk of attrition bias and unclear risk of selective reporting bias) and very serious imprecision.

Subgroup analyses

2 Long-acting versus short-acting SSRIs

2.1 Participant perception of change with treatment

The RR for participant perception of change with treatment as being 'better' or 'much better' was 8.48 (95% CI 2.21 to 32.51) for long-acting SSRIs and 1.87 (95% CI 1.66 to 2.10) for short-acting SSRIs (Analysis 2.1). The test for interaction was significant (P = 0.03; I^2 = 79.3%).

2.2 Participant satisfaction with intercourse

There were no studies of long-acting SSRIs that evaluated participant satisfaction with intercourse.

2.3 Study withdrawal due to adverse events

The RR for study withdrawal due to adverse events was 2.00 (95% CI 0.92 to 4.34) for long-acting SSRIs and 4.33 (95% CI 2.60 to 7.23) for short-acting SSRIs (Analysis 2.3). The test for interaction was not significant (P = 0.10; I^2 = 62.4%).

2.4 Perceived control over ejaculation

There were no studies of long-acting SSRIs that evaluated perceived control over ejaculation.

2.5 Participant distress about premature ejaculation

There were no studies of long-acting SSRIs that evaluated participant distress about PE.

2.6 Relationship difficulties

There were no studies of long-acting SSRIs that evaluated relationship difficulties.

2.7 Adverse events

The RR for adverse events was 1.90 (95% CI 1.37 to 2.64) for long-acting SSRIs and 1.70 (95% CI 1.42 to 2.03) for short-acting SSRIs (Analysis 2.7). The test for interaction was not significant (P = 0.54; I^2 = 0%).

2.8 Intravaginal ejaculatory latency time

The MD for IELT was 3.36 minutes (95% CI 1.62 to 5.10) for long-acting SSRIs and 1.52 minutes (95% CI 1.27 to 1.77) for short-acting SSRIs (Analysis 2.8). The test for interaction was significant (P = 0.04; I^2 = 76.2%).

2.9 Depression

There were no studies of short-acting SSRIs that evaluated depression.

3 Types of long-acting SSRIs

3.1 Participant perception of change with treatment

We found one study of citalopram (Atmaca 2002) and one of duloxetine (Athanasios 2007), which evaluated participant perception of change with treatment. The RR for participant perception of change with treatment as being 'better' or 'much better' was 9.00 (95% CI 1.32 to 61.24) for citalopram and 8.00 (95% CI 1.21 to 52.69) for duloxetine (Analysis 3.1). The test for interaction was not significant (P = 0.93; I^2 = 0%).

3.2 Participant satisfaction with intercourse

There were no studies of long-acting SSRIs that evaluated participant satisfaction with intercourse.

3.3 Study withdrawal due to adverse events

We found 14 studies of long-acting SSRIs that evaluated this outcome.

The RR for study withdrawal due to adverse events was 3.00 (95% CI 0.13 to 70.74) for citalopram, 7.64 (95% CI 0.99 to 58.71) for dapoxetine, not estimable for duloxetine, 2.00 (95% CI 0.37 to 10.74)

for escitalopram, 2.59 (95% CI 0.34 to 19.59) for fluoxetine, 1.54 (95% CI 0.09 to 25.86) for fluvoxamine, 1.76 (95% CI 0.35 to 8.91) for paroxetine and 0.43 (95% CI 0.05 to 3.56) for sertraline (Analysis 3.2). The test for interaction was not significant (P = 0.69; I^2 = 0%).

3.4 Perceived control over ejaculation

There were no studies of long-acting SSRIs that evaluated perceived control over ejaculation.

3.5 Participant distress about premature ejaculation

There were no studies of long-acting SSRIs that evaluated participant distress about PE.

3.6 Relationship difficulties

There were no studies of long-acting SSRIs that evaluated relationship difficulties.

3.7 Adverse events

We found 13 studies of long-acting SSRIs that evaluated adverse effects. The RR for adverse effects was 3.00 (95% CI 0.51 to 17.57) for citalopram, 4.40 (95% CI 1.06 to 18.32) for clomipramine, 2.54 (95% CI 1.34 to 4.81) for dapoxetine, 3.00 (95% CI 0.37 to 24.17) for duloxetine, 1.69 (95% CI 0.69 to 4.15) for escitalopram, 2.50 (95% CI 1.29, to 4.86) for fluoxetine, 2.50 (95% CI 0.91 to 6.90) for paroxetine and 1.33 (95% CI 0.74 to 2.39) for sertraline (Analysis 3.3). The test for interaction was not significant (P = 0.71; I^2 = 0%).

3.8 Intravaginal ejaculatory latency time

We found 14 studies of long-acting SSRIs that evaluated IELT. The MD for IELT was 4.85 (95% CI 3.14 to 6.56) for citalopram, 1.52 (95% CI 0.80 to 2.24) for duloxetine, 2.46 (95% CI 1.51 to 3.39) for fluoxetine, 0.59 (95% CI −0.35 to 1.53) for fluvoxamine, 6.51 (95% CI 0.33 to 12.68) for paroxetine and 2.55 (95% CI 1.54 to 3.56) for sertraline (Analysis 3.4). The test for interaction was significant (P < 0.001, I^2 = 80.0%).

3.9 Depression

We only found one study using long-acting fluoxetine that evaluated depression and were unable to perform any secondary analyses (Kara 1996).

4 Different doses: dapoxetine

4.1 Participant perception of change with treatment

We found four studies that administered dapoxetine at the following doses: 30 mg daily (McMahon 2010), 30 mg on-demand (Buvat 2009; McMahon 2013), 60 mg daily (McMahon 2010), and 60 mg on-demand (Buvat 2009; Kaufman 2009). The RR for participant perception of change with treatment as being 'better' or 'much better' was 1.87 (95% CI 1.37 to 2.54) with 30 mg daily, 2.00 (95% CI 1.33 to 3.01) with 30 mg on-demand, 1.68 (95% CI 1.23 to 2.30) with 60 mg daily and 1.98 (95% CI 1.58 to 2.48) with 60 mg on-demand (Analysis 4.1). The test for interaction was not significant (P = 0.85; I^2 = 0%).

4.2 Participant satisfaction with intercourse

We found three studies that administered dapoxetine at the following doses: 30 mg daily (McMahon 2010), 30 mg on-demand (Pryor 2006), 60 mg daily (McMahon 2010), and 60 mg on-demand (Kaufman 2009). The RR for participant satisfaction with intercourse defined as a rating of 'good' or 'very good' was 1.41 (95% CI 1.08 to 1.85) with 30 mg daily, 1.59 (95% CI 1.33 to 1.90) with 30 mg on-demand, 1.39 (95% CI 1.07 to 1.82) with 60 mg daily and 1.61 (95% CI 1.32 to 1.98) with 60 mg on-demand (Analysis 4.2). The test for interaction was not significant (P = 0.74; I^2 = 0%).

4.3 Study withdrawal due to adverse events

We found three studies that administered dapoxetine at the following doses: 30 mg daily (McMahon 2010), 30 mg on-demand (Buvat 2009; McMahon 2013; Pryor 2006), 60 mg daily (McMahon 2010; Safarinejad 2006b; Safarinejad 2008), and 60 mg on-demand (Buvat 2009; Kaufman 2009; Pryor 2006). The RR for study withdrawal due to adverse events was 3.03 (95% CI 0.37 to 25.01) with 30 mg daily, 2.44 (95% CI 1.06 to 5.59) with 30 mg on-demand, 8.76 (95% CI 2.10 to 36.49) with 60 mg daily and 6.51 (95% CI 3.64 to 11.66) with 60 mg on-demand (Analysis 4.3). The test for interaction was not significant (P = 0.22, I^2 = 33%).

4.4 Perceived control over ejaculation

We found three studies that administered dapoxetine at the following doses: 30 mg daily (McMahon 2010), 30 mg on-demand (Pryor 2006), 60 mg daily (McMahon 2010), and 60 mg on-demand (Kaufman 2009; Pryor 2006). The RR of participants' control over ejaculation defined as a rating of 'good' or 'very good' was 1.79 (95% CI 1.26 to 2.53) with 30 mg daily, 3.70 (95% CI 2.72 to 5.04) with 30 mg on-demand, 1.78 (95% CI 1.26 to 2.52) with 60 mg daily and 2.28 (95% CI 1.65 to 3.16) with 60 mg on-demand (Analysis 4.4). The test for interaction was significant (P = 0.004; I^2 = 77.2%).

4.5 Participant distress about premature ejaculation

We found one study that administered dapoxetine 60 mg on-demand (Kaufman 2009). The RR for PE-related distress defined as a rating of its severity of only 'a little bit' or 'not at all' was 1.54 (95% CI 1.26 to 1.88; Analysis 4.5). We could not test for subgroup differences.

4.6 Relationship difficulties

We found one study that administered dapoxetine 60 mg on-demand (Kaufman 2009). The RR for reducing relationship difficulties to only 'a little bit' or 'not at all' with this study was 1.20 (95% CI 1.07 to 1.34; Analysis 4.6). We could not test for subgroup differences.

4.7 Adverse events

We found five studies that administered dapoxetine at the following doses: 30 mg daily (McMahon 2010; McMahon 2013), 30 mg on-demand (Buvat 2009), 60 mg daily (McMahon 2010; Safarinejad 2006b; Safarinejad 2008), and 60 mg on-demand (Buvat 2009; Kaufman 2009). The RR for adverse events was 1.64 (95% CI 1.30 to 2.07) with 30 mg daily, 1.47 (95% CI 1.20 to 1.79) with 30 mg on-demand, 2.73 (95% CI 2.03 to 3.66) with 60 mg daily and 1.56 (95% CI 1.23 to 1.99) with 60 mg on-demand (Analysis 4.7). The test for interaction was significant (P = 0.006; I^2 = 76.2%).

4.8 Intravaginal ejaculatory latency time

We found four studies that administered dapoxetine as the following doses: 30 mg daily (McMahon 2010), 30 mg on-demand (Buvat 2009; McMahon 2013; Pryor 2006), 60 mg daily (McMahon 2010), and 60 mg on-demand (Buvat 2009; Pryor 2006). The MD for IELT was 1.80 (95% CI 1.27 to 2.33) with 30 mg daily, 1.37 (95% CI 0.86 to 1.89) with 30 mg on-demand, 1.50 (95% CI 0.98 to 2.02) with

60 mg daily and 1.53 (95% CI 1.09 to 1.97) with 60 mg on-demand (Analysis 4.8). The test for interaction was not significant (P = 0.71, I^2 = 0%).

4.9 Depression

We found no studies using dapoxetine that evaluated depression.

5 Different doses: fluoxetine

5.1 Participant perception of change with treatment

We found no studies using fluoxetine that evaluated participant perception of change with treatment.

5.2 Participant satisfaction with intercourse

We found no studies using fluoxetine that evaluated participant satisfaction with intercourse.

5.3 Study withdrawal due to adverse events

We found three studies that administered fluoxetine 20 mg daily (Kara 1996; Waldinger 1998; Yilmaz 1999). The RR for study withdrawal due to adverse events using this dose was 2.09 (95% CI 0.26 to 16.82; Analysis 5.1). We could not test for subgroup differences.

5.4 Perceived control over ejaculation

We found no studies using fluoxetine that evaluated perceived control over ejaculation.

5.5 Participant distress about premature ejaculation

We found no studies using fluoxetine that evaluated participant distress about PE.

5.6 Relationship difficulties

We found no studies using fluoxetine that evaluated relationship difficulties.

5.7 Adverse events

We found four studies that administered fluoxetine at the following doses: 20 mg daily (Kara 1996; Yilmaz 1999), 40 mg daily (Ahn 1996), and 90 mg daily (Mattos 2008). The RR for adverse events was 9.32 (95% CI 1.88 to 46.26) with 20 mg daily, 2.29 (95% CI 0.55 to 9.49) with 40 mg daily and 1.78 (95% CI 0.76 to 4.17) with 90 mg daily (Analysis 5.2). The test for interaction was not significant (P = 0.2; I^2 = 37.9%).

5.8 Intravaginal ejaculatory latency time

We found five studies that administered fluoxetine at the following doses: 20 mg daily (Kara 1996; Waldinger 1998; Yilmaz 1999), 40 mg daily (Ahn 1996), and 90 mg daily (Mattos 2008). The MD for IELT was 2.87 (95% CI 1.26 to 4.48) with 20 mg daily, −0.54 (95% CI −3.54 to 2.46) with 40 mg daily and 2.72 (95% CI 1.83 to 3.61) with 90 mg daily (Analysis 5.3). The test for interaction was not significant (P = 0.11, I^2 = 54.1%).

5.9 Depression

We found one study that administered fluoxetine 20 mg daily (Kara 1996). The RR for depression in this study was 2.00 (95% CI 0.23 to 17.34; Analysis 5.4). We could not test for subgroup differences.

DISCUSSION

Summary of main results

We included 31 RCTs with 8254 participants and found that compared to placebo, SSRI treatment for PE probably improves perception of change with treatment, satisfaction with intercourse, perceived control over ejaculation, participant distress about PE, relationship difficulties and IELT. However, the administration of SSRIs may increase study withdrawals due to adverse events and probably increases adverse events.

Overall completeness and applicability of evidence

- This review included 31 RCTs of 8254 participants with PE with diverse clinical characteristics that, therefore, likely reflect the population encountered in day-to-day clinical practice. They also included a range of SSRI drugs and dosing schedules utilized in the included trials.
- The review did not include any active comparators and, therefore, is unable to address how these drugs compare to other management approaches such as topical anesthetics, tramadol or α1-adrenoreceptor antagonists, which are recommended as treatment alternatives in the recent AUA guideline (Shindel 2020).
- A specific concern in the use of SSRI for depression is the potential risk of promoting suicidal ideation, although this remains an issue of controversy (Khan 2003; Sharma 2016). The reported adverse events and study withdrawals of the included studies did not provide a signal for this outcome, but we also recognize that the overall number of participants and the relatively short follow-up of these studies limit the ability to identify infrequent outcomes that might be associated with long-term use.

Quality of the evidence

We consistently downgraded the certainty of evidence by one or two steps to moderate or low. Our confidence in the estimates of effect were primarily limited by study limitations and heterogeneity. Most studies were classified at unclear or high risk of bias for multiple domains and, therefore, the potential biases in those studies introduced a degree of uncertainty in the calculated summary estimates.

Potential biases in the review process

- Despite a comprehensive search strategy without any publication or language restrictions, there is a possibility that we may have missed studies published in a language other than English, published in non-indexed journals or unpublished.
- There were fewer than 10 studies included for most outcomes and, therefore, we were unable to generate funnel plots thus possibly underestimating the risk of publication bias.
- We contacted authors of each of the studies for further information, but only one responded to these requests (Mattos 2008), and this may be a further source of bias.
- One author contributing several individual studies to this review, which were all at unclear risk of selective bias (as most included studies of this review) has had six studies on men's sexual health retracted due to alleged fraud (Retractionwatch 2015). Since none of the included studies were involved (Safarinejad 2006b; Safarinejad 2006c; Safarinejad 2007; Safarinejad 2008),

we included these studies in this review. However, it does underscore the issue of how important a priori trial registration is (Roberts 2015).

Agreements and disagreements with other studies or reviews

There is a limited number of reviews that have compared SSRIs with placebo for PE. In contrast to our review, which focused on outcome of direct patient importance, they typically used IELT as a primary outcome. Also, none applied the same methodologic rigor as we applied in this review.

- Castiglione 2016 assessed various pharmacologic interventions for PE using IELT as the primary outcome found that SSRIs prolonged IELT compared to placebo based on the 14 included trials.
- Zhang 2019 found that paroxetine was more effective than fluoxetine and escitalopram in delaying ejaculation. The review also found that paroxetine combined with tadalafil or behavior therapy was more effective than paroxetine alone. This is consistent with Sun 2017, which reported that the pooled effects of SSRIs were superior to placebo in prolonging IELT in men with PE but found that SSRI alone was inferior to combination treatment of SSRI and phosphodiesterase-5 inhibitors. However, there was no difference in IELT between paroxetine, tramadol, sertraline, phosphodiesterase 5 inhibitors, topical lidocaine gel, behavioral therapy or dapoxetine (Zhang 2019). These assessments were outside the scope of this review which focused on the comparison with placebo/no intervention.
- Again using IELT as the primary outcome, one network meta-analysis reported that a range of SSRI agents outperformed placebo (Jian 2018). However, this study reported that topical anesthetics or phosphodiesterase-5 inhibitors plus SSRIs were likely to be the most efficacious treatment strategies for PE.
- Another network meta-analysis of 44 studies including a range of pharmacologic agents for PE reported that dapoxetine was likely to be the most efficacious (Sridharan 2018). Similar to this review, Sridharan 2018 also found that dapoxetine, venlafaxine and fluoxetine all increased the incidence of adverse events.

Other relevant document are currently available guidelines on this topic. These use varying methodology when it comes not only to the framework of moving from evidence to recommendations but also to what extent these are supported by rigorous systematic reviews.

- The European Association for Urology (EAU) guidelines on ED, PE, penile curvature and priapism recommend pharmacotherapy as first-line therapy of lifelong PE (grade A) states that on-demand dapoxetine (as the only approved pharmacologic therapy for PE) or other off-label antidepressants such as daily SSRIs (Hatzimouratidis 2010). This report was supported by a literature search; then "… the panel reviewed and selected the articles with the highest evidence available." The EAU did not perform its own meta-analysis.
- The International Society of Sexual Medicine's Guidelines for the Diagnosis and Treatment of PE states that there is "robust evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of lifelong and acquired PE" and to "support the efficacy and safety of off-label daily dosing of the SSRIs paroxetine sertraline, citalopram, fluoxetine" (Althof 2014). These recommendations were supported by a comprehensive literature search and a consensus-based process.
- Guidelines of the AUA are the most recent; they are also the most methodologically rigorous supported by a systematic review conducted by the Pacific Northwest Evidence-based Practice Centre that was up-to-date up to March 2019 (Shindel 2020). This document makes a strong recommendation that "clinicians should recommend daily SSRIs; on-demand clomipramine or dapoxetine (where available) … as first-line pharmacotherapies in the treatment of PE." However, the guideline group did not conduct their meta-analysis or own update meta-analyses from previously published reviews systematic reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Compared to placebo, the administration of selective serotonin re-uptake inhibitors (SSRIs) for premature ejaculation (PE) may improve perception of change with treatment and satisfaction with intercourse. SSRIs may also improve perceived control over ejaculation and reduce both distress about PE and relationship difficulties. These potential benefits need to be weighed up against the possible increase in adverse events with SSRIs. Moreover, men should be counseled about the low certainty of evidence in this subject and, therefore, the possibility that the effects they experience from SSRI treatment for PE may be different to that shown in this review.

Implications for research

Considering the moderate- to low-certainty evidence for the patient-centered outcomes assessed in this review, future trials should be designed and conducted with higher methodologic standards so that we can have more certainty in the estimates. Future studies should also focus on patient-important outcomes such as perception of change with treatment, satisfaction with intercourse, perceived control over ejaculation, participant distress about PE and relationship difficulties, which only a limited number of trials included in this review measured. Additionally, it is important that the effectiveness of SSRIs is compared to other active treatments directly to characterize the most efficacious management option. Currently, we are mostly relying on indirect evidence when trying to choose between the available pharmacologic agents (Sridharan 2018).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahn 1996

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Department of Urology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea Dates study conducted: NR
Participants	Inclusion criteria: • Heterosexual sexually active men with PE • Age 18–75 years • PE defined as IELT ≤ 2 minutes after vaginal intromission in half of the intercourse Exclusion criteria: • ED • Alcohol and drug abuse • Physical illness • Use of psychoactive drugs Number of participants randomized: 23 Group 1 (fluoxetine) • Number of participants randomized: 12 • Age (mean): 39.8 (range 34–48) years Group 2 (placebo) • Number of participants randomized: 11 • Age (mean): 41.8 (range 31–61) years
Interventions	Group 1: fluoxetine 20 mg daily for first 1 week and 40 mg daily for remaining 5 weeks after breakfast Group 2: multivitamin as placebo daily
Outcomes	Primary outcomes: • IELT • How measured: NR • Time points measured: 0, 3, 6 weeks Safety outcomes: • Adverse effects • How measured: reported • Time points measured: anytime
Funding sources	NR
Declarations of interest	NR
Notes	

Ahn 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants and investigator were blinded for the randomization," "randomized placebo controlled trial."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Quote: "participants and investigator were blinded for the randomization," "randomized placebo controlled trial."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Quote: "investigator were blinded for the randomization."
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Unclear risk	Unpublished protocol/prespecified outcomes (intercourse frequency, libido) in method were not or were partially reported in the results.
Other bias	Low risk	No additional sources of bias identified.

Athanasios 2007

Study characteristics	
Methods	Study design: parallel-group, randomized controlled trial Setting/country: Urology Department, ELPIS Hospital, Volos, Greece Dates study conducted: NR
Participants	Inclusion criteria: • Married men diagnosed with PE Exclusion criteria: • ED • Severe physical illness • History of alcohol or any drug abuse

Athanasios 2007 *(Continued)*

	• Did not require psychotropic medication during the last 3 months. Number of participants randomized: 20 Study length: 12 months Group 1 (duloxetine): • Number of participants randomized: 10 • Age (mean): 31.35 (SD 8.23) years • Baseline IELT: 38.21 (16.45) seconds Group 2 (placebo): • Number of participants randomized: 10 • Age (mean): 32.65 (SD 7.49) years • Baseline IELT: 34.79 (18.35) seconds
Interventions	Group 1: duloxetine 20 mg daily for 1 week followed by 40 mg daily Group 2: placebo daily
Outcomes	Primary outcome: • IELT • How measured: using a chronometer • Time point measured: NR Secondary outcome: • CGI • How measured: CGI questionnaire at interview • Time points measured: 0, 2, 4, 6, 8, 10, 12 weeks Safety outcome: • Adverse effects • How measured: reported • Time points measured: anytime
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Did not explicitly state that personnel were blinded, only "double blind."

Athanasios 2007 *(Continued)*

Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants appeared to be appropriately blinded.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	No explicit description as to how these outcomes were assessed.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many participants were included in analyses.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Atmaca 2002

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Firat University, Elazig, Turkey Dates study conducted: NR
Participants	Inclusion criteria: • Married, heterosexual men with PE Exclusion criteria: • ED and inhibited male orgasm • Severe physical illness • History of alcohol and any substance abuse or dependence • Presence of any endocrinologic state • Treatment with any psychotropic medication within last 2 weeks Number of total participants randomized: 26 Group 1 (citalopram): • Number of participants randomized: 13 • Age (mean): 32.74 (SD 10.54) years • Baseline IELT: 33.46 (17.96) seconds Group 2 (placebo): • Number of participants randomized: 13 • Age (mean): 31.51 (SD 9.88) years

Atmaca 2002 *(Continued)*

	• Baseline IELT (mean): 30.38 (SD 14.64) seconds
Interventions	Group 1: citalopram 20 mg daily up to 60 mg Group 2: placebo daily
Outcomes	Primary outcome: • IELT • How measured: using a chronometer • Time points measured: 0, 2, 4, 6, 8 weeks Secondary outcomes: • CGI • How measured: CGI questionnaire • Time points measured: 2, 4, 6, 8 weeks Safety outcomes: • General sexual function • How measured: Yonsei Sexual Function Inventory-II questionnaire • Time point measured: NR Other outcomes: • Adverse events • How measured: reported
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Appropriate use of placebo. Quote: "In group II, the patients received initially identical one placebo tablet per day and placebo was titrated to three capsules according to the clinical response, with increase of one tablet in two weeks' period."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants appropriately blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	No blinding of outcome assessors explicitly described.

Atmaca 2002 *(Continued)*

Investigator-assessed outcomes		
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not explicit whether all participants included in final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Biri 1998

Study characteristics	
Methods	Study design: double blind, parallel-group, randomized controlled trial Setting/country: Department of Urology, Medical School of Gazi University, Ankara, Turkey Dates study conducted: January 1995 to April 1997
Participants	Inclusion criteria: • Normally potent men with PE • Married • Participants were assessed for concomitant neurologic or psychiatric disorders and for alcohol or drug abuse Exclusion criteria: • Not explicitly stated Total number of participants randomized: 37 Total length of study: 4 weeks Group 1 (sertraline): • Number of participants randomized: 22 • Age: NR • Baseline IELT (mean): 40.93 (SD 12.6) seconds Group 2 (placebo): • Number of participants randomized: 15 • Age: NR • Baseline IELT (mean): 43.53 (SD 20.2) seconds
Interventions	Group 1: sertraline 50 mg daily Group 2: placebo daily
Outcomes	Primary outcomes:

Biri 1998 *(Continued)*

- IELT
- How measured: using a clock with a second hand
- Time points measured: 0, 4 weeks

Safety outcomes:

- Adverse effects
- How measured: reported by participants
- Time points measured: anytime

Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not addressed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel appeared appropriately blinded. Quote: "double-blind treatment with sertraline or placebo."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants appeared to be blinded.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Blinding of outcome assessors not explicitly addressed.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all participants were included in final analyses.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Buvat 2009

Study characteristics	
Methods	Study design: parallel group, randomized controlled trial Setting/country: Centre ETPARP, Rue Carolus, Lille, France Dates study conducted: December 2004 to October 2006
Participants	Inclusion criteria: • Age ≥ 18 years in a stable monogamous relationship for 6 months • Met DSM-IV-TR criteria for PE for 6 months • At least moderate PE-related distress or interpersonal difficulty • IELT of 2 minutes in 75% of evaluable events during a 4-week screening/baseline period Exclusion criteria: • History of medical or psychiatric illness • Uncontrolled hypertension or cardiac impairment • Medical events associated with the onset of PE • ED (currently treated for ED or score < 21 on the Erectile Function Domain of the IIEF) • Other forms of sexual dysfunction • Partner sexual dysfunction • Known hypersensitivity to SSRIs or serotonin-norepinephrine reuptake inhibitors • Concomitant use of SSRIs, tricyclic antidepressants or other disallowed medications during the study • Receiving other forms of PE therapy (pharmacologic or behavioral) • Alcohol consumption limited to 2 drinks per day Total number of participants randomized: 1162 Total length of study: 24 weeks Group 1 (dapoxetine 30 mg): • Number of participants randomized: 388 • Age (mean): 39.6 (SD 9.53) years • Baseline IELT (mean): 0.9 (SD 0.50) minutes Group 2 (dapoxetine 60 mg): • Number of participants randomized: 389 • Age (mean): 40.5 (SD 9.62) years • Baseline IELT (mean): 0.9 (SD 0.49) minutes Group 3 (placebo): • Number of participants randomized: 385 • Age (mean): 40.1 (SD 9.98) years • Baseline IELT (mean): 0.9 (SD 0.51) minutes
Interventions	Group 1: dapoxetine 30 mg on-demand Group 2: dapoxetine 60 mg on-demand Group 3: placebo daily
Outcomes	Primary outcomes: • IELT

Buvat 2009 *(Continued)*

- How measured: using stopwatch held by partner
- Time points measured: 0, 4, 8, 12, 16, 20, 24 weeks

Secondary outcomes:

- PEP
- How measured: questionnaire using the PEP
- Time points measured: 0, 4, 8, 12, 16, 20, 24 weeks

Safety outcomes:

- Adverse effects and withdrawal symptoms
- How measured: Beck Depression Inventory, IIEF, Hamilton Anxiety Scale, Montgomery-Asberg Depression Rating Scale, Barnes Akathisia Rating Scales
- Time points measured: 4, 12, 24 weeks

Other outcomes:

- CGI
- How measured: questionnaire using the CGIC in PE
- Time points measured: 0, 4, 8, 12, 16, 20, 24 weeks

Funding sources	Johnson & Johnson Pharmaceutical Research & Development, LLC provided funding or other financial support and material support for this research or work that included the following: design and conduct of the study, management of the data, analysis, interpretation of the data, preparation, review, and approval of the manuscript.
Declarations of interest	Buvan and Giuliano are consultants or investigators (or both) for Johnson & Johnson Rivas, Rothamn and Tsfaye are employees of Johnson & Johnson.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Low risk	Allocation concealed. Quote: "computer-generated randomization schedule (assigned and coded using an interactive voice response system)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind; no information beyond that.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Unclear risk	Study described as double-blind; no information beyond that.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	No explicit blinding reported.

Buvat 2009 *(Continued)*

Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Large proportions of participants not included in the final analysis; > 20% per treatment arm.
Selective reporting (reporting bias)	Low risk	Protocol was provided (NCT00229073) and all outcomes were reported.
Other bias	Low risk	No additional sources of bias identified.

Farnia 2009

Study characteristics	
Methods	Study design: parallel group, randomized controlled trial Setting/country: Department of Psychiatry, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran Dates study conducted: May 2006 to June 2007
Participants	Inclusion criteria: • Married, heterosexual men with PE • Age 23–54 years Exclusion criteria: • Organic sexual dysfunction • ED and inhibited male orgasm • Severe physical or mental illness • History of alcohol and any substance abuse or dependence • Presence of any endocrinologic state • Use of psychotropic medications within last 2 weeks. Total number of participants randomized: 80 Total length of study: 4 weeks Group 1 (citalopram): • Number of participants randomized: 42 • Age (mean): 34.28 (SD 6.67) years • Baseline IELT (mean): 1.11 (SD 0.61) minutes Group 2 (placebo): • Number of participants randomized: 38 • Age (mean): 33.76 (SD 5.93) years • Baseline IELT (mean): 1.10 (SD 0.56) minutes
Interventions	Group 1: citalopram 20 mg 4 hours prior to sexual intercourse Group 2: placebo 4 hours prior to sexual intercourse

Farnia 2009 *(Continued)*

Outcomes	Primary outcomes: • IELT • How measured: using chronometer • Time point measured: 4 weeks Secondary outcomes: • Sexual function • How measured: Chinese Index of Premature Ejaculation • Time point measured: 4 weeks Other outcomes: • Study withdrawal due to adverse events • How measured: reported by participants • Time point measured: 4 weeks
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of allocation concealment not described.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided beyond "double-blind" design.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Unclear risk	No information provided beyond "double-blind" design.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Unclear whether outcome assessors blinded.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/49 (14.2%) in SSRI arm and 5/43 (11.6%) in placebo arm did not complete the trial.

Farnia 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Gameel 2013

Study characteristics	
Methods	Study design: single-blind, parallel-group randomized controlled trial Setting/country: Urology Department, Tanta University Hospitals, Tanta, Egypt Dates study conducted: November 2009 to January 2012
Participants	Inclusion criteria: • Men with PE for > 1 year and who had an IELT of < 2 minutes in > 75% of episodes of vaginal sexual intercourse over a 2-week period Exclusion criteria: • IIEF-5 score of < 22 • Unstable relationship with the partner • Drug abuse • Medical conditions such as diabetes mellitus, urogenital diseases, hepatic or renal impairments • Receiving medication for psychiatric problems Total number of participants randomized: 150 Total length of study: 4 weeks Group 1 (paroxetine): • Number of participants randomized: 30 • Age: NR • Baseline IELT (mean): 69.6 (SD 28.1) seconds Group 2 (placebo): • Number of participants randomized: 30 • Age: NR • Baseline IELT (mean): 61.3 (SD 30.5) seconds
Interventions	Group 1: paroxetine 20 mg on-demand + lubricating jelly Group 2: placebo on-demand + lubricating jelly
Outcomes	Primary outcomes: • IELT • How measured: reported • Time points measured: 0, 4 weeks Secondary outcomes: • Sexual satisfaction • How measured: participant-reported using sexual satisfaction scale (0–5)

Gameel 2013 *(Continued)*

- Time points measured: 0, 4 weeks

Safety outcomes:

- Adverse effects
- How measured: reported by participants
- Time point measured: 4 weeks

Funding sources	None
Declarations of interest	None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence created from "shuffling coded cards."
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel not blinded. Quote: "single blind study."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Appropriate use of placebo, participants likely blinded. Quote: "Group 5 was a placebo arm and received oral multivitamin pills 1–4 h before intercourse. To ensure that patients were unaware of the drug used, those receiving oral medication were also given local penile lubricating jelly before intercourse, whilst group 4 was also given oral multivitamin pills 1–4 h before intercourse."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	High risk	Assessors unlikely blinded. Quote: "single blind study."
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low proportion of missing data (28/30 (94%) in SSRI arm and 27/30 (90%) in placebo arm included in final analysis).
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Gong 2011

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Outpatient/Department of Urology, The affiliated hospital of Chuanbei Medical University, Nanchong, China Dates study conducted: NR
Participants	Inclusion criteria: • Met the PE diagnostic criteria • Had a fixed sexual partner • Sexual partners have a willingness to co-operate • No other complications Exclusion criteria: • NR Number of participants randomized: 80 Group 1 (paroxetine): • Number of participants randomized: 40 • Age (mean): 26.8 (SD 5.5) years • Baseline IELT (mean): 0.89 (SD 0.21) minutes Group 2 (placebo): • Number of participants randomized: 40 • Age (mean): 29.2 (SD 6.7) years • Baseline IELT (mean): 0.97 (SD 0.18) minutes
Interventions	Group 1: paroxetine 20 mg daily orally Group 2: oral soda tablets as a placebo
Outcomes	Primary outcomes: • IELT/sexual satisfaction • How measured: stopwatch/sexual intercourse satisfaction score quantified as 1–10 points (1 = very dissatisfied, 10 = very satisfied) • Time points measured: at baseline, 30 days Safety outcomes: • NR
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Gong 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not explicitly stated whether personnel were blinded; participants appeared to be blinded.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants likely blinded through the use of placebo.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were followed up for 6 to 10 weeks."
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Hamidi Madani 2016

Study characteristics	
Methods	Study design: double-blind, placebo-controlled randomized trial Setting/country: Department of Urology, Guilan University of Medical Sciences Rasht, Iran Dates study conducted: NR
Participants	Inclusion criteria: • Men with PE Exclusion criteria: • NR Total number of participants randomized: 150 Total length of study: 12 weeks Group 1 (tramadol):

Hamidi Madani 2016 *(Continued)*

- Number of participants randomized: NR
- Age: NR
- Baseline IELT: NR

Group 2 (paroxetine):

- Number of participants randomized: NR
- Age: NR
- Baseline IELT: NR

Group 3 (placebo):

- Number of participants randomized: NR
- Age: NR
- Baseline IELT: NR

Interventions	Group 1: tramadol 50 mg Group 2: paroxetine 20 mg Group 3: placebo
Outcomes	Primary outcomes: • IELT • How measured: IELT questionnaire • Time points measured: 0, 12 weeks Other outcomes: • PEP • How measured: PEP questionnaire • Time points measured: 0, 12 weeks
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only; insufficient information to judge domain.
Allocation concealment (selection bias)	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Unclear risk	Abstract only; insufficient information to judge domain.

Hamidi Madani 2016 *(Continued)*

Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to judge domain.
Other bias	Unclear risk	Abstract only; insufficient information to judge domain.

Kara 1996

Study characteristics	
Methods	Study design: double-blind, placebo-controlled, parallel-group trial Setting/country: Department of Psychiatry and Urology Yuzunku Yil University, Van, Turkey Dates study conducted: NR
Participants	Inclusion criteria: • Men with PE as defined by the DSM-IV Exclusion criteria: • ED • Inhibited orgasms • History of alcohol or substance abuse • Mental retardation Total number of participants randomized: 14 Total length of study: 4 weeks Group 1 (fluoxetine): • Number of participants randomized: 7 • Age: range 15–50 years • Baseline IELT (mean): 25 (SD 12.6) seconds Group 2 (placebo): • Number of participants randomized: 7 • Age: range 15–50 years • Baseline IELT (mean): 30 (SD 8.6) seconds
Interventions	Group 1: fluoxetine 20 mg daily for 1 week and fluoxetine 40 mg afterwards

Kara 1996 *(Continued)*

	Group 2: placebo 1 tablet at breakfast daily for week and 2 tablets afterwards
Outcomes	Primary outcomes: • IELT • How measured: using chronometer • Time points measured: 0, 4 weeks Other outcomes: • Adverse effects • How measured: reported by participants • Time points measured: every week
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not addressed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants may be blinded but blinding of personnel was not described.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants likely blinded appropriately.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	7/9 participants in fluoxetine arm and 7/8 participants in placebo arm included in final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Kaufman 2009

Study characteristics	
Methods	Study design: blind, randomized controlled, parallel-group trial Setting/country: multi-institutional Aurora, USA Dates study conducted: November 2009 to January 2012
Participants	Inclusion criteria: • Age ≥ 18 years; in a stable monogamous, heterosexual relationship for ≥ 6 months; expected to maintain the relationship for the duration of the study • Met DSM-IV-TR criteria for PE, to have had PE for ≥ 6 months and to have reported at least 'moderate' distress or interpersonal difficulty related to their PE at baseline. The DSM-IV-TR criteria required an ejaculatory latency before, upon or shortly after penetration; a threshold IELT was not an inclusion criterion Exclusion criteria: • Presence of a serious condition that affected overall physical or mental health status • Previous event or condition associated with PE (such as spinal trauma or pelvic surgery) • Presence of another sexual dysfunction in the man (such as ED) or his partner • Known allergy to SSRIs • History of drug abuse within past 2 years • Alcohol consumption > 2 drinks per day Total number of participants randomized: 736 Total length of study: 9 weeks Group 1 (dapoxetine): • Number of participants randomized: 491 • Age (mean): 41.8 (SD 9.80) years • Baseline IELT: NR Group 2 (placebo): • Number of participants randomized: 245 • Age (mean): 40.98 (SD 9.71) years • Baseline IELT: NR
Interventions	Group 1: dapoxetine 60 mg on-demand Group 2: placebo on-demand
Outcomes	Primary outcomes: • Perceived control over ejaculation • How measured: PEP questionnaire • Time points measured: days 28, 63 and study end Secondary outcomes: • Satisfaction with sexual intercourse • How measured: PEP questionnaire • Time point measured: NR

Kaufman 2009 *(Continued)*

Safety outcomes:

- Adverse effects
- How measured: reported by participants
- Time points measured: anytime and each visit

Other outcomes:

- Personal distress related to ejaculation
- How measured: PEP questionnaire
- Time points measured: days 0, 28, 63 and study end

Other outcomes:

- Interpersonal difficulty related to ejaculation
- How measured: PEP questionnaire
- Time points measured: days 0, 28, 63 and study end

Other outcomes:

- Change in PE
- How measured: participant-reported global impression of change in PE questionnaire
- Time points measured: days 28, 63 and study end

Funding sources	Funded by Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ
Declarations of interest	Funded by Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ, USA. Drs Mudumbi, Tesfaye and Rivas are employees of Johnson & Johnson; Dr Hashmonay was an employee of Johnson & Johnson at the time of the study. Dr Kaufman is an investigator for Johnson & Johnson. Dr Rosen is an investigator/consultant for Johnson & Johnson.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriately blinded. Quote: "dosing carried out in a double-blind, double-dummy fashion."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants likely to be appropriately blinded. Quote: "dosing carried out in a double-blind, double-dummy fashion."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described who was assessing adverse effects.

Kaufman 2009 *(Continued)*

Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large numbers excluded from analysis and not even lost to follow-up between groups (60/491 in dapoxetine arm and 24/245 in placebo arm were excluded).
Selective reporting (reporting bias)	High risk	Data on participants receiving dapoxetine 60 mg daily NR.
Other bias	Low risk	No additional sources of bias identified.

Khelaia 2012

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: National Center of Urology, Department of Urology Tbilisi, Georgia Dates study conducted: NR
Participants	Inclusion criteria: • Not specified Exclusion criteria: • No libido • Poor responders to behavioral strategies and topical agents Total number of participants randomized: 78 Total length of study: 4 weeks Group 1 (paroxetine 20 mg): • Number of participants randomized: 26 • Age (mean): 22.7 (SD 19–39) years • Baseline IELT: NR Group 2 (paroxetine 20 mg 2–3 hours before intercourse): • Number of participants randomized: 28 • Age (mean): 22.7 (SD 19–39) years • Baseline IELT: NR Group 3 (placebo): • Number of participants randomized: 24 • Age (mean): 22.7 (SD 19–39) years • Baseline IELT: NR
Interventions	Group 1: paroxetine 20 mg Group 2: paroxetine 20 mg 2–3 hours before intercourse

Khelaia 2012 *(Continued)*

	Group 3: placebo
Outcomes	Primary outcomes: • IELT • How measured: NR • Time points measured: 0, 4 weeks Secondary outcomes: • Intercourse satisfaction • How measured: using an unspecified scale • Time points measured: 0, 4 weeks Secondary outcomes: • Overall satisfaction • How measured: using the IIEF Questionnaire • Time points measured: 0, 4 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: NR
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only; insufficient information to judge domain.
Allocation concealment (selection bias)	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Blinding of outcome assessment (detection bias)	Low risk	Objective measurement that was unlikely to be influenced by blinding.

Khelaia 2012 *(Continued)*
IELT

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only; insufficient information to judge domain.
Selective reporting (reporting bias)	Unclear risk	Abstract only; insufficient information to judge domain.
Other bias	Unclear risk	Abstract only; insufficient information to judge domain.

Kim 1998

Study characteristics	
Methods	Study design: cross-over randomized controlled trial Setting/country: College of Medicine, Chung-Ang University, Seoul, Korea Dates study conducted: NR
Participants	Inclusion criteria: • Men with PE defined as IELT < 2 minutes that occurred in > 50% of sexual intercourse • Married or living with a female sexual partner for ≥ 1 year and possible sexual intercourse at least once per week. Exclusion criteria: • Presence of major psychiatric disorders • Concurrent ED • Urethritis or chronic prostatitis • Presence of significant mental illness • History of alcoholism or other substance abuse • Use of any drug that may affect sexual function Total number of participants randomized: 37 Total length of study: 16 weeks total (4 weeks each intervention) Group 1 (fluoxetine): • Number of participants randomized: 37 • Age (mean): 44 (range 30–60) years • Baseline IELT (mean): 46 (SD 41) seconds Group 2 (sertraline): • Number of participants randomized: 37 • Age (mean): 44 (range 30–60) years • Baseline IELT (mean): 46 (SD 41) seconds (Note that the comparison in this study was the placebo cross-over period)
Interventions	Group 1: fluoxetine 40 mg daily for 1 week then 80 mg for 3 weeks Group 2: sertraline 100 mg for 1 week then 200 mg for 3 weeks

Kim 1998 *(Continued)*

Outcomes	Primary outcomes: • IELT • How measured: reported by participants • Time points measured: every 4 weeks Secondary outcomes: • Sexual satisfaction score of participant and partner • How measured: self-reported questionnaire • Time points measured: every 4 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: every 4 weeks (after each washout period)
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described whether order of treatment was randomized.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Title stated "double-blind" and described medication being identical but did not explicitly state that personnel were blinded.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants likely blinded appropriately. Quote: "capsules were identical."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	16/53 participants did not complete the study and no details provided on when or why they dropped out.

Kim 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Mattos 2008

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Universidade de Sao Paulo, Institute of Urology, Sao Paulo, Brazil Dates study conducted: NR
Participants	Inclusion criteria: • Age 24–59 years with a clinical diagnosis of lifelong PE according to the DSM-IV criteria • IELT ≤ 90 seconds, without previous treatments • A score at the IIEF-Erectile Function domain ≥ 26 • In a stable relationship with the same partner for previous ≥ 6 months Exclusion criteria: • Diabetes • Contraindication to the use of any medication involved in study • Abuse of alcohol or use of illicit narcotics Total number of participants randomized: 60 Total length of study: 12 weeks Group 1 (fluoxetine): • Number of participants randomized: 15 • Age (mean): 50 (SD 8.51) years • Baseline IELT (mean): 56.55 (SD 18.55) seconds Group 2 (placebo): • Number of participants randomized: 15 • Age (mean): 45.93 (SD 9.96) years • Baseline IELT (mean): 49.86 (SD 18.53) seconds Group 3 (fluoxetine + tadalafil): • Number of participants randomized: 15 • Age (mean): 42.81 (SD 7.73) years • Baseline IELT (mean): 49.57 (SD 25.57) seconds Group 4 (placebo + tadalafil): • Number of participants randomized: 15 • Age (mean): 43.2 (SD 11.3) years • Baseline IELT (mean): 49.26 (SD 19.43) seconds
Interventions	Group 1: fluoxetine 90 mg daily

Mattos 2008 *(Continued)*

	Group 2: placebo daily Group 3: fluoxetine 90 mg daily + tadalafil 20 mg on-demand Group 4: placebo + tadalafil 20 mg on-demand
Outcomes	Primary outcomes: • IELT • How measured: wrist stopwatch measured by participant • Time points measured: every 3 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: anytime
Funding sources	None
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "four groups were randomly distributed…chosen blindly from one envelope with numbers and another envelope with colors designating a treatment."
Allocation concealment (selection bias)	Low risk	Quote: "…were concealed by a third party that blinded the placebo and active capsules to the investigator and patients alike."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Appropriate blinding. Quote: "neither the investigator nor the patient knew which treatment was being used."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Quote: "… were concealed by a third party that blinded the placebo and active capsules to the investigator and patients alike."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described who was assessing adverse effects.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomized were included.

Mattos 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No source identified.

McMahon 1998

Study characteristics	
Methods	Study design: randomized controlled, cross-over study Setting/country: St. Luke's Hospital, Sydney, Australia Dates study conducted: NR
Participants	Inclusion criteria: • Age ≥ 18 years • In a stable, monogamous heterosexual relationship for ≥ 6 months • Planning to maintain this relationship for the duration of the study • PE according to DSM-IV-TR criteria for PE for ≥ 6 months prior to enrolment and had a baseline IELT ≤ 2 minutes in ≥ 75% of a minimum of 4 evaluable sexual intercourse events during a treatment-free 4-week baseline period, and reported at least "moderate" ejaculation-related personal distress or interpersonal difficulty Exclusion criteria: • History of medical or psychiatric illness, including uncontrolled hypertension, hyperprolactinemia or untreated hypothyroidism • History of medical events that were associated with the onset of PE • Sexual dysfunction in either partner except PE in the man (including history of ED based on an IIEF Erectile Function domain score < 21 at screening) • History of HIV, HBsAg or hepatitis C (except for people from Korea, inactive HBsAg carriers with normal liver function tests were allowed into the trial) • Concomitant use of SSRIs or tricyclic antidepressants • Known hypersensitivity to SSRIs or serotonin-norepinephrine reuptake inhibitors Total number of participants randomized: 37 Total length of study: 12 weeks Group 1 (sertraline): • Number of participants randomized: 19 • Age (mean): 41 (range 19–70) years • Baseline IELT (mean): 0.3 minutes Group 2 (placebo): • Number of participants randomized: 18 • Age (mean): 41 (range 19–70) years • Baseline IELT (mean): 0.3 minutes
Interventions	Group 1: sertraline 50 mg Group 2: placebo daily

McMahon 1998 *(Continued)*

Outcomes	Primary outcomes: • IELT • How measured: using a stopwatch by partner • Time points measured: every week for 12 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: anytime
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blind;" "placebo tablets were identical to the active drug." Likely participants were blinded but personnel were not blinded
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Single blind. Likely participants were blinded. Quote: "placebo were identical to the active drug."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	High risk	Assessors unlikely blinded. Quote: "single blind study."
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants that were randomized appeared to be included in final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

McMahon 1999

Study characteristics	
Methods	Study design: controlled, single-blind, cross-over study Setting/country: St. Luke's Hospital, Sydney, Australia Dates study conducted: NR
Participants	Inclusion criteria: • Age ≥ 18 years • In a stable, monogamous heterosexual relationship for ≥ 6 months • Planning to maintain this relationship for the duration of the study • PE according to DSM-IV-TR criteria for PE for ≥ 6 months prior to enrolment and had a baseline IELT ≤ 2 minutes or in ≥ 75% of a minimum of 4 evaluable sexual intercourse events during a treatment-free 4-week baseline period, and reported at least "moderate" ejaculation-related personal distress or interpersonal difficulty Exclusion criteria: • History of medical or psychiatric illness, including uncontrolled hypertension, hyperprolactinemia or untreated hypothyroidism • History of medical events that were associated with the onset of PE • Sexual dysfunction in either partner except PE in the man (including a history of ED based on an IIEF Erectile Function domain score < 21 at screening) • History of HIV, HBsAg or hepatitis C (except for people from Korea, inactive HBsAg carriers with normal liver function tests were allowed into the trial) • Concomitant use of SSRIs or tricyclic antidepressants • Known hypersensitivity to SSRIs or serotonin-norepinephrine reuptake inhibitors Length of study: 17 weeks **Study 1:** Total number of participants randomized: 26 Number of participants with primary ejaculation: 19 Number of participants with secondary ejaculation: 7 Group 1 (paroxetine 20 mg): • Age (mean): 39.5 years • Baseline IELT (mean): 0.3 minutes Group 2 (paroxetine as needed 3–4 hours before planned sexual intercourse): • Age (mean): 39.5 years • Baseline IELT (mean): 0.3 minutes **Study 2:** Total number of participants randomized in study 2: 42 Number of participants with primary ejaculation: 32 Number of participants with secondary ejaculation: 10 Group 3 (paroxetine 10 mg for 3 weeks then 20 mg paroxetine as needed for 4 weeks): • Age (mean): 40.5 years

McMahon 1999 *(Continued)*

	• Baseline IELT (mean): 0.5 minutes Group 4 (placebo daily for 3 weeks then placebo daily for 4 weeks): • Age (mean): 40.5 years • Baseline IELT (mean): 0.5 minutes
Interventions	Group 1: paroxetine 20 mg Group 2: paroxetine as needed 3–4 hours before planned sexual intercourse Group 3: paroxetine 10 mg for 3 weeks then 20 mg paroxetine as needed for 4 weeks Group 4: placebo daily for 3 weeks then placebo daily for 4 weeks
Outcomes	Primary outcomes: • IELT • How measured: using a stopwatch by partners • Time points measured: every week for 12 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: anytime
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blind;" "placebo were identical to the active drug." Likely participants were blinded but personnel were not blinded.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Single blind. Likely participants were blinded. Quote: "placebo tablets were identical to the active drug."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	High risk	Assessors unlikely blinded. Quote: "single blind study."
Blinding of outcome assessment (detection bias)	Low risk	Objective measurement that was unlikely to be influenced by blinding.

McMahon 1999 *(Continued)*
IELT

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who were randomized appeared to be included in final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

McMahon 2010

Study characteristics	
Methods	Study design: blinded, randomized controlled, parallel-group trial Setting/country: multicenter in Asia Pacific Dates study conducted: March 2005 to June 2006
Participants	Inclusion criteria: • Age ≥ 18 years • In a stable, monogamous heterosexual relationship for ≥ 6 months • Planning to maintain this relationship for the duration of the study • PE according to DSM-IV-TR criteria for PE for ≥ 6 months prior to enrolment and had a baseline IELT ≤ 2 minutes in ≥ 75% of a minimum of 4 evaluable sexual intercourse events during a treatment-free 4-week baseline period, and reported at least "moderate" ejaculation-related personal distress or interpersonal difficulty Exclusion criteria: • History of medical or psychiatric illness, including uncontrolled hypertension, hyperprolactinemia or untreated hypothyroidism • History of medical events that were associated with the onset of PE • Sexual dysfunction in either partner except PE in the man (including a history of ED based on an IIEF Erectile Function domain score < 21 at screening) • History of HIV, HBsAg or hepatitis C (except for people from Korea, inactive HBsAg carriers with normal liver function tests were allowed into the trial) • Concomitant use of SSRIs or tricyclic antidepressants • Known hypersensitivity to SSRIs or serotonin-norepinephrine reuptake inhibitors Total number of participants randomized: 1067 Total length of study: 12 weeks Group 1 (dapoxetine 30 mg): • Number of participants randomized: 354 • Age (mean): 41.2 (SD 10.74) years • Baseline IELT (mean): 3.9 minutes • Number of participants with primary PE: 92 (42.2%) Group 2 (dapoxetine 60 mg): • Number of participants randomized: 356 • Age (mean): 41.0 (SD 10.78) years

McMahon 2010 *(Continued)*

	• Baseline IELT (mean): 4.2 minutes • Number of participants with primary PE: 92 (42.2%) Group 3 (placebo): • Number of participants randomized: 357 • Age (mean): 40.6 (SD 9.71) years • Baseline IELT (mean): 2.4 minutes • Number of participants with primary PE: 96 (45.9%)
Interventions	Group 1: dapoxetine 30 mg on-demand Group 2: dapoxetine 60 mg on-demand Group 3: placebo on-demand
Outcomes	Primary outcomes: • IELT • How measured: by female partner using a stopwatch • Time points measured: 0, 4, 8, 12 weeks Secondary outcomes: • Participant-reported outcome measures • How measured: CGIC in PE and PEP questionnaires • Time points measured: every 4 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: anytime
Funding sources	Study funded by Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ, USA.
Declarations of interest	Dr McMahon is a consultant/investigator for Johnson & Johnson. Drs Kim, Park and Chang are investigators for Johnson & Johnson. Drs Rivas, Tesfaye, Rothman and Aquilina are employees of Johnson & Johnson.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind; no further information.
Blinding of outcome assessment (detection bias)	Low risk	Likely appropriate blinding, "double-blind" and placebo was used.

McMahon 2010 *(Continued)*

Participant-reported outcomes		
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	62/395 (17%) in placebo, 70/354 (20%) in dapoxetine 30 mg, 77/356 (22%) in dapoxetine 60 mg were not included in the analysis.
Selective reporting (reporting bias)	Low risk	As reported in protocol in ClinicalTrials.gov.
Other bias	Low risk	No additional sources of bias identified.

McMahon 2013

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Berry Road Medical Center, the Leonards, Australia Dates study conducted: April 2010 to August 2011
Participants	Inclusion criteria: • Age ≥ 18 years • In a stable, monogamous heterosexual relationship for ≥ 6 months • Planning to maintain this relationship for the duration of the study • PE according to DSM-IV-TR criteria for PE for ≥ 6 months prior to enrolment and had a baseline IELT ≤ 2 minutes in ≥ 75% of a minimum of 4 evaluable sexual intercourse events during a treatment-free 4-week baseline period, and reported at least "moderate" ejaculation-related personal distress or interpersonal difficulty Exclusion criteria: • History of medical or psychiatric illness, including uncontrolled hypertension, hyperprolactinemia or untreated hypothyroidism • History of medical events that were associated with the onset of PE • Sexual dysfunction in either partner except PE in the man (including a history of ED based on IIEF Erectile Function domain score < 21 at screening) • History of HIV, HBsAg or hepatitis C (except for people from Korea, inactive HBsAg carriers with normal liver function tests were allowed into the trial) • Concomitant use of SSRIs or tricyclic antidepressants • Known hypersensitivity to SSRIs or serotonin-norepinephrine reuptake inhibitors Total number of participants randomized: 495 Total length of study: 18 weeks Group 1 (dapoxetine):

McMahon 2013 *(Continued)*

- Number of participants randomized: 250
- Age (mean): 49.5 (SD 11.23) years
- Baseline IELT: NR
- Number of participants with primary PE: 92 (42.2%)

Group 2 (placebo):

- Number of participants randomized: 245
- Age (mean): 47.9 (11.96) years
- Baseline IELT: NR
- Number of participants with primary PE: 96 (45.9%)

Interventions	Group 1: dapoxetine 30 mg on-demand, from week 4 up to 60 mg if tolerated + PDE5 inhibitor taken 1–3 hours prior to sexual intercourse Group 2: placebo daily + PDE5 inhibitor taken 1–3 hours prior to intercourse
Outcomes	Primary outcomes: • IELT • How measured: by female partner using a stopwatch • Time points measured: 0, 4, 8, 12 weeks Secondary outcomes: • Participant-reported outcome measures • How measured: CGIC in PE and PEP questionnaires • Time points measured: every 4 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: anytime
Funding sources	Janssen Research & Development, LLC funded this study (R096769PRE3008) and provided formal review of the article.
Declarations of interest	Janssen Research & Development, LLC funded this study (R096769PRE3008) and provided formal review of the article. Bradford Challis, PhD, an employee of the company, provided writing assistance for the manuscript.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization relied on a computer-generated random sequence and an interactive voice response system."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization relied on a computer-generated random sequence and an interactive voice response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only the IDMC statistician was unblinded to the treatment assignments at the interim analysis." Therefore, can assume that participants, investigators and personnel were blinded.

McMahon 2013 *(Continued)*

Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriately blinded. Quote: "subjects were instructed to administer study drug (dapoxetine or matching placebo)."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Quote: "Only the IDMC statistician was unblinded to the treatment assignments at the interim analysis." Therefore, can assume that investigators and personnel were blinded.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large number of discontinuations and not balanced between groups (29/250 in dapoxetine arm and 37/245 in placebo arm).
Selective reporting (reporting bias)	Low risk	As reported in protocol in ClinicalTrials.gov.
Other bias	Low risk	No additional sources of bias identified.

Mendels 1995

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Philadelphia Medical Institute, USA Dates study conducted: NR
Participants	Inclusion criteria: • Heterosexual men • Only 1 sexual partner in the past 6 months • Involuntary ejaculation during foreplay or within 1 minute of intercourse in > 50% of times Exclusion criteria: • Using psychotropic medications • Clinically significant depression • Medical disease or symptomatology • Receiving therapy for sexual dysfunction • Consuming alcohol Total number of participants randomized: 52 Total length of study: 10 weeks Group 1 (sertraline): • Number of participants randomized: 26 • Age: NR • Baseline IELT (mean): 0.98 (SD 1.15) minutes

Mendels 1995 *(Continued)*

	Group 2 (placebo): • Number of participants randomized: 26 • Age: NR • Baseline IELT (mean): 1.10 (SD 1.35) minutes
Interventions	Group 1: sertraline 50 mg daily that could be titrated up to 200 mg daily Group 2: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: NR • Time points measured: 1–4, 6, 8, 19 Secondary outcomes: • CGIC in PE • How measured: CGIC in PE questionnaire • Time points measured: 0, 4, 8 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: anytime Other outcomes: • Depression • How measured: Hamilton Depression Rating Scale • Time point measured: 8 weeks
Funding sources	None
Declarations of interest	Pfizer involved but not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely blinded appropriately as study was "double blind" and patients received "matching placebo."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriately blinded. Quote: "patients were provided with bottles containing 50mg sertraline tablets or matching placebo."

Mendels 1995 *(Continued)*

Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy analysis; 3/26 (11.5%) in sertraline arm and 2/26 (7.6%) in placebo arm were not included in the efficacy analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Quote: "sertraline patients had a longer previous Hx of premature ejaculation" (baseline imbalance), and "1 week single blind washout period," which may both exaggerate treatment effect.

Na 1996

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Outpatient/Department of Urology, Korea University College of Medicine, Seoul, South Korea Dates study conducted: NR
Participants	Inclusion criteria: • Healthy men age ≥ 20 years, IELT ≤ 1 minute (over 50% of intercourse) Exclusion criteria: • NR Number of participants randomized: 40 Group 1 (sertraline): • Number of participants randomized: 20 • Age: NR • Baseline IELT: NR Group 2 (placebo): • Number of participants randomized: 20 • Age: NR • Baseline IELT: NR
Interventions	Group 1: sertraline 50 mg at night that could be titrated up to 100 mg daily Group 2: digestive medicine with same manner of intervention
Outcomes	Primary outcomes:

Na 1996 *(Continued)*

- IELT/penile rigidity/vaginal penetration
- How measured: stopwatch/NR/NR
- Time points measured: at baseline, 3, 6 weeks

Safety outcomes:

- Adverse effects
- How measured: NR
- Time point measured: likely cumulative

Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind; no further information.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Unclear risk	No information.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	No information.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	12/20 in sertraline arm and 8/20 participants in placebo arm were included in analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available and review outcomes were not clearly defined in method section.
Other bias	Low risk	No additional sources of bias identified.

Novaretti 2002

Study characteristics	
Methods	Study design: cross-over RCT Setting/country: University of São Paulo (USP), São Paulo, SP, Brazil Dates study conducted: June 1998 to January 2000
Participants	Inclusion criteria: • NR Exclusion criteria: • ED • Taking antidepressant medication • No fixed partner or irregular sexual intercourse. Total number of participants randomized: 55 Total length of study: 20 weeks Group 1 (fluoxetine): • Number of participants randomized: NR • Age (mean): 37.4 (SD 10.7) years • Baseline IELT (mean): 60.6 (SD 51.83) seconds Group 2 (placebo): • Number of participants randomized: NR • Age (mean): 37.4 (SD 10.7) years • Baseline IELT (mean): 62.7 (SD 64.12) seconds
Interventions	Group 1: fluoxetine 20 mg daily Group 2: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: partner with a clock marking seconds • Time points measured: weekly Secondary outcomes: • Satisfaction level • How measured: questionnaire • Time points measured: every sexual activity Safety outcomes: • Adverse effects • How measured: reported by participants • Time point measured: NR Other outcomes: • Anxiety • How measured: Hamilton Anxiety Scale • Time points measured: start and end of study

Novaretti 2002 *(Continued)*

	Other outcomes: • Depression • How measured: Beck Depression Index • Time points measured: start and end of study
Funding sources	FARMASA laboratory provided the fluoxetine and the placebo.
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	The code (the letter corresponding to the fluoxetine or the letter corresponding to the placebo) was kept in a sealed envelope until the completion of data collection from all participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the researcher and the patients did not know who was taking the active drug and who was taking the placebo."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Quote: "Both the researcher and the patients did not know who was taking the active drug and who was taking the placebo."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Quote: "Both the researcher and the patients did not know who was taking the active drug and who was taking the placebo."
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Pryor 2006

Study characteristics

Methods	Study design: blinded, randomized controlled, parallel-group trial

Pryor 2006 *(Continued)*

	Setting/country: multi-institution, Dapoxetine Study Group in DE&MN, USA Dates study conducted: June 2003 to June 2004
Participants	Inclusion criteria: • Men with PE who were more severely affected with the condition than the general population of men self-identifying with symptoms of PE in surveys • Age > 18 years and in a stable sexual relationship with a female partner for ≥ 6 months • Men had to meet the diagnostic criteria for PE as specified in the DSM-IV-TR: onset of orgasm • Participant and partner must agree to attempt sexual intercourse at minimum intervals specified in the protocol • Participant's partner must have had a negative urine pregnancy test at time of screening Exclusion criteria: • Severity of PE was further assessed by patients' responses to the statement: "I consider the severity of my rapid ejaculation problem to be (none, mild, moderate, severe)." • Men who regarded themselves as having no or mild PE • ED or other forms of sexual dysfunction • Concomitant use of SSRIs or tricyclic antidepressants • History of major psychiatric disorder • Use of other forms of therapy for PE (pharmacologic or behavioral) • Men whose partners had problems with self-reported female sexual dysfunction • No known allergy or hypersensitivity to dapoxetine or other SSRIs • No partners with decreased interest in or painful intercourse or other forms of sexual dysfunction Total number of participants randomized: NR Total length of study: 12 weeks Group 1 (dapoxetine 30 mg): • Number of participants randomized: 870 • Age (mean): 40.3 (SD 9.10) years • Baseline IELT (mean): 0.90 (SD 0.47) minutes • Number of participants with primary PE: 563 • Number of participants with secondary PE: 227 Group 2 (dapoxetine 60 mg): • Number of participants randomized: 874 • Age (mean): 40.9 (SD 9.09) years • Baseline IELT (mean): 0.92 (SD 0.50) minutes • Number of participants with primary PE: 571 • Number of participants with secondary PE: 234 Group 3 (placebo): • Number of participants randomized: 870 • Age (mean): 40.3 (SD 9.55) years • Baseline IELT (mean): 0.91 (SD 0.48) minutes • Number of participants with primary PE: 560 • Number of participants with secondary PE: 248
Interventions	Group 1: dapoxetine 30 mg on-demand 1–3 hours before anticipated sexual activity Group 2: dapoxetine 60 mg on-demand 1–3 hours before anticipated sexual activity

Pryor 2006 *(Continued)*

	Group 3: placebo on-demand 1–3 hours before anticipated sexual activity
Outcomes	Primary outcomes: • IELT • How measured: using a stopwatch • Time points measured: 0, 4, 8, 12 weeks Secondary outcomes: • Participant satisfaction with sexual intercourse • How measured: participant-reported scale (0–5) • Time points measured: 0, 4, 8, 12 weeks Other outcomes: • Participant perception of control over ejaculation • How measured: participant-reported scale (0–5) • Time points measured: 0, 4, 8, 12 weeks Other outcomes: • Partner satisfaction with sexual intercourse • How measured: participant-reported scale (0–5) • Time points measured: 0, 4, 8, 12 weeks Other outcomes: • Participant rating of severity of PE • How measured: participant-reported scale (0–5) • Time points measured: 0, 4, 8, 12 weeks Other outcomes: • Adverse events • How measured: participant reported • Time points measured: anytime
Funding sources	NR
Declarations of interest	SE Althof, RC Rosen, WJG Hellstrom and R Shabsigh have served as consultants for Johnson & Johnson. R Shabsigh has also received grant/research support from Johnson & Johnson. M Miloslavsky and S Kell are employees of ALZA Corporation. JL Pryor and C Steidle have served on advisory boards for ALZA Corporation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned within each stratum 1:1:1 by a computerised interactive voice recognition system."
Allocation concealment (selection bias)	Low risk	Randomly assigned within each stratum 1:1:1 by a computerized interactive voice recognition system.
Blinding of participants and personnel (performance bias)	Low risk	Probably double blind.

Pryor 2006 *(Continued)*

All outcomes		Quote: "tablets in all groups were identical in appearance;" "Investigator assessed adverse event severity."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Tablets in all groups were identical in appearance.
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Investigator assessed adverse event severity.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that is unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All analyses were done on an intention-to-treat basis." All participants were included in the analysis.
Selective reporting (reporting bias)	Low risk	As reported in protocol in ClinicalTrials.gov.
Other bias	Low risk	No clear source identified.

Safarinejad 2006b

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: single institute, Tehran, Iran Dates study conducted: March 2003 to April 2005
Participants	Inclusion criteria: • Married men with PE defined as IELT < 2 minutes that occurred in > 90% of sexual intercourse. None of the participants had received other treatment for PE for ≥ 4 weeks before the start of study • No other sexual disorders • In a stable relationship with their wives for the previous ≥ 6 months and possible sexual intercourse ≥ 1 per week • Did not use condoms or topical anesthetics. They were also instructed not to pause during intercourse or to have interrupted intromission • No obvious organic cause of PE, possible sexual intercourse ≥ 1 per week, and initiation of the participant to seek medical help for what they considered PE Exclusion criteria: • ED according to IIEF • Reduced sexual desire • Inhibited male orgasm • Chronic psychiatric or physical illness • Alcohol or substance abuse • Use of medication such as psychotropic medication

Safarinejad 2006b *(Continued)*

- Organic cause of PE including anatomical abnormalities, genital infection and neurologic disorder; organic illness causing limitation in SSRI use
- Serious relationship problems

Total number of participants randomized: 340

Total length of study: 12 weeks

Group 1 (dapoxetine):

- Number of participants randomized: 115
- Age (mean): 33.4 (range 20–50) years
- Baseline IELT (mean): 38 seconds
- Number of participants with primary PE: 64/104 (61.5%)

Group 2 (paroxetine):

- Number of participants randomized: 113
- Age (mean): 34.6 (range 21–49) years
- Baseline IELT (mean): 31 seconds
- Number of participants with primary PE: 63/105 (60.0%)

Group 3 (placebo):

- Number of participants randomized: 112
- Age (mean): 34.3 (range 21–50) years
- Baseline IELT (mean): 34 seconds
- Number of participants with primary PE: 11/25 (44.0%)

Interventions	Group 1: dapoxetine 60 mg daily Group 2: paroxetine 20 mg daily Group 3: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: using a stopwatch • Time points measured: every 2 weeks Secondary outcomes: • Sexual satisfaction • How measured: 0–5 scale proposed by Kim and Paick • Time points measured: every 2 weeks Safety outcomes: • Adverse effects • How measured: reported by participants • Time points measured: every 2 weeks and end of the treatment
Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Safarinejad 2006b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Likely random Quote: "a randomization table generated by the method of randomly permuted blocks."
Allocation concealment (selection bias)	Low risk	Quote: "Each eligible patient was given a randomization number using an interactive voice response system … Persons who geographically and operationally were independent from the study investigator did the randomization of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriate. Quote: "Treatment was administered in a randomized sequence that remained unknown to the patient and to the physician."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriate blinding as participants received a placebo. Quote: "Active drugs and placebo were identical in color and size."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Adverse effects were evaluated by investigator that was likely blinded appropriately. Quote: "For the analysis of efficacy and safety, all patients were evaluated in each visit by the author" and an individual "independent from the study investigator did the randomization of the study."
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of participants excluded from each arm (10/115 in dapoxetine arm, 11/113 in paroxetine arm and 10/112 in placebo arm, including 3 in dapoxetine arm vs 2 in paroxetine vs 6 in placebo arm excluded for lack of efficacy).
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Safarinejad 2006c

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: University of Medical Sciences, Tehran, Iran Dates study conducted: NR
Participants	Inclusion criteria: • Married men with PE defined as IELT < 2 minutes that occurred in > 90% of sexual intercourse. None of the participants had received other treatment for PE for ≥ 4 weeks before the start of study • No other sexual disorders

Safarinejad 2006c *(Continued)*

- In a stable relationship with their wives for the previous ≥ 6 months and possible sexual intercourse ≥ 1 per week
- Did not use condoms or topical anesthetics. They were also instructed not to pause during intercourse or to have interrupted intromission
- No obvious organic cause of PE, possible sexual intercourse ≥ 1 per week and initiation of the participant to seek medical help for what they considered PE.

Exclusion criteria:

- ED according to IIEF
- Reduced sexual desire
- Inhibited male orgasm
- Chronic psychiatric or physical illness
- Alcohol or substance abuse
- Use of medication such as psychotropic medication
- Organic cause of PE including anatomical abnormalities, genital infection and neurologic disorder; organic illness causing limitation in SSRI use
- Serious relationship problems

Total number of participants randomized: 58

Total length of study: 6 months

Group 1 (citalopram):

- Number of participants randomized: 29
- Age (mean): 32 (range 21–49) years
- Baseline IELT (mean): 0.53 minutes
- Number of participants with primary PE: 10
- Number of participants with secondary PE: 16

Group 2 (placebo):

- Number of participants randomized: 29
- Age (mean): 34 (range 21–49) years
- Baseline IELT (mean): 0.47 minutes
- Number of participants with primary PE: 11
- Number of participants with secondary PE: 14

Interventions	Group 1: citalopram 20 mg daily Group 2: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: NR • Time points measured: every 2 weeks for 12 weeks, 3 and 6 months Secondary outcomes: • Sexual satisfaction • How measured: 0–5 scale proposed by Kim and Paick • Time points measured: every 2 weeks for 12 weeks, 3 and 6 months Secondary outcomes: • IIEF • How measured: IIEF Questionnaire

Safarinejad 2006c *(Continued)*

- Time points measured: every 2 weeks for 12 weeks, 3 and 6 months

Safety outcomes:

- Adverse effects
- How measured: reported by participants
- Time points measured: each visit

Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was determined by a computer-generated schedule."
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriate blinding. Quote: "Treatment was administered in a randomized sequence that remained unknown to the patient and to the physicians."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriate blinding. Quote: "Treatment was administered in a randomized sequence that remained unknown to the patient and to the physicians."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that is unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/29 (10.3%) in citalopram arm and 4/39 (13.7%) in placebo arm were not included.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Safarinejad 2007

Study characteristics

Safarinejad 2007 *(Continued)*

Methods	Study design: randomized controlled, parallel-group trial Setting/country: single institute, Tehran, Iran Dates study conducted: March 2003 to April 2005
Participants	Inclusion criteria: • Married men with PE defined as IELT < 2 minutes that occurred in > 90% of sexual intercourse. None of the participants had received other treatment for PE for ≥ 4 weeks before the start of the study • No other sexual disorders • In a stable relationship with their wives for previous ≥ 6 months and possible sexual intercourse ≥ 1 per week • Did not use condoms or topical anesthetics. They were also instructed not to pause during intercourse or to have interrupted intromission • No obvious organic cause of PE, possible sexual intercourse ≥ 1 per week, and initiation of the participant to seek medical help for what they considered PE. Exclusion criteria: • ED according to IIEF • Reduced sexual desire • Inhibited male orgasm • Chronic psychiatric or physical illness • Alcohol or substance abuse • Use of medication such as psychotropic medication • Organic cause of PE including anatomical abnormalities, genital infection and neurologic disorder; organic illness causing limitation in SSRI use • Serious relationship problems Total number of participants randomized: 276 Total length of study: 12 weeks Group 1 (escitalopram): • Number of participants randomized: 138 • Age (mean): 33.5 (range 21–44) years • Baseline IELT: NR • Number of participants with primary PE: 87/128 (70%) Group 2 (placebo): • Number of participants randomized: 138 • Age (mean): 33.3 (range 19–46) years • Baseline IELT: NR • Number of participants with primary PE: 88/126 (69.8%)
Interventions	Group 1: escitalopram 10 mg daily Group 2: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: using a stopwatch • Time points measured: every 2 weeks Secondary outcomes:

Safarinejad 2007 *(Continued)*

- Sexual satisfaction
- How measured: 0–5 scale proposed by Kim and Paick
- Time points measured: every 2 weeks

Safety outcomes:

- Adverse effects
- How measured: reported by participants
- Time points measured: every 2 weeks

Funding sources	None
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a randomization table generated by the method of random permuted block. Patient randomization numbers were allocated to each site in ascending sequence in blocks."
Allocation concealment (selection bias)	Low risk	Quote: "Assignment to treatment group was performed using an interactive voice response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriate blinding. Quote: "Group 2 received a similar regimen of placebo. Placebo and escitalopram tablets were identical in appearance, allowing for blinding of treatment assignment." Randomization was done by an individual separate from the single investigator who assessed each participant.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriate blinding. Quote: "Group 2 received a similar regimen of placebo. Placebo and escitalopram tablets were identical in appearance, allowing for blinding of treatment assignment."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Low risk	Single investigator who was likely blinded interviewed participants at each visit.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/138 in the escitalopram arm and 12/138 in the placebo arm excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Safarinejad 2008

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: single institute, Tehran, Iran Dates study conducted: February 2004 to March 2006
Participants	Inclusion criteria: • Married men with PE defined as IELT < 2 minutes that occurred in > 90% of sexual intercourse. None of the participants had received other treatment for PE for ≥ 4 weeks before the start of the study • No other sexual disorders • In a stable relationship with their wives for previous ≥ 6 months and possible sexual intercourse ≥ 1 per week • Did not use condoms or topical anesthetics. They were also instructed not to pause during intercourse or to have interrupted intromission • No obvious organic cause of PE, possible sexual intercourse ≥ 1 per week and initiation of the participant to seek medical help for what they considered PE. Exclusion criteria: • ED according to IIEF • Reduced sexual desire • Inhibited male orgasm • Chronic psychiatric or physical illness • Alcohol or substance abuse • Use of medication like including psychotropic medication • Organic cause of PE including anatomical abnormalities, genital infection and neurologic disorder; organic illness causing limitation in SSRI use • Serious relationship problems Total number of participants randomized: 212 Total length of study: 12 weeks Group 1 (dapoxetine): • Number of participants randomized: 106 • Age (mean): 35.7 (range 21–54) years • Baseline IELT (mean): 22 seconds • Number of participants with primary PE: 40 (37.7%) Group 2 (placebo): • Number of participants randomized: 106 • Age (mean): 36.3 (range 19–56) years • Baseline IELT (mean): 29 seconds • Number of participants with primary PE: 43 (40.6%)
Interventions	Group 1: dapoxetine 30 mg twice daily Group 2: placebo daily
Outcomes	Primary outcomes: • IELT

Safarinejad 2008 *(Continued)*

- How measured: using a stopwatch
- Time points measured: every 2 weeks

Secondary outcomes:

- Sexual satisfaction
- How measured: 0–5 scale proposed by Kim and Paick
- Time points measured: every 2 weeks

Safety outcomes:

- Adverse effects
- How measured: reported by participants
- Time points measured: every 2 weeks and at end of treatment

Funding sources	None
Declarations of interest	None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Likely random. Quote: "randomization table generated by the method of random permuted blocks."
Allocation concealment (selection bias)	Low risk	Quote: "interactive voice response system … Persons who geographically and operationally were independent from the study investigator did the randomization of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriately blinded. Quote: "Treatment was administered in a randomized sequence that remained unknown to the patient and to the physician."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriately blinded. Quote: "Treatment was administered in a randomized sequence that remained unknown to the patient."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that is unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13/106 (12.2%) in dapoxetine arm and 10/106 (9.4%) in placebo arm excluded from final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Safarinejad 2008 *(Continued)*

Other bias	Low risk	No additional sources of bias identified.

Shang 2012

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: multi-institution, China Dates study conducted: May 2011 to May 2012
Participants	Inclusion criteria: • Age 20–50 years • Matches with PE diagnostic criteria • Disease duration > 3 months • Signed informed consent Exclusion criteria: • IELT > 2 minutes • Genitourinary system has inflammation, such as prostatitis, urethritis, epididymitis, seminal vesiculitis, etc • Heart, liver, kidney and nervous system and other primary diseases • ED • Alcohol, drugs or psychotropic substance abuse • Serious relationship problems • Taking other treatments for PE drugs during treatment • Did not take the medicine on time, halfway out, irregular sexual life, loss of contact and loss of follow-up • Psychotherapy or behavioral therapy is not allowed during the study period or within 3 months prior to the screening visit • Participants who had participated in investigative studies have also been excluded • Treatment with certain prescription or non-prescription medications (including any psychoactive drugs) Number of participants randomized: 80 Group 1 (citalopram 20 mg daily): • Number of participants randomized: 40 • Age (mean): 39.1 (SD 2.5) years • Baseline IELT (mean): 0.91 (SD 0.18) minutes Group 2 (placebo): • Number of participants randomized: 40 • Age (mean): 37.8 (SD 2.8) years • Baseline IELT (mean): 0.95 (SD 0.17) minutes
Interventions	Group 1: paroxetine 20 mg daily orally Group 2: soda tablets as a placebo orally
Outcomes	Primary outcomes:

Shang 2012 *(Continued)*

- IELT/sexual satisfaction
- How measured: stopwatch/sexual intercourse satisfaction score quantified as 1–10 points (1 = very dissatisfied, 10 = very satisfied)
- Time points measured: at baseline, 2 and 4 weeks

Safety outcomes:

- Heart, liver and kidney function
- How measured: blood and urine test
- Time points measured: at baseline, 4 weeks

Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Did not explicitly state whether investigators were blinded; participants appeared to be blinded.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Participants appeared to be appropriately blinded. Quote: "In the control group, oral placebo medication is the same colour and size as treatment group containing starch complexes."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Tuncel 2008

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Third Department of Urology, Ministry of Health, Ankara Numune Research and Training Hospital, Ankara, Turkey Dates study conducted: NR
Participants	Inclusion criteria: • Men with PE defined according to the International Classification of Diseases of the World Health Organization – Version 10 as the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction • Married men or had been in a stable relationship with a female sexual partner for ≥ 12 months. Exclusion criteria: • ED according to the first 5 questions of the IIEF (score < 21) • Alcohol and drug abuse • Mental retardation • Low libido • Orthostatic hypotension • Thyroid disease • Previous use of any drugs for PE • Recent history of myocardial infarction, uncontrolled diabetes mellitus • History of major depression including other psychiatric or psychological illness • History of organic illness causing limitations in selective SSRIs use • Presence of organic disorders such as prostatitis or genital tract infection. Total number of participants randomized: 90 Total length of study: 8 weeks Group 1 (sertraline): • Number of participants randomized: 20 • Age (median): 36.9 (SD 6.9) years • Baseline IELT: NR Group 2 (placebo): • Number of participants randomized: 22 • Age (median): 34.9 (SD 9.0) years • Baseline IELT: NR
Interventions	Group 1: sertraline 50 mg nightly for 2 months Group 2: placebo daily
Outcomes	Primary outcomes: • Perceived control over ejaculation • How measured: reported by participants • Time point measured: NR Safety outcomes: • Adverse effects

Tuncel 2008 *(Continued)*

- How measured: reported by participants
- Time points measured: anytime

Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel not blinded. Quote: "single blind study."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriate blinding with use of placebo. Quote: "Group 1 (n = 22 took placebo)"
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	High risk	Assessors unlikely blinded. Quote: "single blind study."
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who were randomized appeared to be included in final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Waldinger 1994

Study characteristics	
Methods	Study design: randomized controlled, parallel-group trial Setting/country: Department of Psychiatry and Neurosexology, Leyenburg Hospital, The Hague, The Netherlands

Waldinger 1994 *(Continued)*

	Dates study conducted: NR
Participants	Inclusion criteria: • Heterosexual men age 18–75 years who experience PE • In a steady sexual relationship with a female partner who was able to participate in the study Exclusion criteria: • ED • Inhibited male orgasm • Alcohol and substance abuse • Mental disorders • Physical illnesses • Use of medication including psychoactive medication Total number of participants randomized: 17 Total length of study: 6 weeks Group 1 (paroxetine): • Number of participants randomized: 8 • Age (mean): 41 (range 27–48) years • Baseline IELT: NR • Number of participants with primary PE: 7/8 (87.5%) Group 2 (placebo): • Number of participants randomized: 9 • Age (mean): 38 (range 30–47) years • Baseline IELT: NR • Number of participants with primary PE: 7/9 (77.7%)
Interventions	Group 1: paroxetine 20 mg daily for 1 week and then 40 mg daily from week 2–6 Group 2: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: NR • Time points measured: 0, 3, 6 weeks Secondary outcomes: • Psychopathology • How measured: SCL-90 questionnaire • Time points measured: 0, 3, 6 weeks Safety outcomes: • Adverse effects • How measured: reported by participants using a questionnaire • Time points measured: 0, 3, 6 weeks
Funding sources	NR
Declarations of interest	NR

Waldinger 1994 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriate blinding. Quote: "capsules [treatment and placebo] were identical."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Use of placebo and participants likely appropriately blinded. Quote: "capsules were identical."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants from paroxetine arm (2/8 (25%)), 1 participant from placebo arm (1/9 (10.1%)) were dropped out.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

Waldinger 1998

Study characteristics

Methods	Study design: randomized controlled, parallel-group trial Setting/country: Department of Psychiatry and Neurosexology, Leyenburg Hospital, The Hague, The Netherlands Dates study conducted: NR
Participants	Inclusion criteria: • Heterosexual men age 18–75 years who experienced PE • In a steady sexual relationship with a female partner who was able to participate in the study Exclusion criteria:

Waldinger 1998 *(Continued)*

- ED
- Inhibited male orgasm
- Alcohol and substance abuse
- Mental disorders
- Physical illnesses
- Use of medication including psychoactive medications

Total number of participants randomized: 60

Total length of study: 6 weeks

Group 1 (fluoxetine):

- Number of participants randomized: 12
- Age (mean): 38 (SD 7) years
- Baseline IELT (mean): 18 (SD 13) seconds

Group 2 (fluvoxamine):

- Number of participants randomized: 12
- Age (mean): 44 (SD 10) years
- Baseline IELT (mean): 18 (SD 13) seconds

Group 3 (paroxetine):

- Number of participants randomized: 12
- Age (mean): 41 (SD 8) years
- Baseline IELT (mean): 18 (SD 13) seconds

Group 4 (sertraline):

- Number of participants randomized: 12
- Age (mean): 40 (SD 9) years
- Baseline IELT (mean): 18 (SD 13) seconds

Group 5 (placebo):

- Number of participants randomized: 12
- Age (mean): 45 (SD 4) years
- Baseline IELT (mean): 18 (SD 13) seconds

Interventions	Group 1: fluoxetine 20 mg daily Group 2: fluvoxamine 100 mg daily Group 3: paroxetine 20 mg daily Group 4: sertraline 50 mg daily Group 5: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: by using stopwatch • Time points measured: 0, 3, 6 weeks Secondary outcomes: • Sexual desire • How measured: questionnaire, designed by the investigators

Waldinger 1998 *(Continued)*

- Time points measured: 0, 6 weeks

Safety outcomes:

- Adverse effects
- How measured: Udvalg for Kliniske Undersøgelser Adverse Effect questionnaire
- Time points measured: on day before treatment and at weekly intervals at home during the 6 weeks of study

Other outcomes:

- Psychopathology
- How measured: SCL-90 questionnaire
- Time points measured: 0, 3, 6 weeks

Funding sources	Solvay Pharmaceuticals
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "standard random number generator."
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely appropriate blinding. Quote: "capsules [treatment and placebo] were identical."
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriately blinded. Quote: "patients in the first study were randomly assigned, in a double-blind manner, to receive either fluoxetine 20 mg/day, fluvoxamine 100 mg/day, paroxetine 20 mg/day, sertraline 50 mg/day, or placebo in the form of 2 identical capsules per day given in a single morning dose."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described who was assessing adverse effects.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large proportion of participants excluded from final analysis (9/60) with no ITT performed.
Selective reporting (reporting bias)	High risk	No protocol available and adverse effects outcome was only partially reported in the results.

Waldinger 1998 *(Continued)*

Other bias	Low risk	No additional sources of bias identified.

Yilmaz 1999

Study characteristics	
Methods	Study design: blinded, randomized controlled, parallel-group trial Setting/country: Department of Urology and Neurology, Erciyes University Medical Faculty, Gevher Nesiber Research and Training Hospital, Kayseri, Turkey Dates study conducted: January 1997 to November 1997
Participants	Inclusion criteria: • Not clearly described: men with PE (defined as uncontrolled occurrence of ejaculation just before or in the first few minutes of vaginal penetration) Exclusion criteria: • Impotence • Excessive alcohol intake or drug abuse • Presence of psychopathology, mental retardation or organic disorder Total number of participants randomized: 40 Total length of study: 1 month Group 1 (fluoxetine): • Number of participants randomized: 20 • Age (mean): 36.5 (range 22–56) years • Baseline IELT (mean): 1.2 (SD 1.0) minutes Group 2 (placebo): • Number of participants randomized: 20 • Age (mean): 37.3 (range 24–58) years • Baseline IELT (mean): 1.1 (SD 1.1) minutes
Interventions	Group 1: fluoxetine 20 mg daily Group 2: placebo daily
Outcomes	Primary outcomes: • IELT • How measured: by participant according to participant choice • Time points measured: 0, 4 weeks Secondary outcomes: • Penile sensory threshold • How measured: using ring electrode and electromyography machine • Time points measured: 0, 4 weeks Safety outcomes: • Adverse effects

Yilmaz 1999 *(Continued)*

- How measured: reported by participants
- Time points measured: anytime

Other outcomes:

- Cortical sensory threshold
- How measured: using ring electrode and electromyography machine
- Time points measured: 0, 4 weeks

Other outcomes:

- Sacral-evoked response test
- How measured: using ring electrode and electromyography machine
- Time points measured: 0, 4 weeks

Funding sources	NR
Declarations of interest	NR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as "double blind," but not clear whether personnel who interviewed participants at the end regarding adverse effects were blinded.
Blinding of outcome assessment (detection bias) Participant-reported outcomes	Low risk	Likely appropriately blinded. Quote: "control group received placebo."
Blinding of outcome assessment (detection bias) Investigator-assessed outcomes	Unclear risk	Not explicitly described.
Blinding of outcome assessment (detection bias) IELT	Low risk	Objective measurement that was unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants included in the final analysis was not clearly described.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No additional sources of bias identified.

CGI: Clinical Global Impression; CGIC: Clinical Global Impression of Change; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; ED: erectile dysfunction; HBsAg: hepatitis B surface antigen; IELT: intravaginal ejaculatory latency time; IIEF: International Index of Erectile Function; ITT: intention to treat; NR: not reported; PDE5: phosphodiesterase-5; PE: premature ejaculation; PEP: Premature Ejaculation Profile; SCL-90: Symptom Checklist-90; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdel-Hamid 2001	Wrong intervention
Abdollahian 2006	Wrong patient population
Abu El-Hamd 2018	Multivitamin used instead of placebo.
Akgul 2008	No placebo control arm
Alghobary 2010	No placebo control arm
Althof 2010b	Duplicate
Alza 2006	Duplicate
Arafa 2006	Wrong outcomes
Arafa 2007b	No placebo control arm
Boulos 2015	No placebo control arm
Brock 2009	Wrong study design
Catalán 2002	Wrong study design
Chen 2016	Wrong comparator
Crenshaw 1992	Unable to obtain full text article
Culba 2008	Wrong intervention
Dhikav 2007	Wrong comparator
Eltonsi 2017	Wrong setting
Ghaffar 2010	Unable to obtain full text article
Giammusso 1997	Wrong comparator
Giammusso 1997a	No placebo control arm
Guo 2016	Wrong comparator
Hosseini 2007	Wrong intervention
Khazaie 2015	Wrong patient population
Khelaia 2012a	Duplicate

Study	Reason for exclusion
Kilic 2005	Wrong intervention
Kim 2018a	Wrong intervention
Kirecci 2014	Wrong outcomes
Kirecci 2014a	Wrong outcomes
Lee 2013	Wrong intervention
Li 2015	Wrong comparator
Li 2015a	Wrong intervention
Luigi 2012	Wrong comparator
Manasia 2003	No placebo control arm
Mathers 2009	No placebo control arm
McMahon 2002	Wrong study design
McMahon 2007	Commentary
McMahon 2010a	Duplicate
McMahon 2010b	Duplicate
McMahon 2016	Wrong study design
Mostafa 2017	Wrong comparator
Murat 1999	No placebo control arm
Nada 2009	Duplicate
Nada 2012	Only SSRI vs SSRI; protocol stated SSRI vs placebo.
Okulu 2013	Wrong outcomes
Otunctemur 2014	Only SSRI vs SSRI; protocol stated SSRI vs placebo.
Ozcan 2015	No placebo control arm
Pastore 2011	Wrong comparator
Pastore 2012	Wrong comparator
Polat 2015	Wrong comparator
Rezakhaniha 2010	No placebo control arm
Rezakhaniha 2014	Wrong patient population
Rivera 2005	Wrong study design

Study	Reason for exclusion
Safarinejad 2008a	Wrong intervention
Sahin 2016	Wrong comparator
Sahin 2016a	Wrong comparator
Salokangas 2006	Commentary
Sanzovo 2011	Wrong comparator
Schmidt 2001	Wrong setting
Shang 2010	No placebo control arm
Shao 2008	Wrong comparator
Shin 2017	Wrong study design
Sun 2004	No placebo control arm
Sun 2007	Wrong comparator
Sun 2010	Wrong comparator
Sunay 2011	Wrong comparator
Swartz 1994	Wrong study design
Vella 2015	Wrong comparator
Waldinger 1997	Only SSRI vs SSRI; protocol stated SSRI vs placebo.
Waldinger 2000	Wrong comparator
Waldinger 2001	No placebo control arm
Waldinger 2001a	No placebo control arm
Waldinger 2001b	Wrong comparator
Waldinger 2003	Wrong comparator
Waldinger 2004b	No placebo control arm
Waldinger 2006b	Commentary
Weixing 2012	No placebo control arm
Xu 2014	Wrong comparator
Yang 2015	No placebo control arm
Yang 2016	No placebo control arm
Yang 2017	Only SSRI vs SSRI; protocol stated SSRI vs placebo.

Study	Reason for exclusion
Yang 2017a	No placebo control arm
Yuan 2008	Wrong comparator
Zhang 2005	Wrong comparator
Zhu 2015	Wrong comparator

SSRI: selective serotonin reuptake inhibitor.

Characteristics of studies awaiting classification *[ordered by study ID]*

Kolomazník 2002

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	Awaiting translation of full text into English

DATA AND ANALYSES

Comparison 1. SSRI versus placebo

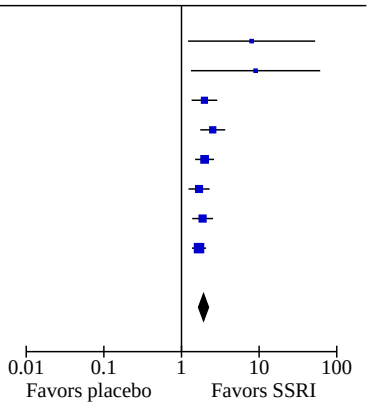
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Participant perception of change with treatment	6	3260	Risk Ratio (M-H, Random, 95% CI)	1.92 [1.66, 2.23]
1.2 Participant satisfaction with intercourse	3	4273	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.42, 1.87]
1.3 Study withdrawal due to adverse events	20	7367	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.61, 5.51]
1.4 Perceived control over ejaculation	3	4273	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.72, 3.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Participant distress about PE	1	652	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.26, 1.88]
1.6 Relationship difficulties	1	652	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.07, 1.34]
1.7 Adverse events	17	4624	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.48, 1.99]
1.8 Intravaginal ejaculatory latency time	20	5872	Mean Difference (IV, Random, 95% CI)	3.09 [1.94, 4.25]
1.9 Depression	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]

Analysis 1.1. Comparison 1: SSRI versus placebo, Outcome 1: Participant perception of change with treatment

	SSRI		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Athanasios 2007	8	10	1	10	0.6%	8.00 [1.21 , 52.69]	
Atmaca 2002	9	13	1	13	0.6%	9.00 [1.32 , 61.24]	
Buvat 2009	110	359	27	174	11.6%	1.97 [1.35 , 2.89]	
Buvat 2009	138	352	27	174	12.1%	2.53 [1.74 , 3.66]	
Kaufman 2009	178	431	46	221	18.1%	1.98 [1.50 , 2.63]	
McMahon 2010	123	329	38	171	15.5%	1.68 [1.23 , 2.30]	
McMahon 2010	140	337	38	171	15.9%	1.87 [1.37 , 2.54]	
McMahon 2013	139	250	81	245	25.6%	1.68 [1.36 , 2.07]	
Total (95% CI)		**2081**		**1179**	**100.0%**	**1.92 [1.66 , 2.23]**	
Total events:	845		259				

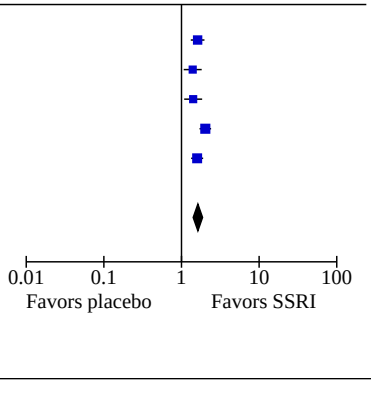
Heterogeneity: Tau² = 0.01; Chi² = 9.27, df = 7 (P = 0.23); I² = 24%
Test for overall effect: Z = 8.75 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: SSRI versus placebo, Outcome 2: Participant satisfaction with intercourse

	SSRI		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Kaufman 2009	236	431	75	221	21.0%	1.61 [1.32 , 1.98]	
McMahon 2010	137	336	50	171	15.8%	1.39 [1.07 , 1.82]	
McMahon 2010	136	329	50	171	15.8%	1.41 [1.08 , 1.85]	
Pryor 2006	454	870	112	435	24.1%	2.03 [1.71 , 2.41]	
Pryor 2006	358	874	112	435	23.4%	1.59 [1.33 , 1.90]	
Total (95% CI)		**2840**		**1433**	**100.0%**	**1.63 [1.42 , 1.87]**	
Total events:	1321		399				

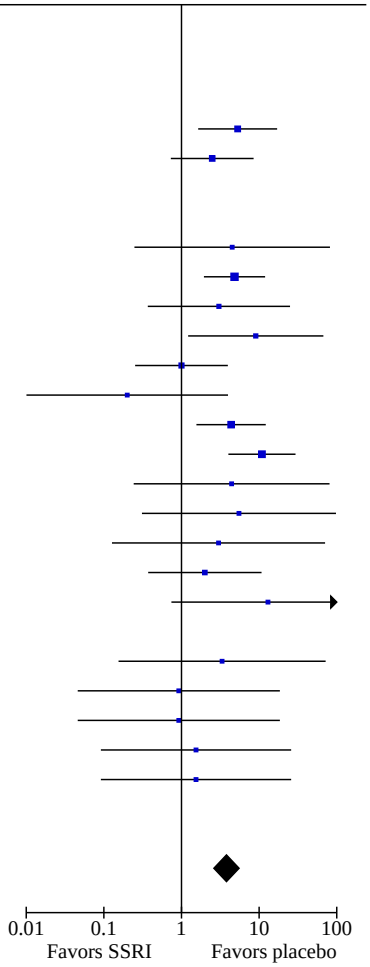
Heterogeneity: Tau² = 0.01; Chi² = 8.54, df = 4 (P = 0.07); I² = 53%
Test for overall effect: Z = 6.90 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: SSRI versus placebo, Outcome 3: Study withdrawal due to adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Athanasios 2007	0	10	0	10		Not estimable
Atmaca 2002	0	13	0	13		Not estimable
Biri 1998	0	22	0	15		Not estimable
Buvat 2009	32	389	3	193	10.1%	5.29 [1.64 , 17.06]
Buvat 2009	15	388	3	193	9.2%	2.49 [0.73 , 8.49]
Gameel 2013	0	28	0	27		Not estimable
Gong 2011	0	40	0	40		Not estimable
Kara 1996	2	9	0	8	1.7%	4.50 [0.25 , 81.76]
Kaufman 2009	47	431	5	221	16.9%	4.82 [1.94 , 11.95]
McMahon 2010	6	354	1	179	3.1%	3.03 [0.37 , 25.01]
McMahon 2010	18	356	1	179	3.5%	9.05 [1.22 , 67.25]
McMahon 2013	4	250	4	250	7.4%	1.00 [0.25 , 3.95]
Mendels 1995	0	26	2	26	1.6%	0.20 [0.01 , 3.97]
Pryor 2006	35	874	4	435	13.2%	4.35 [1.56 , 12.17]
Pryor 2006	87	870	4	435	14.0%	10.88 [4.02 , 29.43]
Safarinejad 2006b	4	115	0	56	1.6%	4.42 [0.24 , 80.74]
Safarinejad 2006b	5	113	0	56	1.7%	5.50 [0.31 , 97.74]
Safarinejad 2006c	1	29	0	29	1.4%	3.00 [0.13 , 70.74]
Safarinejad 2007	4	138	2	138	4.9%	2.00 [0.37 , 10.74]
Safarinejad 2008	6	106	0	106	1.7%	13.00 [0.74 , 227.89]
Shang 2012	0	40	0	40		Not estimable
Waldinger 1994	1	8	0	9	1.5%	3.33 [0.15 , 71.90]
Waldinger 1998	1	12	0	3	1.5%	0.92 [0.05 , 18.50]
Waldinger 1998	1	12	0	3	1.5%	0.92 [0.05 , 18.50]
Waldinger 1998	2	12	0	3	1.7%	1.54 [0.09 , 25.86]
Waldinger 1998	2	12	0	3	1.7%	1.54 [0.09 , 25.86]
Yilmaz 1999	0	20	0	20		Not estimable
Total (95% CI)		**4677**		**2690**	**100.0%**	**3.80 [2.61 , 5.51]**
Total events:	273		29			

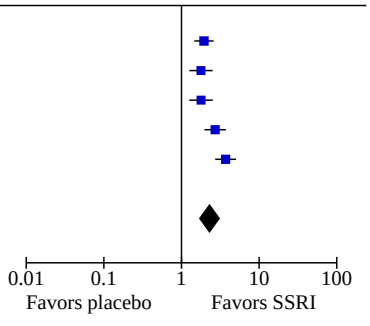
Heterogeneity: Tau² = 0.00; Chi² = 18.10, df = 19 (P = 0.52); I² = 0%
Test for overall effect: Z = 7.01 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: SSRI versus placebo, Outcome 4: Perceived control over ejaculation

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaufman 2009	171	431	45	221	21.1%	1.95 [1.46 , 2.59]
McMahon 2010	112	336	32	171	19.2%	1.78 [1.26 , 2.52]
McMahon 2010	110	329	32	171	19.2%	1.79 [1.26 , 2.53]
Pryor 2006	218	874	40	435	20.1%	2.71 [1.98 , 3.72]
Pryor 2006	296	870	40	435	20.4%	3.70 [2.72 , 5.04]
Total (95% CI)		**2840**		**1433**	**100.0%**	**2.29 [1.72 , 3.05]**
Total events:	907		189			

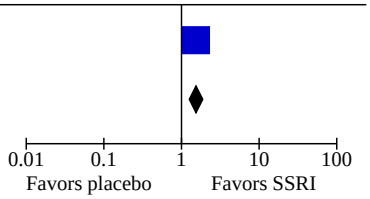
Heterogeneity: Tau² = 0.08; Chi² = 15.92, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 5.70 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: SSRI versus placebo, Outcome 5: Participant distress about PE

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaufman 2009	234	431	78	221	100.0%	1.54 [1.26 , 1.88]
Total (95% CI)		**431**		**221**	**100.0%**	**1.54 [1.26 , 1.88]**
Total events:	234		78			

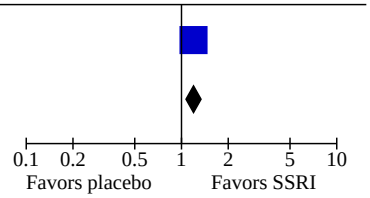
Heterogeneity: Not applicable
Test for overall effect: Z = 4.25 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: SSRI versus placebo, Outcome 6: Relationship difficulties

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaufman 2009	331	431	142	221	100.0%	1.20 [1.07 , 1.34]
Total (95% CI)		**431**		**221**	**100.0%**	**1.20 [1.07 , 1.34]**
Total events:	331		142			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.14 (P = 0.002)
Test for subgroup differences: Not applicable



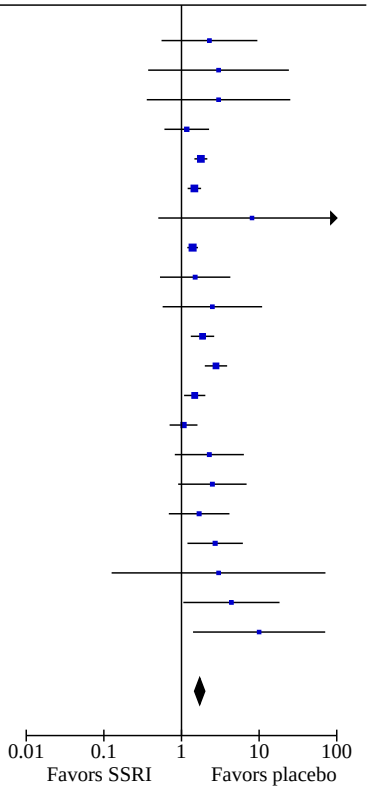
Analysis 1.7. Comparison 1: SSRI versus placebo, Outcome 7: Adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahn 1996	5	12	2	11	1.1%	2.29 [0.55 , 9.49]
Athanasios 2007	3	10	1	10	0.5%	3.00 [0.37 , 24.17]
Atmaca 2002	3	13	1	13	0.5%	3.00 [0.36 , 25.21]
Biri 1998	12	22	7	15	4.0%	1.17 [0.60 , 2.27]
Buvat 2009	265	389	74	193	14.1%	1.78 [1.47 , 2.15]
Buvat 2009	218	388	74	193	13.8%	1.47 [1.20 , 1.79]
Kara 1996	4	9	0	8	0.3%	8.10 [0.50 , 130.50]
Kaufman 2009	301	491	108	245	15.2%	1.39 [1.19 , 1.63]
Mattos 2008	6	15	4	15	1.9%	1.50 [0.53 , 4.26]
Mattos 2008	5	15	2	15	1.0%	2.50 [0.57 , 10.93]
McMahon 2010	118	354	32	179	9.3%	1.86 [1.32 , 2.64]
McMahon 2010	177	356	32	179	9.7%	2.78 [2.00 , 3.87]
McMahon 2013	74	250	49	245	10.1%	1.48 [1.08 , 2.03]
Mendels 1995	17	26	16	26	7.7%	1.06 [0.70 , 1.61]
Safarinejad 2006b	19	104	4	50	1.9%	2.28 [0.82 , 6.36]
Safarinejad 2006b	21	105	4	50	2.0%	2.50 [0.91 , 6.90]
Safarinejad 2007	12	128	7	126	2.4%	1.69 [0.69 , 4.15]
Safarinejad 2008	19	101	7	101	2.8%	2.71 [1.19 , 6.17]
Shang 2012	1	40	0	40	0.2%	3.00 [0.13 , 71.51]
Tuncel 2008	8	20	2	22	1.0%	4.40 [1.06 , 18.32]
Yilmaz 1999	10	20	1	20	0.6%	10.00 [1.41 , 70.99]
Total (95% CI)		**2868**		**1756**	**100.0%**	**1.71 [1.48 , 1.99]**
Total events:	1298		427			

Heterogeneity: Tau² = 0.03; Chi² = 33.90, df = 20 (P = 0.03); I² = 41%

Test for overall effect: Z = 7.03 (P < 0.00001)

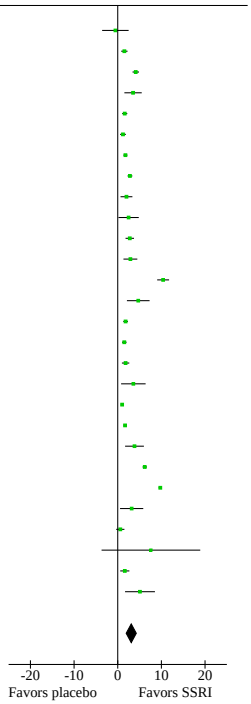
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: SSRI versus placebo, Outcome 8: Intravaginal ejaculatory latency time

Study or Subgroup	SSRI Mean [minutes]	SSRI SD [minutes]	SSRI Total	Placebo Mean [minutes]	Placebo SD [minutes]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [minutes]
Ahn 1996	0.42	5.3	12	0.96	0.77	11	3.1%	-0.54 [-3.57 , 2.49]
Athanasios 2007	2.16	1.13	10	0.64	0.28	10	3.9%	1.52 [0.80 , 2.24]
Atmaca 2002	4.73	1.34	13	0.6	0.23	13	3.9%	4.13 [3.39 , 4.87]
Biri 1998	5.42	4.36	22	1.91	1.56	15	3.5%	3.51 [1.52 , 5.50]
Buvat 2009	3.5	3.8	355	1.9	2.89	170	3.9%	1.60 [1.01 , 2.19]
Buvat 2009	3.1	4.88	363	1.9	2.89	170	3.9%	1.20 [0.54 , 1.86]
Gameel 2013	3.11	1.08	28	1.35	0.54	27	3.9%	1.76 [1.31 , 2.21]
Gong 2011	6.4	1.2	40	3.6	1.3	40	3.9%	2.80 [2.25 , 3.35]
Kara 1996	3	1.66	7	1	0.78	7	3.7%	2.00 [0.64 , 3.36]
Mattos 2008	5.6	3.75	15	3.11	2.65	15	3.4%	2.49 [0.17 , 4.81]
Mattos 2008	3.89	1.75	15	1.13	0.77	15	3.8%	2.76 [1.79 , 3.73]
McMahon 1998	3.4	2.46	19	0.5	2.46	18	3.7%	2.90 [1.31 , 4.49]
McMahon 1999	11	1.77	13	0.6	1.77	13	3.7%	10.40 [9.04 , 11.76]
McMahon 1999	5.8	4.29	21	1.1	4.29	21	3.3%	4.70 [2.11 , 7.29]
McMahon 2010	4.2	3.97	331	2.4	2.05	171	3.9%	1.80 [1.27 , 2.33]
McMahon 2010	3.9	3.94	333	2.4	2.05	171	3.9%	1.50 [0.98 , 2.02]
McMahon 2013	5.2	5.78	250	3.4	3.54	245	3.8%	1.80 [0.96 , 2.64]
Mendels 1995	5.43	5.62	22	1.85	3.68	22	3.2%	3.58 [0.77 , 6.39]
Pryor 2006	2.79	3.35	874	1.78	2.26	435	3.9%	1.01 [0.70 , 1.32]
Pryor 2006	3.46	3.84	870	1.78	2.26	435	3.9%	1.68 [1.35 , 2.01]
Safarinejad 2006c	4.47	3.92	26	0.63	3.92	25	3.5%	3.84 [1.69 , 5.99]
Shang 2012	7.2	1.56	40	1.01	0.21	40	3.9%	6.19 [5.70 , 6.68]
Waldinger 1994	10	0.35	6	0.25	0.35	8	3.9%	9.75 [9.38 , 10.12]
Waldinger 1998	3.52	4.18	10	0.33	0.43	2	3.3%	3.19 [0.53 , 5.85]
Waldinger 1998	0.92	1.17	10	0.33	0.43	2	3.8%	0.59 [-0.35 , 1.53]
Waldinger 1998	7.93	19.1	11	0.33	0.43	2	0.8%	7.60 [-3.70 , 18.90]
Waldinger 1998	1.95	1.45	11	0.33	0.43	2	3.8%	1.62 [0.58 , 2.66]
Yilmaz 1999	6.6	7.7	20	1.5	1.3	20	2.9%	5.10 [1.68 , 8.52]
Total (95% CI)			**3747**			**2125**	**100.0%**	**3.09 [1.94 , 4.25]**

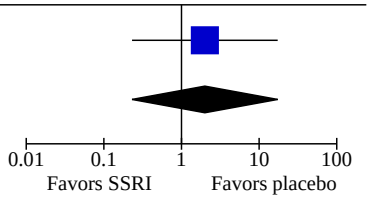
Heterogeneity: Tau² = 8.89; Chi² = 1983.65, df = 27 (P < 0.00001); I² = 99%
Test for overall effect: Z = 5.24 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: SSRI versus placebo, Outcome 9: Depression

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kara 1996	2	7	1	7	100.0%	2.00 [0.23 , 17.34]
Total (95% CI)		**7**		**7**	**100.0%**	**2.00 [0.23 , 17.34]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



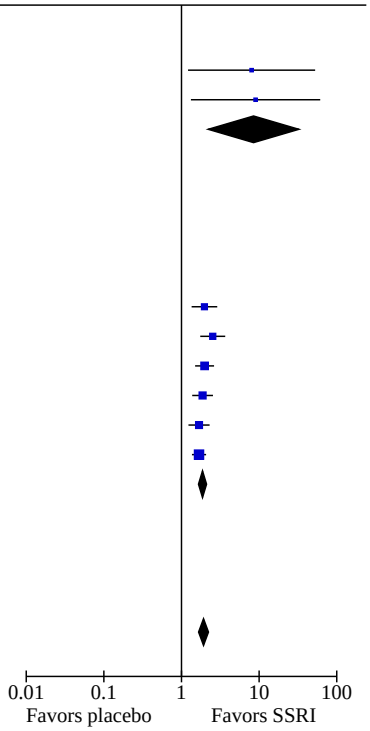
Comparison 2. Subgroup analysis: long-acting versus short-acting SSRI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Participant perception of change with treatment	6	3260	Risk Ratio (M-H, Random, 95% CI)	1.92 [1.66, 2.23]
2.1.1 Long-acting SSRI	2	46	Risk Ratio (M-H, Random, 95% CI)	8.48 [2.21, 32.51]
2.1.2 Short-acting SSRI	4	3214	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.66, 2.10]
2.2 Participant satisfaction with intercourse	3	4273	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.42, 1.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 Short-acting SSRI	3	4273	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.42, 1.87]
2.3 Study withdrawal due to adverse events	20	7367	Risk Ratio (M-H, Random, 95% CI)	3.71 [2.56, 5.38]
2.3.1 Long-acting SSRI	14	1315	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.92, 4.34]
2.3.2 Short-acting SSRI	6	6052	Risk Ratio (M-H, Random, 95% CI)	4.33 [2.60, 7.23]
2.4 Perceived control over ejaculation	3	4273	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.72, 3.05]
2.4.1 Short-acting SSRI	3	4273	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.72, 3.05]
2.5 Participant distress about PE	1	652	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.26, 1.88]
2.5.1 Short-acting SSRI	1	652	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.26, 1.88]
2.6 Relationship difficulties	1	652	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.07, 1.34]
2.6.1 Short-acting SSRI	1	652	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.07, 1.34]
2.7 Adverse events	17	4624	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.48, 1.99]
2.7.1 Long-acting SSRI	13	1162	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.37, 2.64]
2.7.2 Short-acting SSRI	4	3462	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.42, 2.03]
2.8 Intravaginal ejaculatory latency time	19	5804	Mean Difference (IV, Random, 95% CI)	2.74 [1.57, 3.92]
2.8.1 Long-acting SSRI	14	576	Mean Difference (IV, Random, 95% CI)	3.36 [1.62, 5.10]
2.8.2 Short-acting SSRI	5	5228	Mean Difference (IV, Random, 95% CI)	1.52 [1.27, 1.77]
2.9 Depression	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]
2.9.1 Long-acting SSRI	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]

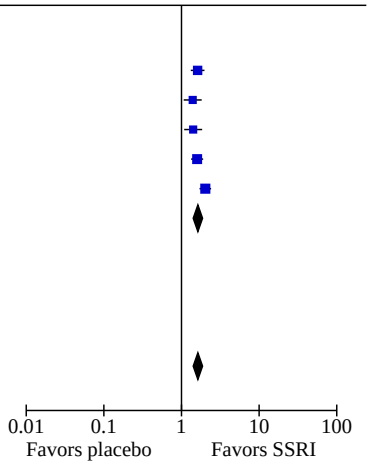
Analysis 2.1. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 1: Participant perception of change with treatment

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Long-acting SSRI						
Athanasios 2007	8	10	1	10	0.6%	8.00 [1.21 , 52.69]
Atmaca 2002	9	13	1	13	0.6%	9.00 [1.32 , 61.24]
Subtotal (95% CI)		**23**		**23**	**1.2%**	**8.48 [2.21 , 32.51]**
Total events:	17		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 3.12 (P = 0.002)						
2.1.2 Short-acting SSRI						
Buvat 2009	110	359	27	174	11.6%	1.97 [1.35 , 2.89]
Buvat 2009	138	352	27	174	12.1%	2.53 [1.74 , 3.66]
Kaufman 2009	178	431	46	221	18.1%	1.98 [1.50 , 2.63]
McMahon 2010	140	337	38	171	15.9%	1.87 [1.37 , 2.54]
McMahon 2010	123	329	38	171	15.5%	1.68 [1.23 , 2.30]
McMahon 2013	139	250	81	245	25.6%	1.68 [1.36 , 2.07]
Subtotal (95% CI)		**2058**		**1156**	**98.8%**	**1.87 [1.66 , 2.10]**
Total events:	828		257			
Heterogeneity: Tau² = 0.00; Chi² = 4.30, df = 5 (P = 0.51); I² = 0%						
Test for overall effect: Z = 10.25 (P < 0.00001)						
Total (95% CI)		**2081**		**1179**	**100.0%**	**1.92 [1.66 , 2.23]**
Total events:	845		259			
Heterogeneity: Tau² = 0.01; Chi² = 9.27, df = 7 (P = 0.23); I² = 24%						
Test for overall effect: Z = 8.75 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.83, df = 1 (P = 0.03), I² = 79.3%						



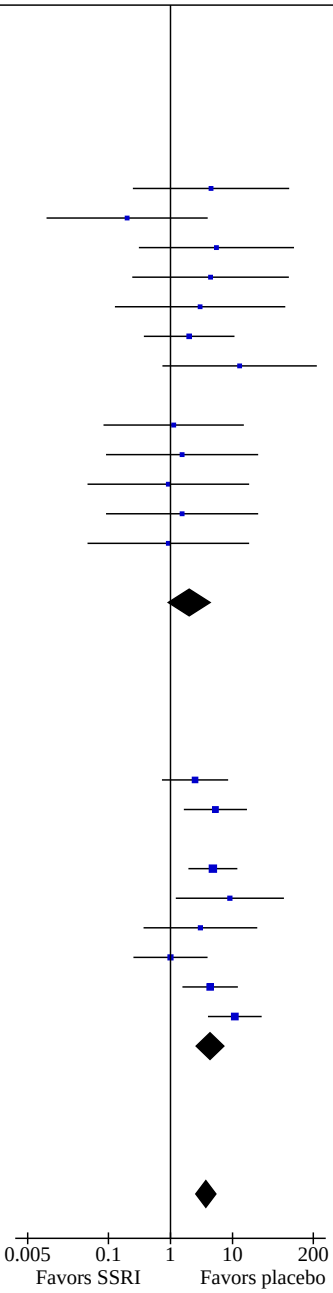
Analysis 2.2. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 2: Participant satisfaction with intercourse

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Short-acting SSRI						
Kaufman 2009	236	431	75	221	21.0%	1.61 [1.32 , 1.98]
McMahon 2010	137	336	50	171	15.8%	1.39 [1.07 , 1.82]
McMahon 2010	136	329	50	171	15.8%	1.41 [1.08 , 1.85]
Pryor 2006	358	874	112	435	23.4%	1.59 [1.33 , 1.90]
Pryor 2006	454	870	112	435	24.1%	2.03 [1.71 , 2.41]
Subtotal (95% CI)		**2840**		**1433**	**100.0%**	**1.63 [1.42 , 1.87]**
Total events:	1321		399			
Heterogeneity: Tau² = 0.01; Chi² = 8.54, df = 4 (P = 0.07); I² = 53%						
Test for overall effect: Z = 6.90 (P < 0.00001)						
Total (95% CI)		**2840**		**1433**	**100.0%**	**1.63 [1.42 , 1.87]**
Total events:	1321		399			
Heterogeneity: Tau² = 0.01; Chi² = 8.54, df = 4 (P = 0.07); I² = 53%						
Test for overall effect: Z = 6.90 (P < 0.00001)						
Test for subgroup differences: Not applicable						



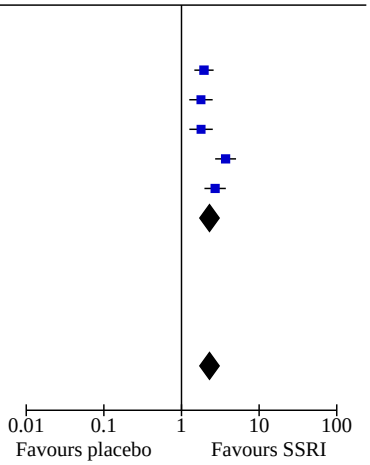
Analysis 2.3. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 3: Study withdrawal due to adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Long-acting SSRI						
Athanasios 2007	0	10	0	10		Not estimable
Atmaca 2002	0	13	0	13		Not estimable
Biri 1998	0	22	0	15		Not estimable
Gong 2011	0	40	0	40		Not estimable
Kara 1996	2	9	0	8	1.6%	4.50 [0.25 , 81.76]
Mendels 1995	0	26	2	26	1.5%	0.20 [0.01 , 3.97]
Safarinejad 2006b	5	113	0	56	1.7%	5.50 [0.31 , 97.74]
Safarinejad 2006b	4	115	0	56	1.6%	4.42 [0.24 , 80.74]
Safarinejad 2006c	1	29	0	29	1.4%	3.00 [0.13 , 70.74]
Safarinejad 2007	4	138	2	138	4.9%	2.00 [0.37 , 10.74]
Safarinejad 2008	6	106	0	106	1.7%	13.00 [0.74 , 227.89]
Shang 2012	0	40	0	40		Not estimable
Waldinger 1994	1	8	1	9	2.0%	1.13 [0.08 , 15.19]
Waldinger 1998	2	12	0	3	1.7%	1.54 [0.09 , 25.86]
Waldinger 1998	1	12	0	3	1.5%	0.92 [0.05 , 18.50]
Waldinger 1998	2	12	0	3	1.7%	1.54 [0.09 , 25.86]
Waldinger 1998	1	12	0	3	1.5%	0.92 [0.05 , 18.50]
Yilmaz 1999	0	20	0	20		Not estimable
Subtotal (95% CI)		**737**		**578**	**23.1%**	**2.00 [0.92 , 4.34]**
Total events:	29		5			
Heterogeneity: Tau² = 0.00; Chi² = 5.95, df = 11 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
2.3.2 Short-acting SSRI						
Buvat 2009	15	388	3	193	9.2%	2.49 [0.73 , 8.49]
Buvat 2009	32	389	3	193	10.1%	5.29 [1.64 , 17.06]
Gameel 2013	0	28	0	27		Not estimable
Kaufman 2009	47	431	5	221	16.8%	4.82 [1.94 , 11.95]
McMahon 2010	18	356	1	179	3.4%	9.05 [1.22 , 67.25]
McMahon 2010	6	354	1	179	3.1%	3.03 [0.37 , 25.01]
McMahon 2013	4	250	4	250	7.3%	1.00 [0.25 , 3.95]
Pryor 2006	35	874	4	435	13.1%	4.35 [1.56 , 12.17]
Pryor 2006	87	870	4	435	13.9%	10.88 [4.02 , 29.43]
Subtotal (95% CI)		**3940**		**2112**	**76.9%**	**4.33 [2.60 , 7.23]**
Total events:	244		25			
Heterogeneity: Tau² = 0.15; Chi² = 9.64, df = 7 (P = 0.21); I² = 27%						
Test for overall effect: Z = 5.61 (P < 0.00001)						
Total (95% CI)		**4677**		**2690**	**100.0%**	**3.71 [2.56 , 5.38]**
Total events:	273		30			
Heterogeneity: Tau² = 0.00; Chi² = 19.01, df = 19 (P = 0.46); I² = 0%						
Test for overall effect: Z = 6.91 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.66, df = 1 (P = 0.10), I² = 62.4%						



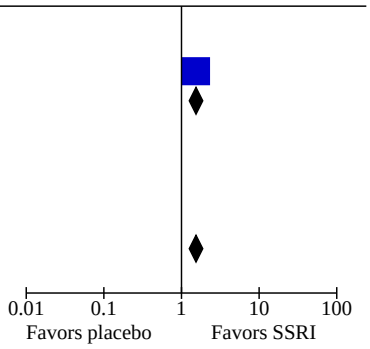
Analysis 2.4. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 4: Perceived control over ejaculation

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Short-acting SSRI						
Kaufman 2009	171	431	45	221	21.1%	1.95 [1.46 , 2.59]
McMahon 2010	112	336	32	171	19.2%	1.78 [1.26 , 2.52]
McMahon 2010	110	329	32	171	19.2%	1.79 [1.26 , 2.53]
Pryor 2006	296	870	40	435	20.4%	3.70 [2.72 , 5.04]
Pryor 2006	218	874	40	435	20.1%	2.71 [1.98 , 3.72]
Subtotal (95% CI)		**2840**		**1433**	**100.0%**	**2.29 [1.72 , 3.05]**
Total events:	907		189			
Heterogeneity: Tau² = 0.08; Chi² = 15.92, df = 4 (P = 0.003); I² = 75%						
Test for overall effect: Z = 5.70 (P < 0.00001)						
Total (95% CI)		**2840**		**1433**	**100.0%**	**2.29 [1.72 , 3.05]**
Total events:	907		189			
Heterogeneity: Tau² = 0.08; Chi² = 15.92, df = 4 (P = 0.003); I² = 75%						
Test for overall effect: Z = 5.70 (P < 0.00001)						
Test for subgroup differences: Not applicable						



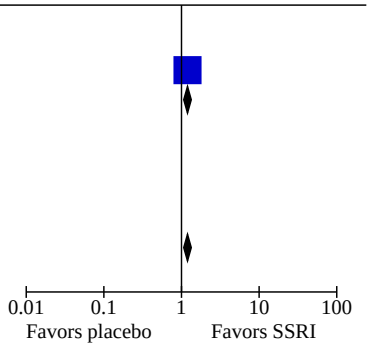
Analysis 2.5. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 5: Participant distress about PE

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Short-acting SSRI						
Kaufman 2009	234	431	78	221	100.0%	1.54 [1.26 , 1.88]
Subtotal (95% CI)		**431**		**221**	**100.0%**	**1.54 [1.26 , 1.88]**
Total events:	234		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
Total (95% CI)		**431**		**221**	**100.0%**	**1.54 [1.26 , 1.88]**
Total events:	234		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
Test for subgroup differences: Not applicable						



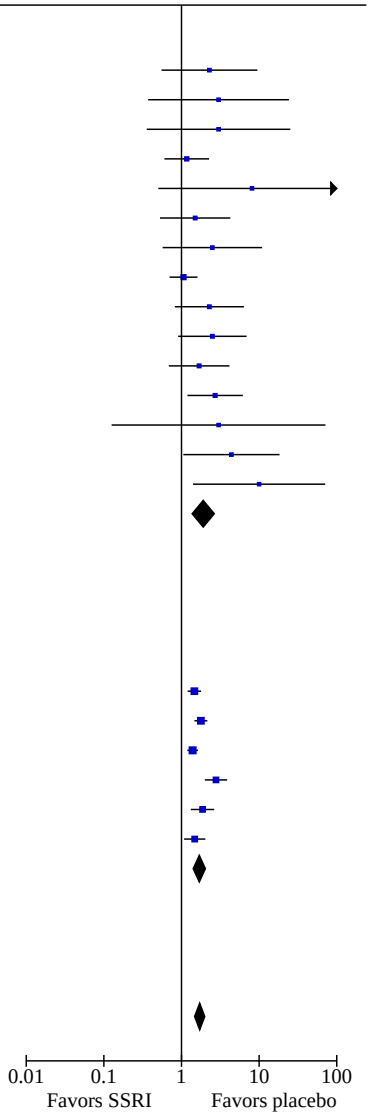
Analysis 2.6. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 6: Relationship difficulties

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Short-acting SSRI						
Kaufman 2009	331	431	142	221	100.0%	1.20 [1.07 , 1.34]
Subtotal (95% CI)		**431**		**221**	**100.0%**	**1.20 [1.07 , 1.34]**
Total events:	331		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
Total (95% CI)		**431**		**221**	**100.0%**	**1.20 [1.07 , 1.34]**
Total events:	331		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
Test for subgroup differences: Not applicable						



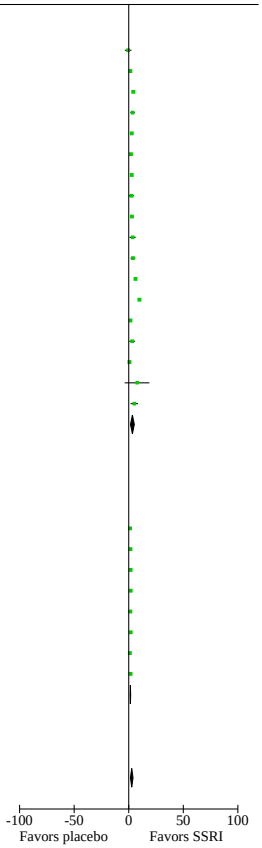
Analysis 2.7. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 7: Adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Long-acting SSRI						
Ahn 1996	5	12	2	11	1.1%	2.29 [0.55 , 9.49]
Athanasios 2007	3	10	1	10	0.5%	3.00 [0.37 , 24.17]
Atmaca 2002	3	13	1	13	0.5%	3.00 [0.36 , 25.21]
Biri 1998	12	22	7	15	4.0%	1.17 [0.60 , 2.27]
Kara 1996	4	9	0	8	0.3%	8.10 [0.50 , 130.50]
Mattos 2008	6	15	4	15	1.9%	1.50 [0.53 , 4.26]
Mattos 2008	5	15	2	15	1.0%	2.50 [0.57 , 10.93]
Mendels 1995	17	26	16	26	7.7%	1.06 [0.70 , 1.61]
Safarinejad 2006b	19	104	4	50	1.9%	2.28 [0.82 , 6.36]
Safarinejad 2006b	21	105	4	50	2.0%	2.50 [0.91 , 6.90]
Safarinejad 2007	12	128	7	126	2.4%	1.69 [0.69 , 4.15]
Safarinejad 2008	19	101	7	101	2.8%	2.71 [1.19 , 6.17]
Shang 2012	1	40	0	40	0.2%	3.00 [0.13 , 71.51]
Tuncel 2008	8	20	2	22	1.0%	4.40 [1.06 , 18.32]
Yilmaz 1999	10	20	1	20	0.6%	10.00 [1.41 , 70.99]
Subtotal (95% CI)		**640**		**522**	**27.9%**	**1.90 [1.37 , 2.64]**
Total events:	145		58			
Heterogeneity: Tau² = 0.09; Chi² = 18.58, df = 14 (P = 0.18); I² = 25%						
Test for overall effect: Z = 3.85 (P = 0.0001)						
2.7.2 Short-acting SSRI						
Buvat 2009	218	388	74	193	13.8%	1.47 [1.20 , 1.79]
Buvat 2009	265	389	74	193	14.1%	1.78 [1.47 , 2.15]
Kaufman 2009	301	491	108	245	15.2%	1.39 [1.19 , 1.63]
McMahon 2010	177	356	32	179	9.7%	2.78 [2.00 , 3.87]
McMahon 2010	118	354	32	179	9.3%	1.86 [1.32 , 2.64]
McMahon 2013	74	250	49	245	10.1%	1.48 [1.08 , 2.03]
Subtotal (95% CI)		**2228**		**1234**	**72.1%**	**1.70 [1.42 , 2.03]**
Total events:	1153		369			
Heterogeneity: Tau² = 0.03; Chi² = 17.16, df = 5 (P = 0.004); I² = 71%						
Test for overall effect: Z = 5.74 (P < 0.00001)						
Total (95% CI)		**2868**		**1756**	**100.0%**	**1.71 [1.48 , 1.99]**
Total events:	1298		427			
Heterogeneity: Tau² = 0.03; Chi² = 33.90, df = 20 (P = 0.03); I² = 41%						
Test for overall effect: Z = 7.03 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						



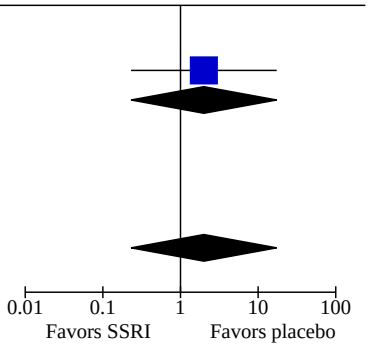
Analysis 2.8. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 8: Intravaginal ejaculatory latency time

Study or Subgroup	SSRI Mean [minutes]	SSRI SD [minutes]	SSRI Total	Placebo Mean [minutes]	Placebo SD [minutes]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [minutes]
2.8.1 Long-acting SSRI								
Ahn 1996	0.42	5.3	12	0.96	0.77	11	3.3%	-0.54 [-3.57 , 2.49]
Athanasios 2007	2.16	1.13	10	0.64	0.28	10	4.2%	1.52 [0.80 , 2.24]
Atmaca 2002	4.73	1.34	13	0.6	0.23	13	4.2%	4.13 [3.39 , 4.87]
Biri 1998	5.42	4.36	22	1.91	1.56	15	3.8%	3.51 [1.52 , 5.50]
Gong 2011	6.4	1.2	40	3.6	1.3	40	4.2%	2.80 [2.25 , 3.35]
Kara 1996	3	1.66	7	1	0.78	7	4.0%	2.00 [0.64 , 3.36]
Mattos 2008	3.89	1.75	15	1.13	0.77	15	4.1%	2.76 [1.79 , 3.73]
Mattos 2008	5.6	3.75	15	3.11	2.65	15	3.6%	2.49 [0.17 , 4.81]
McMahon 1998	3.4	2.46	19	0.5	2.46	18	3.9%	2.90 [1.31 , 4.49]
Mendels 1995	5.43	5.62	22	1.85	3.68	22	3.4%	3.58 [0.77 , 6.39]
Safarinejad 2006c	4.47	3.92	26	0.63	3.92	25	3.7%	3.84 [1.69 , 5.99]
Shang 2012	7.2	1.56	40	1.01	0.21	40	4.2%	6.19 [5.70 , 6.68]
Waldinger 1994	10	0.35	6	0.25	0.35	8	4.2%	9.75 [9.38 , 10.12]
Waldinger 1998	1.95	1.45	11	0.33	0.43	2	4.1%	1.62 [0.58 , 2.66]
Waldinger 1998	3.52	4.18	10	0.33	0.43	2	3.5%	3.19 [0.53 , 5.85]
Waldinger 1998	0.92	1.17	10	0.33	0.43	2	4.1%	0.59 [-0.35 , 1.53]
Waldinger 1998	7.93	19.1	11	0.33	0.43	2	0.9%	7.60 [-3.70 , 18.90]
Yilmaz 1999	6.6	7.7	20	1.5	1.3	20	3.1%	5.10 [1.68 , 8.52]
Subtotal (95% CI)			**309**			**267**	**66.5%**	**3.36 [1.62 , 5.10]**
Heterogeneity: Tau² = 12.80; Chi² = 992.61, df = 17 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 3.78 (P = 0.0002)								
2.8.2 Short-acting SSRI								
Buvat 2009	3.1	4.88	363	1.9	2.89	170	4.2%	1.20 [0.54 , 1.86]
Buvat 2009	3.5	3.8	355	1.9	2.89	170	4.2%	1.60 [1.01 , 2.19]
Gameel 2013	3.11	1.08	28	1.35	0.54	27	4.2%	1.76 [1.31 , 2.21]
McMahon 2010	4.2	3.97	331	2.4	2.05	171	4.2%	1.80 [1.27 , 2.33]
McMahon 2010	3.9	3.94	333	2.4	2.05	171	4.2%	1.50 [0.98 , 2.02]
McMahon 2013	5.2	5.78	250	3.4	3.54	245	4.1%	1.80 [0.96 , 2.64]
Pryor 2006	2.79	3.35	874	1.78	2.26	435	4.2%	1.01 [0.70 , 1.32]
Pryor 2006	3.46	3.84	870	1.78	2.26	435	4.2%	1.68 [1.35 , 2.01]
Subtotal (95% CI)			**3404**			**1824**	**33.5%**	**1.52 [1.27 , 1.77]**
Heterogeneity: Tau² = 0.06; Chi² = 14.68, df = 7 (P = 0.04); I² = 52%								
Test for overall effect: Z = 11.94 (P < 0.00001)								
Total (95% CI)			**3713**			**2091**	**100.0%**	**2.74 [1.57 , 3.92]**
Heterogeneity: Tau² = 8.49; Chi² = 1868.24, df = 25 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 4.58 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.21, df = 1 (P = 0.04), I² = 76.2%								



Analysis 2.9. Comparison 2: Subgroup analysis: long-acting versus short-acting SSRI, Outcome 9: Depression

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Long-acting SSRI						
Kara 1996	2	7	1	7	100.0%	2.00 [0.23 , 17.34]
Subtotal (95% CI)		**7**		**7**	**100.0%**	**2.00 [0.23 , 17.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**7**		**7**	**100.0%**	**2.00 [0.23 , 17.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						

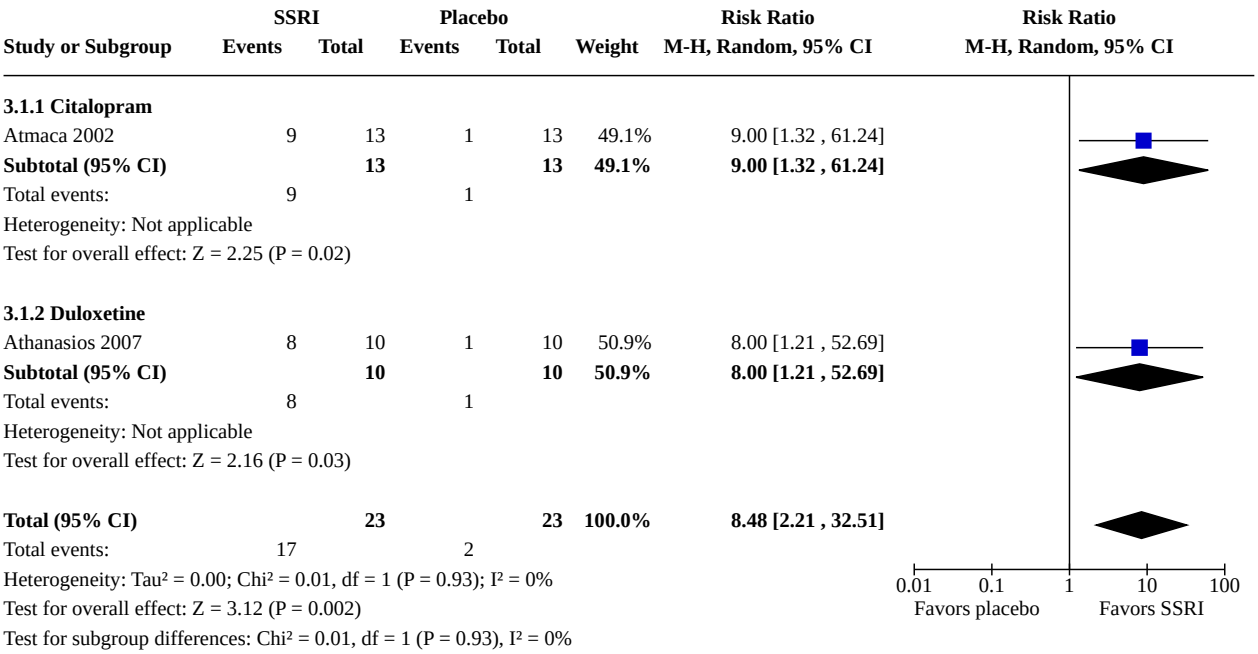


Comparison 3. Subgroup analysis: comparison of long-acting agents

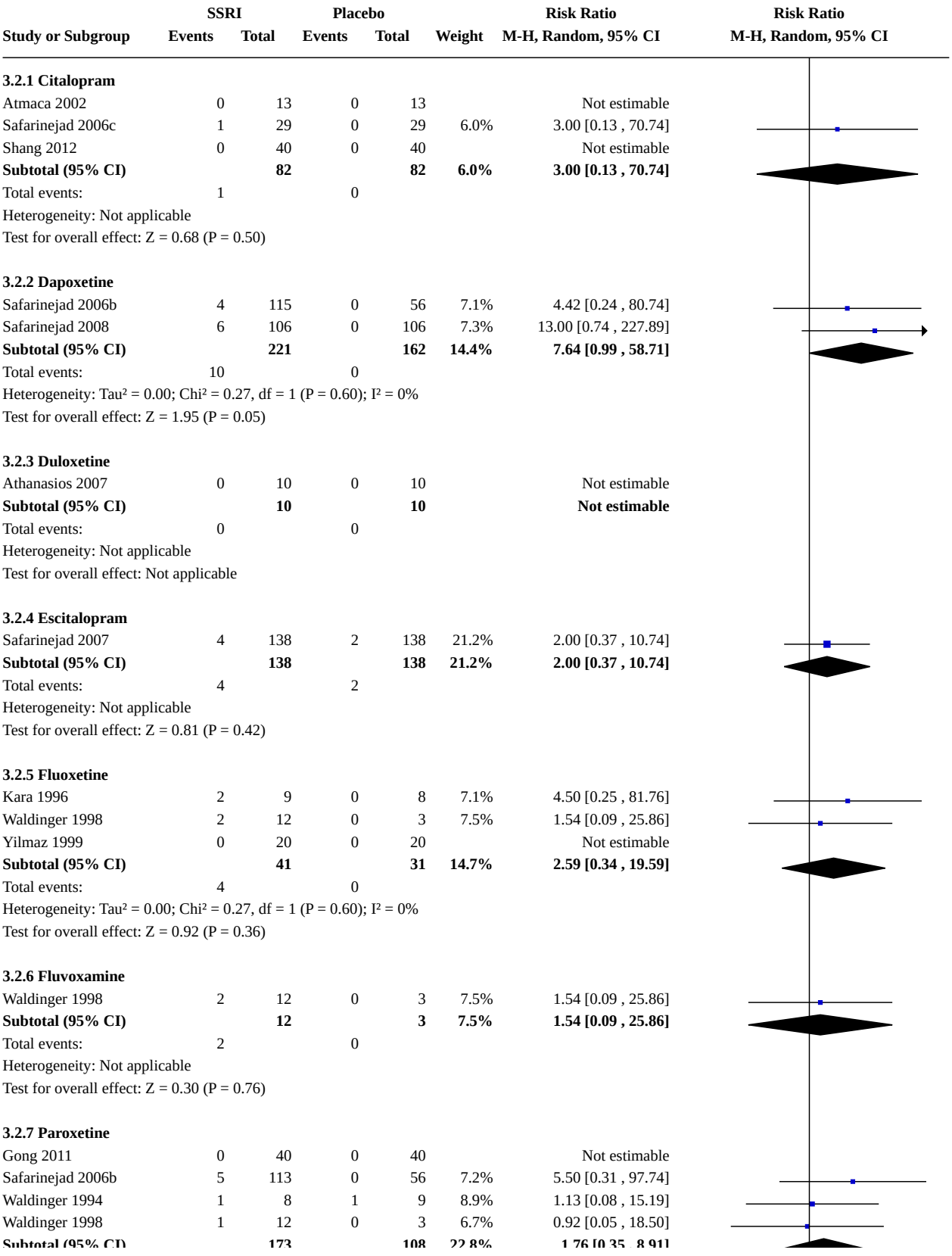
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Participant perception of change with treatment	2	46	Risk Ratio (M-H, Random, 95% CI)	8.48 [2.21, 32.51]
3.1.1 Citalopram	1	26	Risk Ratio (M-H, Random, 95% CI)	9.00 [1.32, 61.24]
3.1.2 Duloxetine	1	20	Risk Ratio (M-H, Random, 95% CI)	8.00 [1.21, 52.69]
3.2 Study withdrawal due to adverse events	14	1315	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.92, 4.34]
3.2.1 Citalopram	3	164	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.74]
3.2.2 Dapoxetine	2	383	Risk Ratio (M-H, Random, 95% CI)	7.64 [0.99, 58.71]
3.2.3 Duloxetine	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2.4 Escitalopram	1	276	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.37, 10.74]
3.2.5 Fluoxetine	3	72	Risk Ratio (M-H, Random, 95% CI)	2.59 [0.34, 19.59]
3.2.6 Fluvoxamine	1	15	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.09, 25.86]
3.2.7 Paroxetine	4	281	Risk Ratio (M-H, Random, 95% CI)	1.76 [0.35, 8.91]
3.2.8 Sertraline	3	104	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.05, 3.56]
3.3 Adverse events	13	1204	Risk Ratio (M-H, Random, 95% CI)	2.00 [1.44, 2.78]
3.3.1 Citalopram	2	106	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.51, 17.57]
3.3.2 Clomipramine	1	42	Risk Ratio (M-H, Random, 95% CI)	4.40 [1.06, 18.32]
3.3.3 Dapoxetine	2	356	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.34, 4.81]
3.3.4 Duloxetine	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.37, 24.17]
3.3.5 Escitalopram	1	254	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.69, 4.15]
3.3.6 Fluoxetine	4	140	Risk Ratio (M-H, Random, 95% CI)	2.50 [1.29, 4.86]
3.3.7 Paroxetine	1	155	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.91, 6.90]
3.3.8 Sertraline	3	131	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.74, 2.39]
3.4 Intravaginal ejaculatory latency time	14	576	Mean Difference (IV, Random, 95% CI)	3.36 [1.62, 5.10]
3.4.1 Citalopram	3	157	Mean Difference (IV, Random, 95% CI)	4.85 [3.14, 6.56]
3.4.2 Duloxetine	1	20	Mean Difference (IV, Random, 95% CI)	1.52 [0.80, 2.24]
3.4.3 Fluoxetine	5	149	Mean Difference (IV, Random, 95% CI)	2.46 [1.52, 3.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4.4 Fluvoxamine	1	12	Mean Difference (IV, Random, 95% CI)	0.59 [-0.35, 1.53]
3.4.5 Paroxetine	3	107	Mean Difference (IV, Random, 95% CI)	6.51 [0.33, 12.68]
3.4.6 Sertraline	4	131	Mean Difference (IV, Random, 95% CI)	2.55 [1.54, 3.56]
3.5 Depression	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]
3.5.1 Fluoxetine	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]

Analysis 3.1. Comparison 3: Subgroup analysis: comparison of long-acting agents, Outcome 1: Participant perception of change with treatment



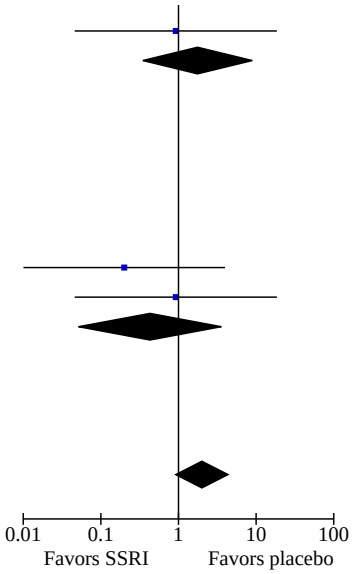
Analysis 3.2. Comparison 3: Subgroup analysis: comparison of long-acting agents, Outcome 2: Study withdrawal due to adverse events



Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Citalopram						
Atmaca 2002	0	13	0	13		Not estimable
Safarinejad 2006c	1	29	0	29	6.0%	3.00 [0.13 , 70.74]
Shang 2012	0	40	0	40		Not estimable
Subtotal (95% CI)		**82**		**82**	**6.0%**	**3.00 [0.13 , 70.74]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
3.2.2 Dapoxetine						
Safarinejad 2006b	4	115	0	56	7.1%	4.42 [0.24 , 80.74]
Safarinejad 2008	6	106	0	106	7.3%	13.00 [0.74 , 227.89]
Subtotal (95% CI)		**221**		**162**	**14.4%**	**7.64 [0.99 , 58.71]**
Total events:	10		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 1.95 (P = 0.05)						
3.2.3 Duloxetine						
Athanasios 2007	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.4 Escitalopram						
Safarinejad 2007	4	138	2	138	21.2%	2.00 [0.37 , 10.74]
Subtotal (95% CI)		**138**		**138**	**21.2%**	**2.00 [0.37 , 10.74]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
3.2.5 Fluoxetine						
Kara 1996	2	9	0	8	7.1%	4.50 [0.25 , 81.76]
Waldinger 1998	2	12	0	3	7.5%	1.54 [0.09 , 25.86]
Yilmaz 1999	0	20	0	20		Not estimable
Subtotal (95% CI)		**41**		**31**	**14.7%**	**2.59 [0.34 , 19.59]**
Total events:	4		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 0.92 (P = 0.36)						
3.2.6 Fluvoxamine						
Waldinger 1998	2	12	0	3	7.5%	1.54 [0.09 , 25.86]
Subtotal (95% CI)		**12**		**3**	**7.5%**	**1.54 [0.09 , 25.86]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
3.2.7 Paroxetine						
Gong 2011	0	40	0	40		Not estimable
Safarinejad 2006b	5	113	0	56	7.2%	5.50 [0.31 , 97.74]
Waldinger 1994	1	8	1	9	8.9%	1.13 [0.08 , 15.19]
Waldinger 1998	1	12	0	3	6.7%	0.92 [0.05 , 18.50]
Subtotal (95% CI)		**173**		**108**	**22.8%**	**1.76 [0.35 , 8.91]**

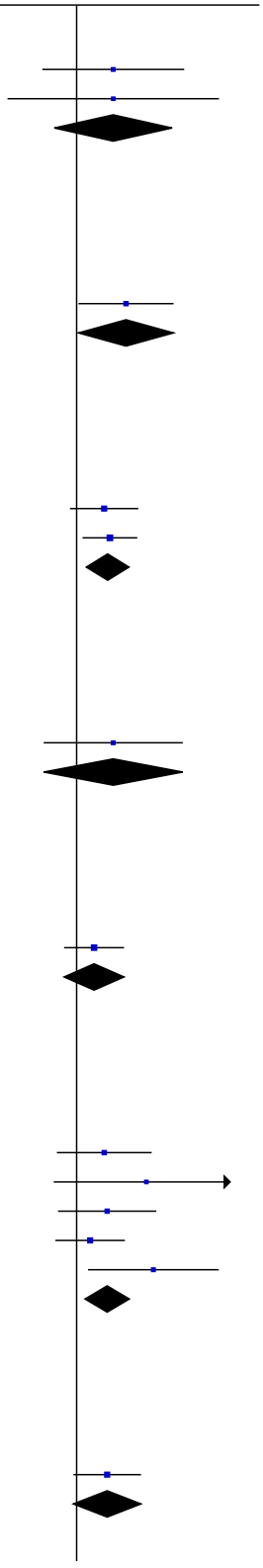
Analysis 3.2. (Continued)

Waldinger 1998	1	12	0	3	6.7%	0.92 [0.05 , 18.50]
Subtotal (95% CI)		**173**		**108**	**22.8%**	**1.76 [0.35 , 8.91]**
Total events:	7		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
3.2.8 Sertraline						
Biri 1998	0	22	0	15		Not estimable
Mendels 1995	0	26	2	26	6.7%	0.20 [0.01 , 3.97]
Waldinger 1998	1	12	0	3	6.7%	0.92 [0.05 , 18.50]
Subtotal (95% CI)		**60**		**44**	**13.4%**	**0.43 [0.05 , 3.56]**
Total events:	1		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
Total (95% CI)		**737**		**578**	**100.0%**	**2.00 [0.92 , 4.34]**
Total events:	29		5			
Heterogeneity: Tau² = 0.00; Chi² = 5.95, df = 11 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 3.88, df = 6 (P = 0.69), I² = 0%						



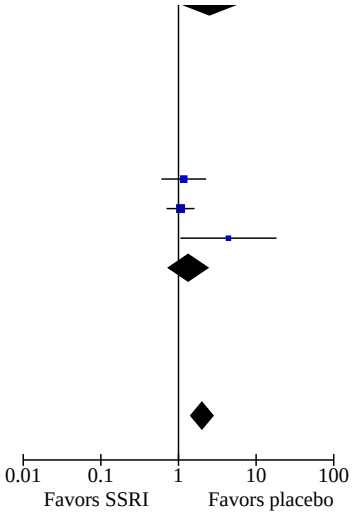
Analysis 3.3. Comparison 3: Subgroup analysis: comparison of long-acting agents, Outcome 3: Adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Citalopram						
Atmaca 2002	3	13	1	13	2.2%	3.00 [0.36 , 25.21]
Shang 2012	1	40	0	40	1.0%	3.00 [0.13 , 71.51]
Subtotal (95% CI)		**53**		**53**	**3.2%**	**3.00 [0.51 , 17.57]**
Total events:	4		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
3.3.2 Clomipramine						
Tuncel 2008	8	20	2	22	4.5%	4.40 [1.06 , 18.32]
Subtotal (95% CI)		**20**		**22**	**4.5%**	**4.40 [1.06 , 18.32]**
Total events:	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
3.3.3 Dapoxetine						
Safarinejad 2006b	19	104	4	50	7.5%	2.28 [0.82 , 6.36]
Safarinejad 2008	19	101	7	101	10.0%	2.71 [1.19 , 6.17]
Subtotal (95% CI)		**205**		**151**	**17.5%**	**2.54 [1.34 , 4.81]**
Total events:	38		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 2.85 (P = 0.004)						
3.3.4 Duloxetine						
Athanasios 2007	3	10	1	10	2.3%	3.00 [0.37 , 24.17]
Subtotal (95% CI)		**10**		**10**	**2.3%**	**3.00 [0.37 , 24.17]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
3.3.5 Escitalopram						
Safarinejad 2007	12	128	7	126	8.9%	1.69 [0.69 , 4.15]
Subtotal (95% CI)		**128**		**126**	**8.9%**	**1.69 [0.69 , 4.15]**
Total events:	12		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
3.3.6 Fluoxetine						
Ahn 1996	5	12	2	11	4.5%	2.29 [0.55 , 9.49]
Kara 1996	4	9	0	8	1.3%	8.10 [0.50 , 130.50]
Mattos 2008	5	15	2	15	4.2%	2.50 [0.57 , 10.93]
Mattos 2008	6	15	4	15	7.3%	1.50 [0.53 , 4.26]
Yilmaz 1999	10	20	1	20	2.6%	10.00 [1.41 , 70.99]
Subtotal (95% CI)		**71**		**69**	**19.8%**	**2.50 [1.29 , 4.86]**
Total events:	30		9			
Heterogeneity: Tau² = 0.00; Chi² = 3.98, df = 4 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.007)						
3.3.7 Paroxetine						
Safarinejad 2006b	21	105	4	50	7.6%	2.50 [0.91 , 6.90]
Subtotal (95% CI)		**105**		**50**	**7.6%**	**2.50 [0.91 , 6.90]**
Total events:	21		4			
Heterogeneity: Not applicable						



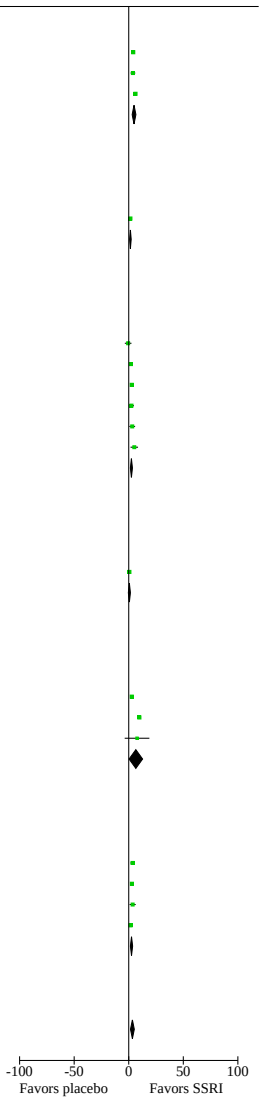
Analysis 3.3. (Continued)

Total events:	21		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
3.3.8 Sertraline						
Biri 1998	12	22	7	15	12.9%	1.17 [0.60 , 2.27]
Mendels 1995	17	26	16	26	18.8%	1.06 [0.70 , 1.61]
Tuncel 2008	8	20	2	22	4.5%	4.40 [1.06 , 18.32]
Subtotal (95% CI)		**68**		**63**	**36.2%**	**1.33 [0.74 , 2.39]**
Total events:	37		25			
Heterogeneity: Tau² = 0.13; Chi² = 4.04, df = 2 (P = 0.13); I² = 50%						
Test for overall effect: Z = 0.96 (P = 0.34)						
Total (95% CI)		**660**		**544**	**100.0%**	**2.00 [1.44 , 2.78]**
Total events:	153		60			
Heterogeneity: Tau² = 0.11; Chi² = 20.57, df = 15 (P = 0.15); I² = 27%						
Test for overall effect: Z = 4.13 (P < 0.0001)						
Test for subgroup differences: Chi² = 4.58, df = 7 (P = 0.71), I² = 0%						



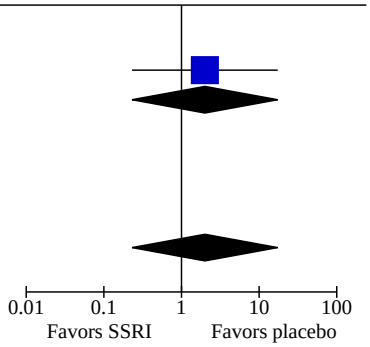
Analysis 3.4. Comparison 3: Subgroup analysis: comparison of long-acting agents, Outcome 4: Intravaginal ejaculatory latency time

Study or Subgroup	SSRI Mean [minutes]	SSRI SD [minutes]	SSRI Total	Placebo Mean [minutes]	Placebo SD [minutes]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [minutes]
3.4.1 Citalopram								
Atmaca 2002	4.73	1.34	13	0.6	0.23	13	6.1%	4.13 [3.39 , 4.87]
Safarinejad 2006c	4.47	3.92	26	0.63	3.92	25	5.6%	3.84 [1.69 , 5.99]
Shang 2012	7.2	1.56	40	1.01	0.21	40	6.1%	6.19 [5.70 , 6.68]
Subtotal (95% CI)			**79**			**78**	**17.9%**	**4.85 [3.14 , 6.56]**
Heterogeneity: Tau² = 1.91; Chi² = 23.17, df = 2 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 5.56 (P < 0.00001)								
3.4.2 Duloxetine								
Athanasios 2007	2.16	1.13	10	0.64	0.28	10	6.1%	1.52 [0.80 , 2.24]
Subtotal (95% CI)			**10**			**10**	**6.1%**	**1.52 [0.80 , 2.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.13 (P < 0.0001)								
3.4.3 Fluoxetine								
Ahn 1996	0.42	5.3	12	0.96	0.77	11	5.2%	-0.54 [-3.57 , 2.49]
Kara 1996	3	1.66	7	1	0.78	7	5.9%	2.00 [0.64 , 3.36]
Mattos 2008	3.89	1.75	15	1.13	0.77	15	6.0%	2.76 [1.79 , 3.73]
Mattos 2008	5.6	3.75	15	3.11	2.65	15	5.6%	2.49 [0.17 , 4.81]
Waldinger 1998	3.52	4.18	10	0.33	0.43	2	5.4%	3.19 [0.53 , 5.85]
Yilmaz 1999	6.6	7.7	20	1.5	1.3	20	5.0%	5.10 [1.68 , 8.52]
Subtotal (95% CI)			**79**			**70**	**33.1%**	**2.46 [1.52 , 3.39]**
Heterogeneity: Tau² = 0.39; Chi² = 7.13, df = 5 (P = 0.21); I² = 30%								
Test for overall effect: Z = 5.14 (P < 0.00001)								
3.4.4 Fluvoxamine								
Waldinger 1998	0.92	1.17	10	0.33	0.43	2	6.1%	0.59 [-0.35 , 1.53]
Subtotal (95% CI)			**10**			**2**	**6.1%**	**0.59 [-0.35 , 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.23 (P = 0.22)								
3.4.5 Paroxetine								
Gong 2011	6.4	1.2	40	3.6	1.3	40	6.1%	2.80 [2.25 , 3.35]
Waldinger 1994	10	0.35	6	0.25	0.35	8	6.1%	9.75 [9.38 , 10.12]
Waldinger 1998	7.93	19.1	11	0.33	0.43	2	1.7%	7.60 [-3.70 , 18.90]
Subtotal (95% CI)			**57**			**50**	**14.0%**	**6.51 [0.33 , 12.68]**
Heterogeneity: Tau² = 23.97; Chi² = 423.78, df = 2 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 2.07 (P = 0.04)								
3.4.6 Sertraline								
Biri 1998	5.42	4.36	22	1.91	1.56	15	5.7%	3.51 [1.52 , 5.50]
McMahon 1998	3.4	2.46	19	0.5	2.46	18	5.9%	2.90 [1.31 , 4.49]
Mendels 1995	5.43	5.62	22	1.85	3.68	22	5.3%	3.58 [0.77 , 6.39]
Waldinger 1998	1.95	1.45	11	0.33	0.43	2	6.0%	1.62 [0.58 , 2.66]
Subtotal (95% CI)			**74**			**57**	**22.9%**	**2.55 [1.54 , 3.56]**
Heterogeneity: Tau² = 0.34; Chi² = 4.39, df = 3 (P = 0.22); I² = 32%								
Test for overall effect: Z = 4.94 (P < 0.00001)								
Total (95% CI)			**309**			**267**	**100.0%**	**3.36 [1.62 , 5.10]**
Heterogeneity: Tau² = 12.80; Chi² = 992.61, df = 17 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 3.78 (P = 0.0002)								
Test for subgroup differences: Chi² = 25.05, df = 5 (P = 0.0001), I² = 80.0%								



Analysis 3.5. Comparison 3: Subgroup analysis: comparison of long-acting agents, Outcome 5: Depression

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Fluoxetine						
Kara 1996	2	7	1	7	100.0%	2.00 [0.23 , 17.34]
Subtotal (95% CI)		**7**		**7**	**100.0%**	**2.00 [0.23 , 17.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**7**		**7**	**100.0%**	**2.00 [0.23 , 17.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						



Comparison 4. Subgroup analysis: different doses of dapoxetine

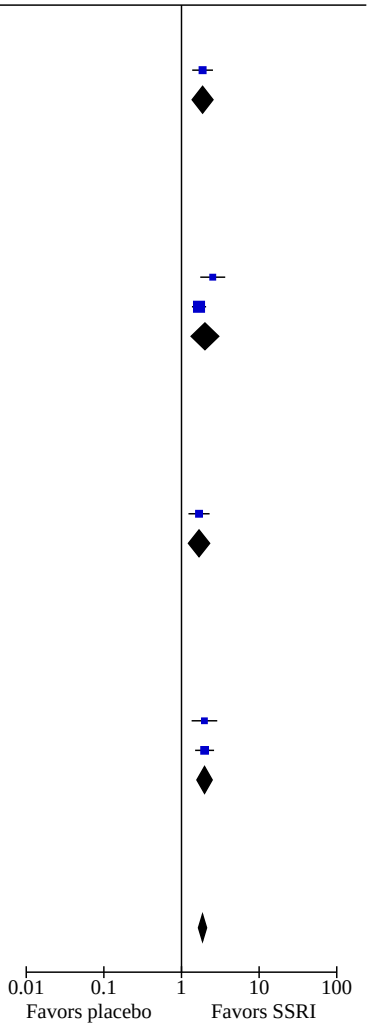
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Participant perception of change with treatment	4	3214	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.66, 2.10]
4.1.1 Dapoxetine 30 mg daily	1	508	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.37, 2.54]
4.1.2 Dapoxetine 30 mg on-demand	2	1021	Risk Ratio (M-H, Random, 95% CI)	2.00 [1.33, 3.01]
4.1.3 Dapoxetine 60 mg daily	1	500	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.23, 2.30]
4.1.4 Dapoxetine 60 mg on-demand	2	1185	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.58, 2.48]
4.2 Participant satisfaction with intercourse	3	2968	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.37, 1.71]
4.2.1 Dapoxetine 30 mg daily	1	500	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.08, 1.85]
4.2.2 Dapoxetine 30 mg on-demand	1	1309	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.33, 1.90]
4.2.3 Dapoxetine 60 mg daily	1	507	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.07, 1.82]
4.2.4 Dapoxetine 60 mg on-demand	1	652	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.32, 1.98]
4.3 Study withdrawal due to adverse events	7	6378	Risk Ratio (M-H, Random, 95% CI)	4.54 [2.89, 7.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.1 Dapoxetine 30 mg daily	1	533	Risk Ratio (M-H, Random, 95% CI)	3.03 [0.37, 25.01]
4.3.2 Dapoxetine 30 mg on-demand	3	2390	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.06, 5.59]
4.3.3 Dapoxetine 60 mg daily	3	916	Risk Ratio (M-H, Random, 95% CI)	8.76 [2.10, 36.49]
4.3.4 Dapoxetine 60 mg on-demand	3	2539	Risk Ratio (M-H, Random, 95% CI)	6.51 [3.64, 11.66]
4.4 Perceived control over ejaculation	3	4273	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.72, 3.05]
4.4.1 Dapoxetine 30 mg daily	1	500	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.26, 2.53]
4.4.2 Dapoxetine 30 mg on-demand	1	1305	Risk Ratio (M-H, Random, 95% CI)	3.70 [2.72, 5.04]
4.4.3 Dapoxetine 60 mg daily	1	507	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.26, 2.52]
4.4.4 Dapoxetine 60 mg on-demand	2	1961	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.65, 3.16]
4.5 Participant distress about PE	1	652	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.26, 1.88]
4.5.1 Dapoxetine 60 mg on-demand	1	652	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.26, 1.88]
4.6 Relationship difficulties	1	652	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.07, 1.34]
4.6.1 Dapoxetine 60 mg on-demand	1	652	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.07, 1.34]
4.7 Adverse events	6	3818	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.46, 2.07]
4.7.1 Dapoxetine 30 mg daily	2	1028	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.30, 2.07]
4.7.2 Dapoxetine 30 mg on-demand	1	581	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.20, 1.79]
4.7.3 Dapoxetine 60 mg daily	3	891	Risk Ratio (M-H, Random, 95% CI)	2.73 [2.03, 3.66]
4.7.4 Dapoxetine 60 mg on-demand	2	1318	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.23, 1.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.8 Intravaginal ejaculatory latency time	4	5173	Mean Difference (IV, Random, 95% CI)	1.48 [1.20, 1.75]
4.8.1 Dapoxetine 30 mg daily	1	502	Mean Difference (IV, Random, 95% CI)	1.80 [1.27, 2.33]
4.8.2 Dapoxetine 30 mg on-demand	3	2329	Mean Difference (IV, Random, 95% CI)	1.37 [0.86, 1.89]
4.8.3 Dapoxetine 60 mg daily	1	504	Mean Difference (IV, Random, 95% CI)	1.50 [0.98, 2.02]
4.8.4 Dapoxetine 60 mg on-demand	2	1838	Mean Difference (IV, Random, 95% CI)	1.53 [1.09, 1.97]

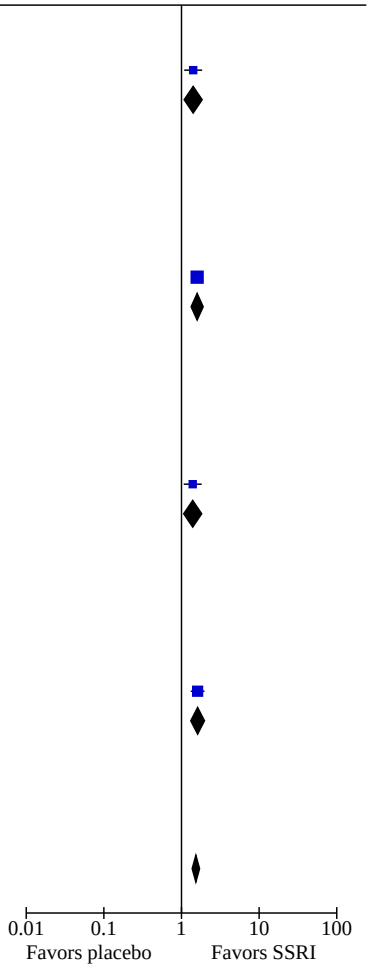
Analysis 4.1. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 1: Participant perception of change with treatment

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Dapoxetine 30 mg daily						
McMahon 2010	140	337	38	171	15.0%	1.87 [1.37 , 2.54]
Subtotal (95% CI)		**337**		**171**	**15.0%**	**1.87 [1.37 , 2.54]**
Total events:	140		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.99 (P < 0.0001)						
4.1.2 Dapoxetine 30 mg on-demand						
Buvat 2009	138	352	27	174	10.4%	2.53 [1.74 , 3.66]
McMahon 2013	139	250	81	245	32.3%	1.68 [1.36 , 2.07]
Subtotal (95% CI)		**602**		**419**	**42.6%**	**2.00 [1.33 , 3.01]**
Total events:	277		108			
Heterogeneity: Tau² = 0.06; Chi² = 3.74, df = 1 (P = 0.05); I² = 73%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
4.1.3 Dapoxetine 60 mg daily						
McMahon 2010	123	329	38	171	14.5%	1.68 [1.23 , 2.30]
Subtotal (95% CI)		**329**		**171**	**14.5%**	**1.68 [1.23 , 2.30]**
Total events:	123		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.25 (P = 0.001)						
4.1.4 Dapoxetine 60 mg on-demand						
Buvat 2009	110	359	27	174	9.8%	1.97 [1.35 , 2.89]
Kaufman 2009	178	431	46	221	18.0%	1.98 [1.50 , 2.63]
Subtotal (95% CI)		**790**		**395**	**27.9%**	**1.98 [1.58 , 2.48]**
Total events:	288		73			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 5.93 (P < 0.00001)						
Total (95% CI)		**2058**		**1156**	**100.0%**	**1.87 [1.66 , 2.10]**
Total events:	828		257			
Heterogeneity: Tau² = 0.00; Chi² = 4.30, df = 5 (P = 0.51); I² = 0%						
Test for overall effect: Z = 10.25 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.78, df = 3 (P = 0.85), I² = 0%						



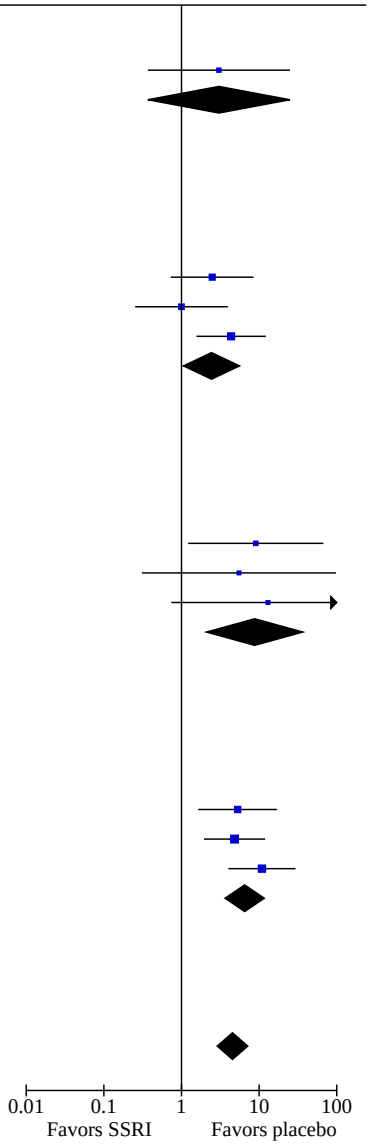
Analysis 4.2. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 2: Participant satisfaction with intercourse

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Dapoxetine 30 mg daily						
McMahon 2010	136	329	50	171	16.8%	1.41 [1.08 , 1.85]
Subtotal (95% CI)		**329**		**171**	**16.8%**	**1.41 [1.08 , 1.85]**
Total events:	136		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
4.2.2 Dapoxetine 30 mg on-demand						
Pryor 2006	358	874	112	435	37.5%	1.59 [1.33 , 1.90]
Subtotal (95% CI)		**874**		**435**	**37.5%**	**1.59 [1.33 , 1.90]**
Total events:	358		112			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.10 (P < 0.00001)						
4.2.3 Dapoxetine 60 mg daily						
McMahon 2010	137	336	50	171	16.8%	1.39 [1.07 , 1.82]
Subtotal (95% CI)		**336**		**171**	**16.8%**	**1.39 [1.07 , 1.82]**
Total events:	137		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.45 (P = 0.01)						
4.2.4 Dapoxetine 60 mg on-demand						
Kaufman 2009	236	431	75	221	28.9%	1.61 [1.32 , 1.98]
Subtotal (95% CI)		**431**		**221**	**28.9%**	**1.61 [1.32 , 1.98]**
Total events:	236		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.62 (P < 0.00001)						
Total (95% CI)		**1970**		**998**	**100.0%**	**1.53 [1.37 , 1.71]**
Total events:	867		287			
Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 7.66 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.25, df = 3 (P = 0.74), I² = 0%						



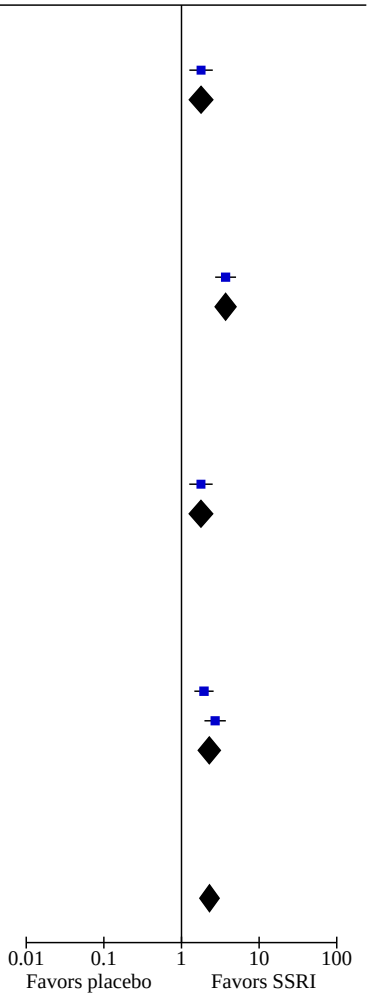
Analysis 4.3. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 3: Study withdrawal due to adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Dapoxetine 30 mg daily						
McMahon 2010	6	354	1	179	4.4%	3.03 [0.37 , 25.01]
Subtotal (95% CI)		**354**		**179**	**4.4%**	**3.03 [0.37 , 25.01]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
4.3.2 Dapoxetine 30 mg on-demand						
Buvat 2009	15	388	3	193	11.8%	2.49 [0.73 , 8.49]
McMahon 2013	4	250	4	250	9.6%	1.00 [0.25 , 3.95]
Pryor 2006	35	874	4	435	15.8%	4.35 [1.56 , 12.17]
Subtotal (95% CI)		**1512**		**878**	**37.2%**	**2.44 [1.06 , 5.59]**
Total events:	54		11			
Heterogeneity: Tau² = 0.17; Chi² = 2.89, df = 2 (P = 0.24); I² = 31%						
Test for overall effect: Z = 2.10 (P = 0.04)						
4.3.3 Dapoxetine 60 mg daily						
McMahon 2010	18	356	1	179	4.8%	9.05 [1.22 , 67.25]
Safarinejad 2006b	5	113	0	56	2.4%	5.50 [0.31 , 97.74]
Safarinejad 2008	6	106	0	106	2.4%	13.00 [0.74 , 227.89]
Subtotal (95% CI)		**575**		**341**	**9.6%**	**8.76 [2.10 , 36.49]**
Total events:	29		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.98 (P = 0.003)						
4.3.4 Dapoxetine 60 mg on-demand						
Buvat 2009	32	389	3	193	12.7%	5.29 [1.64 , 17.06]
Kaufman 2009	47	431	5	221	19.3%	4.82 [1.94 , 11.95]
Pryor 2006	87	870	4	435	16.7%	10.88 [4.02 , 29.43]
Subtotal (95% CI)		**1690**		**849**	**48.8%**	**6.51 [3.64 , 11.66]**
Total events:	166		12			
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 6.31 (P < 0.00001)						
Total (95% CI)		**4131**		**2247**	**100.0%**	**4.54 [2.89 , 7.14]**
Total events:	255		25			
Heterogeneity: Tau² = 0.06; Chi² = 10.18, df = 9 (P = 0.34); I² = 12%						
Test for overall effect: Z = 6.55 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.47, df = 3 (P = 0.22), I² = 32.9%						



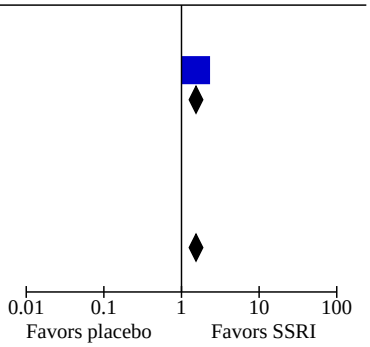
Analysis 4.4. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 4: Perceived control over ejaculation

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Dapoxetine 30 mg daily						
McMahon 2010	110	329	32	171	19.2%	1.79 [1.26 , 2.53]
Subtotal (95% CI)		**329**		**171**	**19.2%**	**1.79 [1.26 , 2.53]**
Total events:	110		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.27 (P = 0.001)						
4.4.2 Dapoxetine 30 mg on-demand						
Pryor 2006	296	870	40	435	20.4%	3.70 [2.72 , 5.04]
Subtotal (95% CI)		**870**		**435**	**20.4%**	**3.70 [2.72 , 5.04]**
Total events:	296		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.29 (P < 0.00001)						
4.4.3 Dapoxetine 60 mg daily						
McMahon 2010	112	336	32	171	19.2%	1.78 [1.26 , 2.52]
Subtotal (95% CI)		**336**		**171**	**19.2%**	**1.78 [1.26 , 2.52]**
Total events:	112		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.26 (P = 0.001)						
4.4.4 Dapoxetine 60 mg on-demand						
Kaufman 2009	171	431	45	221	21.1%	1.95 [1.46 , 2.59]
Pryor 2006	218	874	40	435	20.1%	2.71 [1.98 , 3.72]
Subtotal (95% CI)		**1305**		**656**	**41.3%**	**2.28 [1.65 , 3.16]**
Total events:	389		85			
Heterogeneity: Tau² = 0.03; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 4.95 (P < 0.00001)						
Total (95% CI)		**2840**		**1433**	**100.0%**	**2.29 [1.72 , 3.05]**
Total events:	907		189			
Heterogeneity: Tau² = 0.08; Chi² = 15.92, df = 4 (P = 0.003); I² = 75%						
Test for overall effect: Z = 5.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 13.13, df = 3 (P = 0.004), I² = 77.2%						



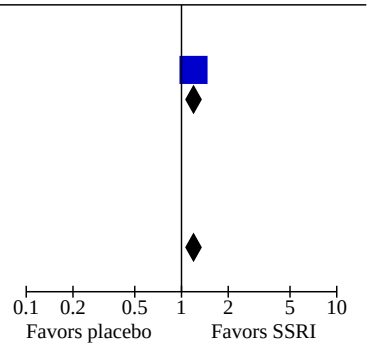
Analysis 4.5. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 5: Participant distress about PE

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 Dapoxetine 60 mg on-demand						
Kaufman 2009	234	431	78	221	100.0%	1.54 [1.26 , 1.88]
Subtotal (95% CI)		**431**		**221**	**100.0%**	**1.54 [1.26 , 1.88]**
Total events:	234		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
Total (95% CI)		**431**		**221**	**100.0%**	**1.54 [1.26 , 1.88]**
Total events:	234		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
Test for subgroup differences: Not applicable						



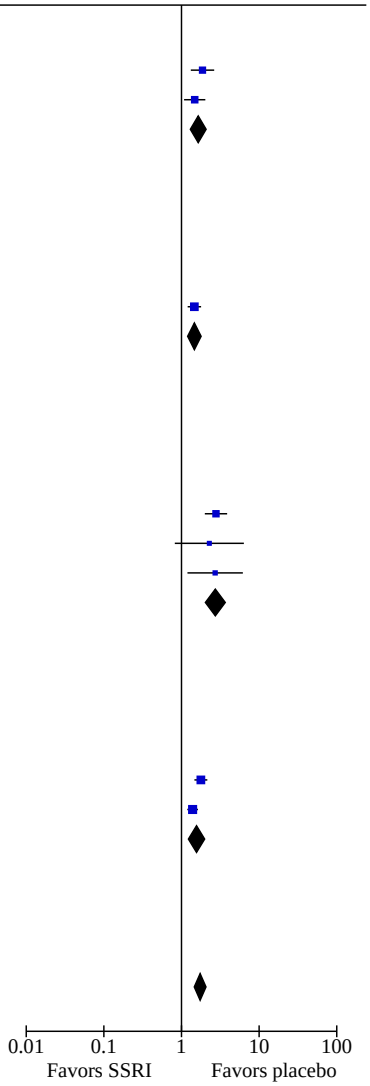
Analysis 4.6. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 6: Relationship difficulties

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Dapoxetine 60 mg on-demand						
Kaufman 2009	331	431	142	221	100.0%	1.20 [1.07 , 1.34]
Subtotal (95% CI)		**431**		**221**	**100.0%**	**1.20 [1.07 , 1.34]**
Total events:	331		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
Total (95% CI)		**431**		**221**	**100.0%**	**1.20 [1.07 , 1.34]**
Total events:	331		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
Test for subgroup differences: Not applicable						

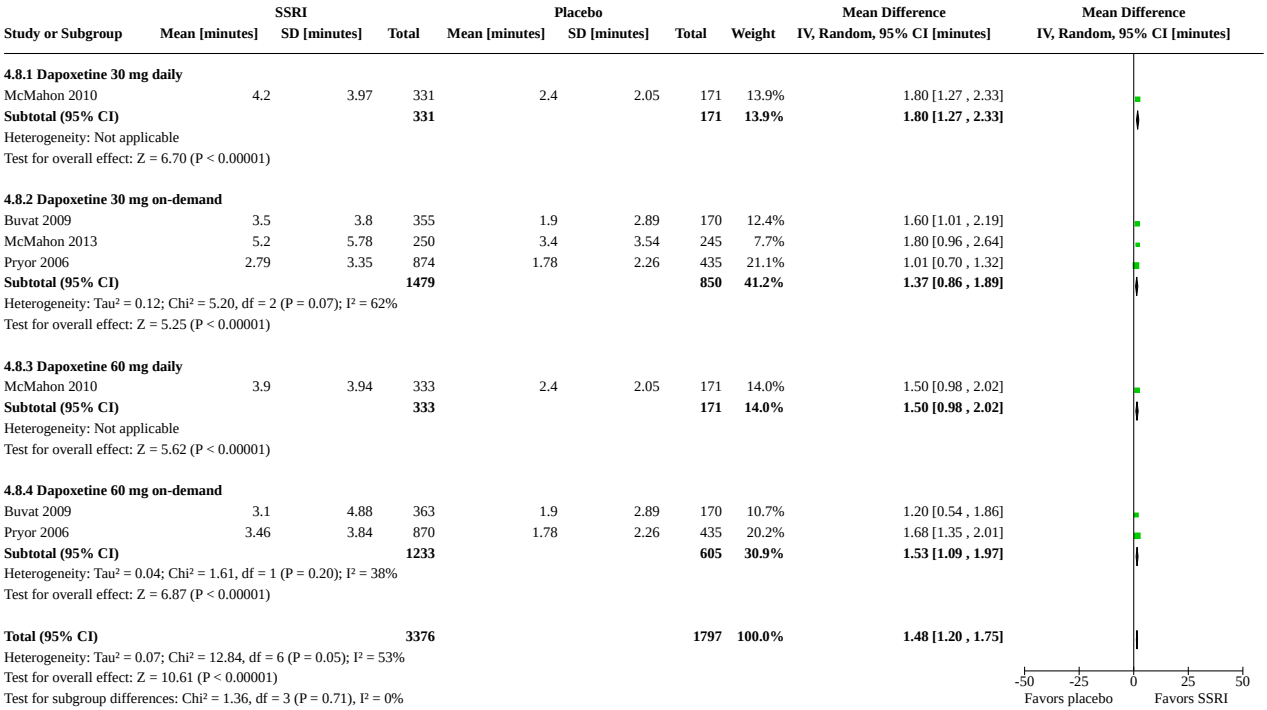


Analysis 4.7. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 7: Adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Dapoxetine 30 mg daily						
McMahon 2010	118	354	32	179	12.1%	1.86 [1.32 , 2.64]
McMahon 2013	74	250	49	245	13.2%	1.48 [1.08 , 2.03]
Subtotal (95% CI)		**604**		**424**	**25.3%**	**1.64 [1.30 , 2.07]**
Total events:	192		81			
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 4.17 (P < 0.0001)						
4.7.2 Dapoxetine 30 mg on-demand						
Buvat 2009	218	388	74	193	17.9%	1.47 [1.20 , 1.79]
Subtotal (95% CI)		**388**		**193**	**17.9%**	**1.47 [1.20 , 1.79]**
Total events:	218		74			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.76 (P = 0.0002)						
4.7.3 Dapoxetine 60 mg daily						
McMahon 2010	177	356	32	179	12.6%	2.78 [2.00 , 3.87]
Safarinejad 2006b	19	104	4	50	2.5%	2.28 [0.82 , 6.36]
Safarinejad 2008	19	101	7	101	3.7%	2.71 [1.19 , 6.17]
Subtotal (95% CI)		**561**		**330**	**18.9%**	**2.73 [2.03 , 3.66]**
Total events:	215		43			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 6.69 (P < 0.00001)						
4.7.4 Dapoxetine 60 mg on-demand						
Buvat 2009	265	389	74	193	18.2%	1.78 [1.47 , 2.15]
Kaufman 2009	301	491	108	245	19.6%	1.39 [1.19 , 1.63]
Subtotal (95% CI)		**880**		**438**	**37.9%**	**1.56 [1.23 , 1.99]**
Total events:	566		182			
Heterogeneity: Tau² = 0.02; Chi² = 3.77, df = 1 (P = 0.05); I² = 73%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
Total (95% CI)		**2433**		**1385**	**100.0%**	**1.74 [1.46 , 2.07]**
Total events:	1191		380			
Heterogeneity: Tau² = 0.03; Chi² = 19.28, df = 7 (P = 0.007); I² = 64%						
Test for overall effect: Z = 6.26 (P < 0.00001)						
Test for subgroup differences: Chi² = 12.62, df = 3 (P = 0.006), I² = 76.2%						



Analysis 4.8. Comparison 4: Subgroup analysis: different doses of dapoxetine, Outcome 8: Intravaginal ejaculatory latency time



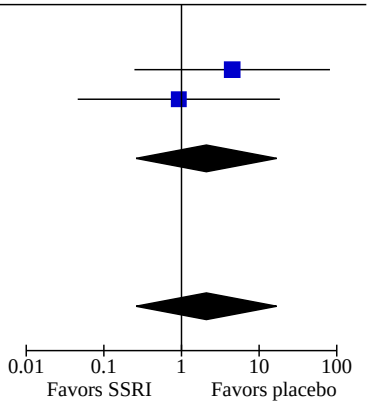
Comparison 5. Subgroup analysis: different doses of fluoxetine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Study withdrawal due to adverse events	3	72	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.26, 16.82]
5.1.1 Fluoxetine 20 mg daily	3	72	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.26, 16.82]
5.2 Adverse events	4	140	Risk Ratio (M-H, Random, 95% CI)	2.50 [1.29, 4.86]
5.2.1 Fluoxetine 20 mg daily	2	57	Risk Ratio (M-H, Random, 95% CI)	9.32 [1.88, 46.26]
5.2.2 Fluoxetine 40 mg daily	1	23	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.55, 9.49]
5.2.3 Fluoxetine 90 mg daily	1	60	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.76, 4.17]
5.3 Intravaginal ejaculatory latency time	5	149	Mean Difference (IV, Random, 95% CI)	2.46 [1.52, 3.39]
5.3.1 Fluoxetine 20 mg daily	3	66	Mean Difference (IV, Random, 95% CI)	2.87 [1.26, 4.48]
5.3.2 Fluoxetine 40 mg daily	1	23	Mean Difference (IV, Random, 95% CI)	-0.54 [-3.57, 2.49]
5.3.3 Fluoxetine 90 mg daily	1	60	Mean Difference (IV, Random, 95% CI)	2.72 [1.83, 3.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Depression	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]
5.4.1 Fluoxetine 20 mg daily	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]

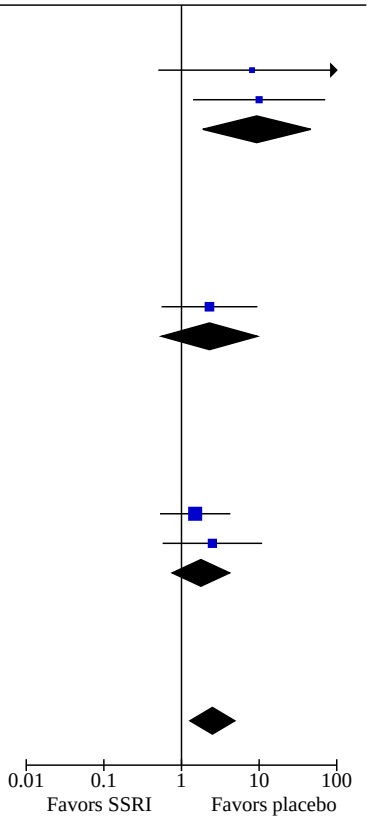
Analysis 5.1. Comparison 5: Subgroup analysis: different doses of fluoxetine, Outcome 1: Study withdrawal due to adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Fluoxetine 20 mg daily						
Kara 1996	2	9	0	8	51.7%	4.50 [0.25 , 81.76]
Waldinger 1998	1	12	0	3	48.3%	0.92 [0.05 , 18.50]
Yilmaz 1999	0	20	0	20		Not estimable
Subtotal (95% CI)		**41**		**31**	**100.0%**	**2.09 [0.26 , 16.82]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**41**		**31**	**100.0%**	**2.09 [0.26 , 16.82]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



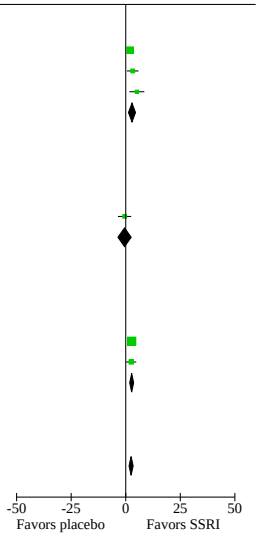
Analysis 5.2. Comparison 5: Subgroup analysis: different doses of fluoxetine, Outcome 2: Adverse events

Study or Subgroup	SSRI Events	SSRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Fluoxetine 20 mg daily						
Kara 1996	4	9	0	8	5.7%	8.10 [0.50 , 130.50]
Yilmaz 1999	10	20	1	20	11.5%	10.00 [1.41 , 70.99]
Subtotal (95% CI)		**29**		**28**	**17.2%**	**9.32 [1.88 , 46.26]**
Total events:	14		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						
5.2.2 Fluoxetine 40 mg daily						
Ahn 1996	5	12	2	11	21.9%	2.29 [0.55 , 9.49]
Subtotal (95% CI)		**12**		**11**	**21.9%**	**2.29 [0.55 , 9.49]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
5.2.3 Fluoxetine 90 mg daily						
Mattos 2008	6	15	4	15	40.6%	1.50 [0.53 , 4.26]
Mattos 2008	5	15	2	15	20.3%	2.50 [0.57 , 10.93]
Subtotal (95% CI)		**30**		**30**	**60.9%**	**1.78 [0.76 , 4.17]**
Total events:	11		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**71**		**69**	**100.0%**	**2.50 [1.29 , 4.86]**
Total events:	30		9			
Heterogeneity: Tau² = 0.00; Chi² = 3.98, df = 4 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.007)						
Test for subgroup differences: Chi² = 3.22, df = 2 (P = 0.20), I² = 37.9%						

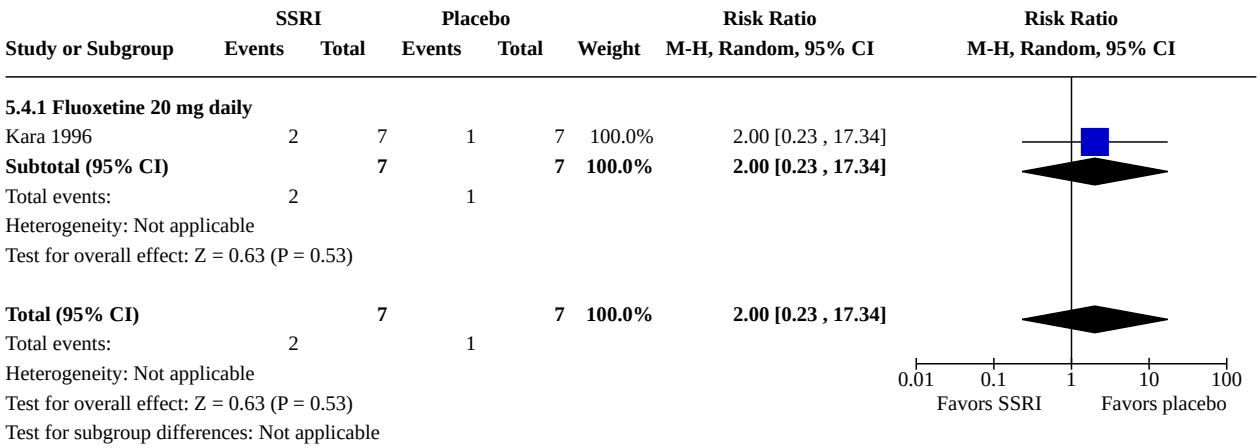


Analysis 5.3. Comparison 5: Subgroup analysis: different doses of fluoxetine, Outcome 3: Intravaginal ejaculatory latency time

Study or Subgroup	SSRI Mean [minutes]	SSRI SD [minutes]	SSRI Total	Placebo Mean [minutes]	Placebo SD [minutes]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [minutes]
5.3.1 Fluoxetine 20 mg daily								
Kara 1996	3	1.66	7	1	0.78	7	26.2%	2.00 [0.64 , 3.36]
Waldinger 1998	3.52	4.18	10	0.33	0.43	2	10.2%	3.19 [0.53 , 5.85]
Yilmaz 1999	6.6	7.7	20	1.5	1.3	20	6.6%	5.10 [1.68 , 8.52]
Subtotal (95% CI)			**37**			**29**	**43.1%**	**2.87 [1.26 , 4.48]**
Heterogeneity: Tau² = 0.73; Chi² = 2.98, df = 2 (P = 0.22); I² = 33%								
Test for overall effect: Z = 3.49 (P = 0.0005)								
5.3.2 Fluoxetine 40 mg daily								
Ahn 1996	0.42	5.3	12	0.96	0.77	11	8.2%	-0.54 [-3.57 , 2.49]
Subtotal (95% CI)			**12**			**11**	**8.2%**	**-0.54 [-3.57 , 2.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								
5.3.3 Fluoxetine 90 mg daily								
Mattos 2008	3.89	1.75	15	1.13	0.77	15	36.0%	2.76 [1.79 , 3.73]
Mattos 2008	5.6	3.75	15	3.11	2.65	15	12.7%	2.49 [0.17 , 4.81]
Subtotal (95% CI)			**30**			**30**	**48.7%**	**2.72 [1.83 , 3.61]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 5.97 (P < 0.00001)								
Total (95% CI)			**79**			**70**	**100.0%**	**2.46 [1.52 , 3.39]**
Heterogeneity: Tau² = 0.39; Chi² = 7.13, df = 5 (P = 0.21); I² = 30%								
Test for overall effect: Z = 5.14 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.28, df = 2 (P = 0.12), I² = 53.2%								



Analysis 5.4. Comparison 5: Subgroup analysis: different doses of fluoxetine, Outcome 4: Depression



ADDITIONAL TABLES

Table 1. Description of the interventions

Study	Intervention(s) (route, frequency, total dose/day)	Comparator(s) (route, frequency, total dose/day)
Ahn 1996	I1: fluoxetine 20 mg daily for first 1 week and 40 mg daily for remaining 5 weeks after breakfast	C1: placebo daily
Athanasios 2007	I1: duloxetine 20 mg daily for 1 week followed by 40 mg daily	C1: placebo daily
Atmaca 2002	I1: citalopram 20 mg daily up to 60 mg	C1: placebo daily up to 3 tablets
Biri 1998	I1: sertraline 50 mg daily	C1: placebo daily
Buvat 2009	I1: dapoxetine 30 mg on-demand I2: dapoxetine 60 mg on-demand	C1: placebo daily C2: placebo daily
Farnia 2009	I1: citalopram 20 mg on-demand	C1: placebo on-demand
Gameel 2013	I1: paroxetine 20 mg on-demand + lubricating jelly	C1: placebo on-demand + lubricating jelly
Gong 2011	I1: paroxetine 20 mg daily	C1: placebo
Hamidi Madani 2016	I1: tramadol 50 mg I2: paroxetine 20 mg	C1: placebo daily
Kara 1996	I1: fluoxetine 20 mg daily	C1: placebo daily
Kaufman 2009	I1: dapoxetine 60 mg on-demand	C1: placebo daily
Khelaia 2012	I1: paroxetine 20 mg I2: paroxetine 20 mg 2–3 hours before intercourse	C1: placebo daily

Table 1. Description of the interventions *(Continued)*

Kim 1998	I1: fluoxetine 40 mg daily for 1 week then 80 mg for 3 weeks I2: sertraline 100 mg for 1 week then 200 mg for 3 weeks	C1: placebo daily C2: placebo daily
Mattos 2008	I1: fluoxetine 90 mg daily I2: fluoxetine 90 mg daily + tadalafil 20 mg on-demand	C1: placebo daily C2: placebo + tadalafil 20 mg on-demand
McMahon 1998	I1: sertraline 50 mg daily	C1: placebo daily
McMahon 1999	I1: paroxetine 20 mg I2: paroxetine as needed 3–4 hours before planned sexual intercourse I3: paroxetine 10 mg for 3 weeks then 20 mg paroxetine as needed for 4 weeks	C1: placebo daily for 3 weeks then placebo daily for 4 weeks
McMahon 2010	I1: dapoxetine 30 mg daily I2: dapoxetine 60 mg daily	C1: placebo daily C2: placebo daily
McMahon 2013	I1: dapoxetine 30 mg on-demand, from week 4 up to 60 mg if tolerated + PDE5 inhibitor	C1: placebo on-demand + PDE5 inhibitor
Mendels 1995	I1: sertraline 50 mg daily that could be titrated up to 200 mg daily	C1: placebo daily
Na 1996	I1: sertraline 50 mg at night that could be titrated up to 100 mg daily	C1: placebo daily
Novaretti 2002	I1: fluoxetine 20 mg daily	C1: placebo daily
Pryor 2006	I1: dapoxetine 30 mg on-demand I2: dapoxetine 60 mg on-demand	C1: placebo on-demand 1–3 hours before anticipated sexual activity
Safarinejad 2006b	I1: dapoxetine 60 mg daily I2: paroxetine 20 mg daily	C1: placebo daily
Safarinejad 2006c	I1: citalopram 20 mg daily	C1: placebo daily
Safarinejad 2007	I1: escitalopram 10 mg daily	C1: placebo daily
Safarinejad 2008	I1: dapoxetine 30 mg twice daily	C1: placebo twice daily
Shang 2012	I1: citalopram 20 mg daily	C1: placebo daily
Tuncel 2008	I1: sertraline 50 mg nightly for 2 months	C1: placebo daily for 2 months
Waldinger 1994	I1: paroxetine 20 mg daily for 1 week and then 40 mg daily from week 2–6	C1: placebo daily
Waldinger 1998	I1: fluoxetine 20 mg daily I2: fluvoxamine 100 mg daily I3: paroxetine 20 mg daily I4: sertraline 50 mg daily	C1: placebo daily

Table 1. Description of the interventions *(Continued)*

Yilmaz 1999	I1: fluoxetine 20 mg daily	C1: placebo daily

C: comparator; I: intervention; PDE5: phosphodiesterase-5.

Table 2. Baseline characteristics

Study	Intervention(s) and comparator(s)	Duration of intervention	Trial period	Country	Setting	Age in years (mean)	Baseline IELT in minutes (mean)	Number of participants with primary/secondary PE
Ahn 1996	I1: fluoxetine 20 mg daily for first 1 week and 40 mg daily for remaining 5 weeks after breakfast	6 weeks	NR	South Korea	Outpatient	39.8 (range 34–48)	0.78 (range 0.17–2.0)	NA/NA
	C1: placebo daily					39.8 (range 34–48)	0.78 (range 0.17–2.0)	NA/NA
Athanasios 2007	I1: duloxetine 20 mg daily for 1 week followed by 40 mg daily	12 weeks	NR	Greece	Academic	31.35 (SD 8.23)	0.63 (SD 0.27)	NA/NA
	C1: placebo daily					32.65 (SD 7.49)	0.58 (SD 0.30)	NA/NA
Atmaca 2002	I1: citalopram 20 mg daily up to 60 mg	8 weeks	NR	Turkey	Outpatient	Range 24–46	0.55 (SD 0.29)	NA/NA
	C1: placebo daily					Range 24–46	0.50 (SD 0.24)	NA/NA
Biri 1998	I1: sertraline 50 mg	4 weeks	1995–1997	Turkey	Outpatient	NR	0.68 (SD 0.21)	NA/NA
	C1: placebo daily					NR	0.72 (SD 0.33)	NA/NA
Buvat 2009	I1: dapoxetine 30 mg on-demand	24 weeks	2004–2006	France	Academic	39.6 (SD 9.53)	0.9 (SD 0.50)	NA/NA
	I2: dapoxetine 60 mg on-demand					40.5 (SD 9.62)	0.9 (SD 0.49)	NA/NA
	C1: placebo daily					40.1 (SD 9.98)	0.9 (SD 0.51)	NA/NA
Farnia 2009	I1: citalopram 20 mg on-demand	4 weeks	2006–2007	Iran	Outpatient	34.28 (SD 6.67)	1.11 (SD 0.61)	NA/NA
	C1: placebo daily					33.76 (SD 5.93)	1.10 (SD 0.56)	NA/NA

Table 2. Baseline characteristics *(Continued)*

Gameel 2013	I1: paroxetine 20 mg on-demand + lubricating jelly C1: placebo on-demand + lubricating jelly	4 weeks	2009–2012	Egypt	Outpatient	NR	0.16 (SD 0.47)	NA/NA
Gong 2011	I1: paroxetine 20 mg daily C1: placebo daily	30 days	NR	China	likely outpatient	26.8 (SD 5.5)	0.89 (SD 0.21)	NA/NA
						29.2 (SD 6.7)	0.97 (SD 0.18)	
Hamidi Madani 2016	I1: tramadol 50 mg I2: paroxetine 20 mg C1: placebo	12 weeks	NR	Iran	Outpatient	NR	NR	NA/NA
						NR	NR	NA/NA
						NR	NR	NA/NA
Kara 1996	I1: fluoxetine 20 mg daily C1: placebo daily	NR	NR	Turkey	Outpatient	Range 15–50	0.42 (SD 0.21)	NA/NA
						Range 15–50	0.5 (SD 0.14)	NA/NA
Kaufman 2009	I1: dapoxetine 60 mg on-demand C1: placebo on-demand	9 weeks	NR	USA and Canada	Outpatient	41.8 (SD 9.80)	NR	NA/NA
						40.98 (SD 9.71)	NR	NA/NA
Khelaia 2012	I1: paroxetine 20 mg I2: paroxetine 20 mg 2–3 hours before intercourse C1: placebo	4 weeks	NR	Georgia	Academic	22.7 (range 19–39)	NR	NA/NA
						22.7 (range 19–39)	NR	NA/NA
						22.7 (range 19–39)	NR	NA/NA
Kim 1998	I1: fluoxetine 40 mg daily for 1 week then 80 mg for 3 weeks I2: sertraline 100 mg for 1 week then 200 mg for 3 weeks C1: placebo daily	16 weeks	NR	South Korea	Academic	44 (range 30–60)	0.77 (SD 0.68)	NA/NA
						44 (range 30–60)	0.77 (SD 0.68)	NA/NA

Table 2. Baseline characteristics *(Continued)*

						44 (range 30–60)	0.77 (SD 0.68)	NA/NA
Mattos 2008	I1: fluoxetine 90 mg daily I2: fluoxetine 90 mg daily + tadalafil 20 mg on-demand C1: placebo daily C2: placebo + tadalafil 20 mg on-demand	12 weeks	NR	Brazil	Academic	50 (SD 8.51)	0.94 (SD 0.31)	NA/NA
						42.81 (SD 7.73)	0.83 (SD 0.43)	NA/NA
						45.93 (SD 9.96)	0.83 (SD 0.31)	NA/NA
						43.2 (SD 11.3)	0.83 (SD 0.32)	NA/NA
McMahon 1998	I1: sertraline 50 mg C1: placebo daily	12 weeks	NR	Australia	Academic	41 (range 19–70)	0.3	NA/NA
						41 (range 19–70)	0.3	NA/NA
McMahon 1999	**Study 1:** I1: paroxetine 20 mg C1: paroxetine as needed 3–4 hours before planned sexual intercourse	17 weeks	NR	Australia	Academic	39.5	0.3	19/7
						39.5	0.3	19/7
	Study 2: I2: paroxetine 10 mg for 3 weeks then 20 mg paroxetine as needed for 4 weeks C2: placebo daily for 3 weeks then placebo daily for 4 weeks					40.5	0.5	32/10
						40.5	0.5	32/10
McMahon 2010	I1: dapoxetine 30 mg on-demand I2: dapoxetine 60 mg on-demand C1: placebo daily	12 weeks	2005–2006	Multicenter in Asia/Pacific	Academic	41.2 (SD 10.74)	3.9	92 (42.2%)/ NA
						41.0 (SD 10.78)	4.2	92 (42.2%)/ NA
						40.6 (SD 9.71)	2.4	96 (45.9%)/ NA

Table 2. Baseline characteristics *(Continued)*

McMahon 2013	I1: dapoxetine 30 mg on-demand, from week 4 up to 60 mg if tolerated + PDE5 inhibitor taken 1–3 hours prior to sexual intercourse C1: placebo daily + PDE5 inhibitor taken 1–3 hours prior to intercourse	12 weeks	2010–2011	Australia	Academic	49.5 (SD 11.23)	NR	92 (42.2%)/ NA
						47.9 (SD 11.96)	NR	96 (45.9%)/ NA
Mendels 1995	I1: sertraline 50 mg daily that could be titrated up to 200 mg daily C1: placebo daily	10 weeks	NR	USA	Academic	NR	0.98 (SD 1.15)	NA/NA
						NR	1.10 (SD 1.35)	NA/NA
Na 1996	I1: sertraline 50 mg at night that could be titrated up to 100 mg daily C1: placebo daily	6 weeks	NR	South Korea	Academic	NR	NR	NA/NA
						NR	NR	
Novaretti 2002	I1: fluoxetine 20 mg C1: placebo daily	20 weeks	1998–2000	Brazil	Academic	37.4 (SD 10.7)	1.01 (SD 0.86)	NA/NA
						37.4 (SD 10.7)	1.05 (SD 1.07)	NA/NA
Pryor 2006	I1: dapoxetine 30 mg on-demand 1–3 hours before anticipated sexual activity I2: dapoxetine 60 mg on-demand 1–3 hours before anticipated sexual activity C1: placebo on-demand 1–3 hours before anticipated sexual activity	12 weeks	2003–2004	USA	Academic	40.3 (SD 9.10)	0.90 (SD 0.47)	563/227
						40.9 (SD 9.09)	0.92 (SD 0.50)	571/234
						40.3 (SD 9.55)	0.91 (SD 0.48)	560/248
Safarinejad 2006b	I1: dapoxetine 60 mg daily I2: paroxetine 20 mg daily C1: placebo daily	12 weeks	2003–2005	Iran	Academic	33.4 (range 20–50)	0.63	64 (61.5%)/ NA
						34.6 (range 21–49)	0.52	63 (60.0%)/ NA
						34.3 (range 21–50)	0.57	11 (44.0%)/ NA

Table 2. Baseline characteristics *(Continued)*

Safarinejad 2006c	I1: citalopram 30 mg C1: placebo daily	6 months	NR	Iran	Academic	32 (21–49) 34 (21–49)	0.53 0.47	10/16 11/14
Safarinejad 2007	I1: escitalopram 10 mg daily C1: placebo daily	12 weeks	2003–2005	Iran	Academic	33.5 (range 21–44) 33.3 (range 19–46)	NR NR	87 (70%)/NA 88 (69.8%)/NA
Safarinejad 2008	I1: dapoxetine 30 mg daily C1: placebo daily	12 weeks	2004–2006	Iran	Academic	35.7 (range 21–54) 36.3 (range 19–56)	0.37 0.48	40 (37.7%)/NA 43 (40.6%)/NA
Shang 2012	I1: citalopram 20 mg daily C1: placebo daily	4 weeks	2011–2012	China	Academic	39.1 (SD 2.5) 37.8 (SD 2.8)	0.91 (SD 0.18) 0.95 (SD 0.17)	NA/NA
Tuncel 2008	I1: sertraline 50 mg nightly for 2 months C1: placebo daily	8 weeks	NR	Turkey	Academic	36.9 (median) (SD 6.9) 34.9 (median) (SD 9.0)	NR NR	NA/NA NA/NA
Waldinger 1994	I1: paroxetine 20 mg daily for 1 week and then 40 mg daily from week 2–6 C1: placebo daily	6 weeks	NR	The Netherlands	Outpatient	41 (range 27–48) 38 (range 30–47)	NR NR	7/8 (87.5%)/NA 7/9 (77.7%)/NA
Waldinger 1998	I1: fluoxetine 20 mg daily I2: fluvoxamine 100 mg daily I3: paroxetine 20 mg daily I4: sertraline 50 mg daily C1: placebo daily	6 weeks	NR	The Netherlands	Outpatient	38 (SD 7.0) 44 (SD 10.0) 41 (SD 8.0) 40 (SD 9.0)	0.3 (SD 0.22) 0.3 (SD 0.22) 0.3 (SD 0.22) 0.3 (SD 0.22)	NA/NA NA/NA NA/NA NA/NA

Table 2. Baseline characteristics *(Continued)*

						45 (SD 4.0)	0.3 (SD 0.22)	NA/NA
Yilmaz 1999	I1: fluoxetine 20 mg daily C1: placebo	1 month	1997–1997	Turkey	Academic	36.5 (range 22–56)	1.2 (SD 1.0)	NA/NA
						37.3 (range 24–58)	1.1 (SD 1.1)	NA/NA

C: comparator; I: intervention; IELT: intravaginal ejaculatory latency time; NA: not available; NR: not reported; PDE5: phosphodiesterase-5; PE: premature ejaculation; SD: standard deviation.

APPENDICES

Appendix 1. Cochrane CENTRAL (Wiley) search strategy

#1	[mh "Premature Ejaculation"]
#2	"early ejaculation":ti,ab,kw OR "rapid ejaculation":ti,ab,kw OR "rapid climax":ti,ab,kw OR "premature climax":ti,ab,kw OR "ejaculatio praecox":ti,ab,kw OR "ejaculatio precox":ti,ab,kw OR "premature ejaculation":ti,ab,kw OR "premature ejaculations":ti,ab,kw OR "early ejaculations":ti,ab,kw OR "premature ejaculator":ti,ab,kw OR "premature ejaculators":ti,ab,kw
#3	#1 OR #2
#4	[mh "Serotonin Uptake Inhibitors"] OR [mh "Serotonin and Noradrenaline Reuptake Inhibitors"]
#5	"5-ht uptake inhibitor":ti,ab,kw OR "5-ht uptake inhibitors":ti,ab,kw OR "5-hydroxytryptamine uptake inhibitor":ti,ab,kw OR "5-hydroxytryptamine uptake inhibitors":ti,ab,kw OR "serotonin and noradrenaline re uptake inhibitor":ti,ab,kw OR "serotonin and noradrenaline reuptake inhibitor":ti,ab,kw OR "serotonin and noradrenaline reuptake inhibitors":ti,ab,kw OR "serotonin and norepinephrine re uptake inhibitor":ti,ab,kw OR "serotonin and norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonin and norepinephrine reuptake inhibitors":ti,ab,kw OR "serotonin norepinephrine re uptake inhibitor":ti,ab,kw OR "serotonin norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonin norepinephrine reuptake inhibitors":ti,ab,kw OR "serotonin reuptake inhibitor":ti,ab,kw OR "serotonin reuptake inhibitor":ti,ab,kw OR "serotonin reuptake inhibitors":ti,ab,kw OR "serotonin uptake inhibitor":ti,ab,kw OR "serotonin uptake inhibitor":ti,ab,kw OR "serotonin uptake inhibitors":ti,ab,kw OR "serotonine and noradrenaline reuptake inhibitor":ti,ab,kw OR "serotonine and noradrenaline reuptake inhibitors":ti,ab,kw OR "serotonine and norepinephrine re uptake inhibitor":ti,ab,kw OR "serotonine and norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonine and norepinephrine reuptake inhibitors":ti,ab,kw OR "serotonine norepinephrine re uptake inhibitor":ti,ab,kw OR "serotonine norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonine norepinephrine reuptake inhibitors":ti,ab,kw OR "serotonine reuptake inhibitor":ti,ab,kw OR "serotonine reuptake inhibitor":ti,ab,kw OR "serotonine reuptake inhibitors":ti,ab,kw OR "serotonine uptake inhibitor":ti,ab,kw OR "serotonine uptake inhibitor":ti,ab,kw OR "serotonine uptake inhibitors":ti,ab,kw OR "serotonine and noradrenaline re uptake inhibitor":ti,ab,kw OR snris:ti,ab,kw OR ssnris:ti,ab,kw OR ssris:ti,ab,kw OR snri:ti,ab,kw OR ssnri:ti,ab,kw OR ssri:ti,ab,kw
#6	Cericlamine:ti,ab,kw OR [mh Citalopram] OR Citalopram:ti,ab,kw OR celexa:ti,ab,kw OR escitalopram:ti,ab,kw OR lexapro:ti,ab,kw OR Cipralex:ti,ab,kw
#7	Dapoxetine:ti,ab,kw OR Priligy:ti,ab,kw OR Westoxetin:ti,ab,kw
#8	[mh "Desvenlafaxine Succinate"] OR Desvenlafaxine:ti,ab,kw OR [mh "Duloxetine Hydrochloride"] OR Duloxetine:ti,ab,kw
#9	femoxetine:ti,ab,kw OR [mh Fluoxetine] OR fluoxetine:ti,ab,kw OR prozac:ti,ab,kw OR Sarafem:ti,ab,kw
#10	[mh Fluvoxamine] OR Fluvoxamine:ti,ab,kw OR luvox:ti,ab,kw
#11	hydroxynefazodone:ti,ab,kw OR hyperforin:ti,ab,kw OR ifoxetine:ti,ab,kw OR indalpine:ti,ab,kw OR liafensine:ti,ab,kw
#12	litoxetine:ti,ab,kw OR lubazodone:ti,ab,kw OR medifoxamine:ti,ab,kw OR milnacipran:ti,ab,kw
#13	moxifetin:ti,ab,kw OR nefazodone:ti,ab,kw OR nomelidine:ti,ab,kw OR norcitalopram:ti,ab,kw

(Continued)

#14	norfluoxetine:ti,ab,kw OR norsertraline:ti,ab,kw OR omiloxetine:ti,ab,kw
#15	[mh Paroxetine] OR Paroxetine:ti,ab,kw OR paxil:ti,ab,kw OR Pexeva:ti,ab,kw OR [mh Sertraline] OR sertraline:ti,ab,kw OR zoloft:ti,ab,kw
#16	tedatioxetine:ti,ab,kw OR [mh Trazodone] OR trazodone:ti,ab,kw OR Desyrel:ti,ab,kw
#17	[mh "Vilazodone Hydrochloride"] OR Vilazodone:ti,ab,kw OR [mh "Venlafaxine Hydrochloride"] OR Venlafaxine:ti,ab,kw OR Pristiq:ti,ab,kw OR Effexor:ti,ab,kw OR Cymbalta:ti,ab,kw
#18	[mh vortioxetine] OR vortioxetine:ti,ab,kw OR [mh Zimeldine] OR Zimeldine:ti,ab,kw OR zimlidine:ti,ab,kw OR zimelidin:ti,ab,kw
#19	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	#3 AND #19

Appendix 2. MEDLINE (PubMed) search strategy

#1	"Premature Ejaculation"[mh]
#2	"early ejaculation"[tw] OR "rapid ejaculation"[tw] OR "rapid climax"[tw] OR "premature climax"[tw] OR "ejaculatio praecox"[tw] OR "ejaculatio precox"[tw] OR "premature ejaculation"[tw] OR "premature ejaculations"[tw] OR "early ejaculations"[tw] OR "premature ejaculator"[tw] OR "premature ejaculators"[tw]
#3	#1 OR #2
#4	Serotonin Uptake Inhibitors[mh] OR Serotonin Uptake Inhibitors[pa] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[mh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[pa]
#5	"5-ht uptake inhibitor"[tw] OR "5-ht uptake inhibitors"[tw] OR "5-hydroxytryptamine uptake inhibitor"[tw] OR "5-hydroxytryptamine uptake inhibitors"[tw] OR "serotonin and noradrenaline re uptake inhibitor"[tw] OR "serotonin and noradrenaline reuptake inhibitor"[tw] OR "serotonin and noradrenaline reuptake inhibitors"[tw] OR "serotonin and norepinephrine re uptake inhibitor"[tw] OR "serotonin and norepinephrine reuptake inhibitor"[tw] OR "serotonin and norepinephrine reuptake inhibitors"[tw] OR "serotonin norepinephrine re uptake inhibitor"[tw] OR "serotonin norepinephrine reuptake inhibitor"[tw] OR "serotonin norepinephrine reuptake inhibitors"[tw] OR "serotonin reuptake inhibitor"[tw] OR "serotonin reuptake inhibitor"[tw] OR "serotonin reuptake inhibitors"[tw] OR "serotonin uptake inhibitor"[tw] OR "serotonin uptake inhibitor"[tw] OR "serotonin uptake inhibitors"[tw] OR "serotonine and noradrenaline reuptake inhibitor"[tw] OR "serotonine and noradrenaline reuptake inhibitors"[tw] OR "serotonine and norepinephrine re uptake inhibitor"[tw] OR "serotonine and norepinephrine reuptake inhibitor"[tw] OR "serotonine and norepinephrine reuptake inhibitors"[tw] OR "serotonine norepinephrine re uptake inhibitor"[tw] OR "serotonine norepinephrine reuptake inhibitor"[tw] OR "serotonine norepinephrine reuptake inhibitors"[tw] OR "serotonine reuptake inhibitor"[tw] OR "serotonine reuptake inhibitor"[tw] OR "serotonine reuptake inhibitors"[tw] OR "serotonine uptake inhibitor"[tw] OR "serotonine uptake inhibitor"[tw] OR "serotonine uptake inhibitors"[tw] OR "serotonine and noradrenaline re uptake inhibitor"[tw] OR snris[tw] OR ssnris[tw] OR ssris[tw] OR snri[tw] OR ssnri[tw] OR ssri[tw]
#6	Cericlamine[tw] OR Citalopram[mh] OR Citalopram[tw] OR celexa[tw] OR escitalopram[tw] OR lexapro[tw] OR Cipralex[tw]

(Continued)

#7	Dapoxetine[tw] OR Dapoxetine[NM] OR Priligy[tw] OR Westoxetin[tw]
#8	"Desvenlafaxine Succinate"[mh] OR Desvenlafaxine[tw] OR "Duloxetine Hydrochloride"[mh] OR Duloxetine[tw]
#9	femoxetine[NM] OR femoxetine[tw] OR Fluoxetine[mh] OR fluoxetine[tw] OR prozac[tw] OR Sarafem[tw]
#10	Fluvoxamine[mh] OR Fluvoxamine[tw] OR luvox[tw]
#11	hydroxynefazodone[tw] OR hyperforin[tw] OR ifoxetine[tw] OR indalpine[NM] OR indalpine[tw] OR liafensine[tw]
#12	litoxetine[tw] OR lubazodone[tw] OR medifoxamine[tw] OR milnacipran[NM] OR milnacipran[tw]
#13	moxifetin[tw] OR nefazodone[tw] OR nomelidine[tw] OR norcitalopram[tw]
#14	norfluoxetine[tw] OR norsertraline[tw] OR omiloxetine[tw]
#15	Paroxetine[mh] OR Paroxetine[tw] OR paxil[tw] OR Pexeva[tw] OR Sertraline[mh] OR sertraline[tw] OR zoloft[tw]
#16	tedatioxetine[tw] OR Trazodone[mh] OR trazodone[tw] OR Desyrel[tw]
#17	"Vilazodone Hydrochloride"[mh] OR Vilazodone[tw] OR "Venlafaxine Hydrochloride"[mh] OR Venlafaxine[tw] OR Pristiq[tw] OR Effexor[tw] OR Cymbalta[tw]
#18	vortioxetine[NM] OR vortioxetine[tw] OR Zimeldine[mh] OR Zimeldine[tw] OR zimlidine[tw] OR zimelidin[tw]
#19	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	randomized controlled trial[pt]
#21	controlled clinical trial[pt]
#22	randomized[tiab]
#23	placebo[tiab]
#24	drug therapy[sh]
#25	randomly[tiab]
#26	trial[tiab]
#27	groups[tiab]
#28	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29	animals[mh] NOT humans[mh]
#30	#28 NOT #29
#31	#3 AND #19 AND #30

Appendix 3. Embase (Elsevier) search strategy

#1	'Premature Ejaculation'/exp
#2	'early ejaculation':ti,ab OR 'rapid ejaculation':ti,ab OR 'rapid climax':ti,ab OR 'premature climax':ti,ab OR 'ejaculatio praecox':ti,ab OR 'ejaculatio precox':ti,ab OR 'premature ejaculation':ti,ab OR 'premature ejaculations':ti,ab OR 'early ejaculations':ti,ab OR 'premature ejaculator':ti,ab OR 'premature ejaculators':ti,ab
#3	#1 OR #2
#4	'Serotonin Uptake Inhibitor'/exp OR 'Serotonin and Noradrenaline Reuptake Inhibitors'/exp
#5	'5-ht uptake inhibitor':ti,ab OR '5-ht uptake inhibitors':ti,ab OR '5-hydroxytryptamine uptake inhibitor':ti,ab OR '5-hydroxytryptamine uptake inhibitors':ti,ab OR 'serotonin and noradrenaline re uptake inhibitor':ti,ab OR 'serotonin and noradrenaline reuptake inhibitor':ti,ab OR 'serotonin and noradrenaline reuptake inhibitors':ti,ab OR 'serotonin and norepinephrine re uptake inhibitor':ti,ab OR 'serotonin and norepinephrine reuptake inhibitor':ti,ab OR 'serotonin and norepinephrine reuptake inhibitors':ti,ab OR 'serotonin norepinephrine re uptake inhibitor':ti,ab OR 'serotonin norepinephrine reuptake inhibitor':ti,ab OR 'serotonin norepinephrine reuptake inhibitors':ti,ab OR 'serotonin reuptake inhibitor':ti,ab OR 'serotonin reuptake inhibitor':ti,ab OR 'serotonin reuptake inhibitors':ti,ab OR 'serotonin uptake inhibitor':ti,ab OR 'serotonin uptake inhibitor':ti,ab OR 'serotonin uptake inhibitors':ti,ab OR 'serotonine and noradrenaline reuptake inhibitor':ti,ab OR 'serotonine and noradrenaline reuptake inhibitors':ti,ab OR 'serotonine and norepinephrine re uptake inhibitor':ti,ab OR 'serotonine and norepinephrine reuptake inhibitor':ti,ab OR 'serotonine and norepinephrine reuptake inhibitors':ti,ab OR 'serotonine norepinephrine re uptake inhibitor':ti,ab OR 'serotonine norepinephrine reuptake inhibitor':ti,ab OR 'serotonine norepinephrine reuptake inhibitors':ti,ab OR 'serotonine reuptake inhibitor':ti,ab OR 'serotonine reuptake inhibitor':ti,ab OR 'serotonine reuptake inhibitors':ti,ab OR 'serotonine uptake inhibitor':ti,ab OR 'serotonine uptake inhibitor':ti,ab OR 'serotonine uptake inhibitors':ti,ab OR 'serotonine and noradrenaline re uptake inhibitor':ti,ab OR snris:ti,ab OR ssnris:ti,ab OR ssris:ti,ab OR snri:ti,ab OR ssnri:ti,ab OR ssri:ti,ab
#6	'Cericlamine'/exp OR cericlamine:ti,ab OR 'Citalopram'/exp OR Citalopram:ti,ab OR celexa:ti,ab OR 'escitalopram'/exp OR escitalopram:ti,ab OR lexapro:ti,ab OR Cipralex:ti,ab
#7	'Dapoxetine'/exp OR Dapoxetine:ti,ab OR Priligy:ti,ab OR Westoxetin:ti,ab
#8	'Desvenlafaxine'/exp OR Desvenlafaxine:ti,ab OR 'Duloxetine Hydrochloride'/exp OR Duloxetine:ti,ab
#9	femoxetine/exp OR femoxetine:ti,ab OR 'Fluoxetine'/exp OR fluoxetine:ti,ab OR prozac:ti,ab OR Sarafem:ti,ab
#10	'Fluvoxamine'/exp OR Fluvoxamine:ti,ab OR luvox:ti,ab
#11	'hydroxynefazodone'/exp OR hydroxynefazodone:ti,ab OR 'hyperforin'/exp OR hyperforin:ti,ab OR 'ifoxetine'/exp OR ifoxetine:ti,ab OR indalpine:ti,ab OR 'liafensine'/exp OR liafensine:ti,ab
#12	'litoxetine'/exp OR litoxetine:ti,ab OR 'lubazodone'/exp OR lubazodone:ti,ab OR 'medifoxamine'/exp OR medifoxamine:ti,ab OR 'milnacipran'/exp OR milnacipran:ti,ab
#13	'moxifetin'/exp OR moxifetin:ti,ab OR 'nefazodone'/exp OR nefazodone:ti,ab OR 'nomelidine'/exp OR nomelidine:ti,ab OR 'norcitalopram'/exp OR norcitalopram:ti,ab

(Continued)

#14	'norfluoxetine'/exp OR norfluoxetine:ti,ab OR 'norsertraline'/exp OR norsertraline:ti,ab OR 'omiloxetine'/exp OR omiloxetine:ti,ab
#15	'Paroxetine'/exp OR Paroxetine:ti,ab OR paxil:ti,ab OR Pexeva:ti,ab OR 'Sertraline'/exp OR sertraline:ti,ab OR zoloft:ti,ab
#16	'tedatioxetine'/exp OR tedatioxetine:ti,ab OR 'Trazodone'/exp OR trazodone:ti,ab OR Desyrel:ti,ab
#17	'Vilazodone'/exp OR Vilazodone:ti,ab OR 'Venlafaxine Hydrochloride'/exp OR Venlafaxine:ti,ab OR Pristiq:ti,ab OR Effexor:ti,ab OR Cymbalta:ti,ab
#18	'vortioxetine'/exp OR vortioxetine:ti,ab OR 'Zimeldine'/exp OR Zimeldine:ti,ab OR zimlidine:ti,ab OR zimelidin:ti,ab
#19	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	'Clinical Trial'/exp
#21	'Randomized Controlled Trial'/exp
#22	'controlled clinical trial'/exp
#23	'multicenter study'/exp
#24	'Phase 3 clinical trial'/exp
#25	'Phase 4 clinical trial'/exp
#26	'Randomization'/exp
#27	'Single Blind Procedure'/exp
#28	'Double Blind Procedure'/exp
#29	'Crossover Procedure'/exp
#30	'Placebo'/exp
#31	randomi?ed controlled trial*:ti,ab
#32	rct:ti,ab
#33	(random* NEAR/2 allocat*):ti,ab
#34	single blind*:ti,ab
#35	double blind*:ti,ab
#36	((treble OR triple) NEAR/1 blind*):ti,ab
#37	placebo*:ti,ab
#38	'Prospective Study'/exp

(Continued)

#39	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
#40	'Case Study'/exp
#41	case report:ti,ab
#42	'abstract report'/exp OR 'letter'/exp
#43	'Conference proceeding':pt
#44	'Conference abstract':pt
#45	Editorial.pt
#46	Letter.pt
#47	Note.pt
#48	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
#49	#39 NOT #48
#50	#3 AND #19 AND #49

Appendix 4. CINAHL (EBSCOhost) search strategy

#1	(MH "Premature Ejaculation+")
#2	TX "early ejaculation" OR TX "rapid ejaculation" OR TX "rapid climax" OR TX "premature climax" OR TX "ejaculatio praecox" OR TX "ejaculatio precox" OR TX "premature ejaculation" OR TX "premature ejaculations" OR TX "early ejaculations" OR TX "premature ejaculator" OR TX "premature ejaculators"
#3	S1 AND S2
#4	(MH "Serotonin Uptake Inhibitors+")
#5	TX "5-ht uptake inhibitor" OR TX "5-ht uptake inhibitors" OR TX "5-hydroxytryptamine uptake inhibitor" OR TX "5-hydroxytryptamine uptake inhibitors" OR TX "serotonin and noradrenaline re uptake inhibitor" OR TX "serotonin and noradrenaline reuptake inhibitor" OR TX "serotonin and noradrenaline reuptake inhibitors" OR TX "serotonin and norepinephrine re uptake inhibitor" OR TX "serotonin and norepinephrine reuptake inhibitor" OR TX "serotonin and norepinephrine reuptake inhibitors" OR TX "serotonin norepinephrine re uptake inhibitor" OR TX "serotonin norepinephrine reuptake inhibitor" OR TX "serotonin norepinephrine reuptake inhibitors" OR TX "serotonin reuptake inhibitor" OR TX "serotonin reuptake inhibitor" OR TX "serotonin reuptake inhibitors" OR TX "serotonin uptake inhibitor" OR TX "serotonin uptake inhibitor" OR TX "serotonin uptake inhibitors" OR TX "serotonine and noradrenaline reuptake inhibitor" OR TX "serotonine and noradrenaline reuptake inhibitors" OR TX "serotonine and norepinephrine re uptake inhibitor" OR TX "serotonine and norepinephrine reuptake inhibitor" OR TX "serotonine and norepinephrine reuptake inhibitors" OR TX "serotonine norepinephrine re uptake inhibitor" OR TX "serotonine norepinephrine reuptake inhibitor" OR TX "serotonine norepinephrine reuptake inhibitors" OR TX "serotonine reuptake inhibitor" OR TX "serotonine reuptake inhibitor" OR TX "serotonine reuptake inhibitors" OR TX "serotonine uptake inhibitor" OR TX "serotonine uptake inhibitor" OR TX "seroto-

(Continued)

	nine uptake inhibitors" OR TX "serotonine and noradrenaline re uptake inhibitor" OR TX snris OR TX ssnris OR TX ssris OR TX snri OR TX ssnri OR TX ssri
#6	TX Cericlamine OR (MH "Citalopram+") OR TX Citalopram OR TX celexa OR TX escitalopram OR TX lexapro OR TX Cipralex
#7	TX Dapoxetine OR TX Priligy OR TX Westoxetin
#8	(MH "Desvenlafaxine Succinate+") OR TX Desvenlafaxine OR (MH "Duloxetine Hydrochloride+") OR TX Duloxetine
#9	TX femoxetine OR (MH "Fluoxetine+") OR TX fluoxetine OR TX prozac OR TX Sarafem
#10	(MH "Fluvoxamine Maleate+") OR TX Fluvoxamine OR TX luvox
#11	TX hydroxynefazodone OR TX hyperforin OR TX ifoxetine OR TX indalpine OR TX liafensine
#12	TX litoxetine OR TX lubazodone OR TX medifoxamine OR TX milnacipran
#13	TX moxifetin OR TX nefazodone OR TX nomelidine OR TX norcitalopram
#14	TX norfluoxetine OR TX norsertraline OR TX omiloxetine
#15	(MH "Paroxetine+") OR TX Paroxetine OR TX paxil OR TX Pexeva OR (MH "Sertraline Hydrochloride+") OR TX sertraline OR TX zoloft
#16	TX tedatioxetine OR (MH "Trazodone+") OR TX trazodone OR TX Desyrel
#17	TX Vilazodone OR (MH "Venlafaxine+") OR TX Venlafaxine OR TX Pristiq OR TX Effexor OR TX Cymbalta
#18	TX vortioxetine OR TX Zimeldine OR TX zimlidine OR TX zimelidin
#19	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
#20	MH "Clinical Trials+"
#21	PT "Clinical trial"
#22	TX clinic* n1 trial*
#23	TX (singl* n1 blind*) OR TX (singl* n1 mask*) OR TX (doubl* n1 blind*) OR TX (doubl* n1 mask*) OR TX (tripl* n1 blind*) OR TX (tripl* n1 mask*) OR TX (trebl* n1 blind*) OR TX (trebl* n1 mask*)
#24	TX randomi* control* trial*
#25	MH "Random Assignment"
#26	TX random* allocat*
#27	TX placebo*
#28	MH "Placebos"
#29	MH "Quantitative Studies"

(Continued)

#30	TX allocat* random*
#31	S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
#32	S3 AND S19 AND S31

Appendix 5. LILACS (BIREME/PAHO/WHO) search strategy

Using iAH Search Interface **; In Field - Words:**

(MH:"Premature Ejaculation" OR MH:"Eyaculación Prematura" OR MH:"Ejaculação Precoce" OR "Ejaculatio Praecox" OR "Premature ejaculation" OR "early ejaculation" OR "rapid ejaculation" OR "rapid climax" OR "premature climax" OR "ejaculatio precox" OR "premature ejaculation" OR "premature ejaculations" OR "early ejaculations" OR "premature ejaculator" OR "premature ejaculators")

AND

(MH:"Serotonin Uptake Inhibitors" OR MH:"Inhibidores de la Captación de Serotonina" OR MH:"Inibidores da Captação de Serotonina" OR "5-ht uptake inhibitor" OR "5-ht uptake inhibitors" OR "5-hydroxytryptamine uptake inhibitor" OR "5-hydroxytryptamine uptake inhibitors" OR "serotonin and noradrenaline re uptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitors" OR "serotonin and norepinephrine re uptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitors" OR "serotonin norepinephrine re uptake inhibitor" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitors" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitors" OR "serotonine and noradrenaline reuptake inhibitor" OR "serotonine and noradrenaline reuptake inhibitors" OR "serotonine and norepinephrine re uptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitors" OR "serotonine norepinephrine re uptake inhibitor" OR "serotonine norepinephrine reuptake inhibitor" OR "serotonine norepinephrine reuptake inhibitors" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitors" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitors" OR "serotonine and noradrenaline re uptake inhibitor" OR snris OR ssnris OR ssris OR snri OR ssnri OR ssri OR Cericlamine OR MH:Citalopram OR Citalopram OR celexa OR escitalopram OR lexapro OR Cipralex OR Dapoxetine OR Priligy OR Westoxetin OR MH:"Desvenlafaxine Succinate" OR MH:"Succinato de Desvenlafaxina" OR Desvenlafaxine OR MH:"Duloxetine Hydrochloride" OR MH:"Clorhidrato de Duloxetina" OR MH:"Cloridrato de Duloxetina" OR Duloxetine OR femoxetine OR MH:Fluoxetine OR MH:Fluoxetina OR fluoxetine OR prozac OR Sarafem OR MH:Fluvoxamine OR MH:Fluvoxamina OR Fluvoxamine OR luvox OR hydroxynefazodone OR hyperforin OR ifoxetine OR indalpine OR liafensine OR litoxetine OR lubazodone OR medifoxamine OR milnacipran OR moxifetin OR nefazodone OR nomelidine OR norcitalopram OR norfluoxetine OR norsertraline OR omiloxetine OR MH:Paroxetine OR MH:Paroxetine OR Paroxetine OR paxil OR Pexeva OR MH:Sertraline OR MH:Sertralina OR sertraline OR zoloft OR tedatioxetine OR MH:Trazodone OR MH:Trazodona OR trazodone OR Desyrel OR MH:"Vilazodone Hydrochloride" OR MH:"Clorhidrato de Vilazodona" OR MH:"Cloridrato de Vilazodona" OR Vilazodone OR MH:"Venlafaxine Hydrochloride" OR MH:"Clorhidrato de Venlafaxina" OR MH:"Cloridrato de Venlafaxina" OR Venlafaxine OR Pristiq OR Effexor OR Cymbalta OR vortioxetine OR MH:Zimeldine OR MH:Zimeldina OR Zimeldine OR zimlidine OR zimelidin)

Appendix 6. Scopus (Elsevier) search strategy

In Advanced Search:

TITLE-ABS-KEY("Premature Ejaculation" OR "early ejaculation" OR "rapid ejaculation" OR "rapid climax" OR "premature climax" OR "ejaculatio praecox" OR "ejaculatio precox" OR "premature ejaculation" OR "premature ejaculations" OR "early ejaculations" OR "premature ejaculator" OR "premature ejaculators") AND TITLE-ABS-KEY("5-ht uptake inhibitor" OR "5-ht uptake inhibitors" OR "5-hydroxytryptamine uptake inhibitor" OR "5-hydroxytryptamine uptake inhibitors" OR "serotonin and noradrenaline re uptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitors" OR "serotonin and norepinephrine re uptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitors" OR "serotonin norepinephrine re uptake inhibitor" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitors" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitors" OR "serotonine and noradrenaline reuptake inhibitor" OR "serotonine and noradrenaline reuptake inhibitors" OR "serotonine and norepinephrine re uptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitors" OR "serotonine norepinephrine re uptake inhibitor" OR "serotonine norepinephrine reuptake inhibitor" OR "serotonine norepinephrine reuptake inhibitors" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitors" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitors" OR "serotonine and noradrenaline re uptake inhibitor" OR snris OR ssnris OR ssris OR snri OR ssnri OR ssri OR Cericlamine OR Citalopram OR celexa OR escitalopram OR lexapro OR Cipralex OR Dapoxetine OR Priligy OR Westoxetin OR Desvenlafaxine OR Duloxetine OR femoxetine OR Fluoxetine OR fluoxetine OR prozac OR Sarafem OR Fluvoxamine

OR luvox OR hydroxynefazodone OR hyperforin OR ifoxetine OR indalpine OR liafensine OR litoxetine OR lubazodone OR medifoxamine OR milnacipran OR moxifetin OR nefazodone OR nomelidine OR norcitalopram OR norfluoxetine OR norsertraline OR omiloxetine OR Paroxetine OR paxil OR Pexeva OR Sertraline OR zoloft OR tedatioxetine OR Trazodone OR Desyrel OR Vilazodone OR Venlafaxine OR Pristiq OR Effexor OR Cymbalta OR vortioxetine OR Zimeldine OR zimlidine OR zimelidin) AND TITLE-ABS-KEY((clinic* w/1 trial*) OR (randomi* w/1 control*) OR (randomi* w/2 trial*) OR (random* w/1 assign*) OR (random* w/1 allocat*) OR (control* w/1 clinic*) OR (control* w/1 trial) OR placebo* OR (Quantitat* w/1 Stud*) OR (control* w/1 stud*) OR (randomi* w/1 stud*) OR (singl* w/1 blind*) or (singl* w/1 mask*) OR (doubl* w/1 blind*) OR (doubl* w/1 mask*) OR (tripl* w/1 blind*) OR (tripl* w/1 mask*) OR (trebl* w/1 blind*) OR (trebl* w/1 mask*)) AND NOT (SRCTYPE(b) OR SRCTYPE(k) OR SRCTYPE(p) OR SRCTYPE(r) OR SRCTYPE(d) OR DOCTYPE(ab) OR DOCTYPE(bk) OR DOCTYPE(ch) OR DOCTYPE(bz) OR DOCTYPE(cr) OR DOCTYPE(ed) OR DOCTYPE(er) OR DOCTYPE(le) OR DOCTYPE(no) OR DOCTYPE(pr) OR DOCTYPE(rp) OR DOCTYPE(re) OR DOCTYPE(sh))

Appendix 7. ClinicalTrials.gov search strategy

clinicaltrials.gov

Advanced Search – Targeted Search (Note: length of search strings limited for this interface)

Condition/Disease: "Premature Ejaculation" OR "early ejaculation" OR "rapid ejaculation" OR "rapid climax" OR "premature climax" OR "ejaculatio praecox" OR "ejaculatio precox" OR "premature ejaculator" OR "premature ejaculators"

Intervention/Treatment: "Serotonin Reuptake Inhibitors" OR "Serotonin Uptake Inhibitors" OR "5-Hydroxytryptamine Uptake Inhibitors" OR "5-HT Uptake Inhibitors" OR SSRI OR "Serotonin and Noradrenaline Reuptake Inhibitors" OR "serotonin and norepinephrine reuptake inhibitors"

Appendix 8. WHO International Clinical Trials Registry Platform (ICTRP) search strategy

apps.who.int/trialsearch/

In Advanced Search:

In Condition: Premature Ejaculation OR early ejaculation OR rapid ejaculation OR rapid climax OR premature climax OR ejaculatio praecox OR ejaculatio precox OR premature ejaculations OR early ejaculations OR premature ejaculator OR premature ejaculators

Appendix 9. ProQuest Dissertations & Theses search strategy

Advanced Search (Leave field choice on "anywhere"):

"Premature Ejaculation" OR "early ejaculation" OR "rapid ejaculation" OR "rapid climax" OR "premature climax" OR "ejaculatio praecox" OR "ejaculatio precox" OR "premature ejaculations" OR "early ejaculations" OR "premature ejaculator" OR "premature ejaculators"

AND

"5-ht uptake inhibitor" OR "5-ht uptake inhibitors" OR "5-hydroxytryptamine uptake inhibitor" OR "5-hydroxytryptamine uptake inhibitors" OR "serotonin and noradrenaline re uptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitors" OR "serotonin and norepinephrine re uptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitors" OR "serotonin norepinephrine re uptake inhibitor" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitors" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitors" OR "serotonine and noradrenaline reuptake inhibitor" OR "serotonine and noradrenaline reuptake inhibitors" OR "serotonine and norepinephrine re uptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitors" OR "serotonine norepinephrine re uptake inhibitor" OR "serotonine norepinephrine reuptake inhibitor" OR "serotonine norepinephrine reuptake inhibitors" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitors" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitors" OR "serotonine and noradrenaline re uptake inhibitor" OR snris OR ssnris OR ssris OR snri OR ssnri OR ssri OR Cericlamine OR Citalopram OR celexa OR escitalopram OR lexapro OR Cipralex OR Dapoxetine OR Priligy OR Westoxetin OR Desvenlafaxine OR Duloxetine OR femoxetine OR Fluoxetine OR fluoxetine OR prozac OR Sarafem OR Fluvoxamine OR luvox OR hydroxynefazodone OR hyperforin OR ifoxetine OR indalpine OR liafensine OR litoxetine OR lubazodone OR medifoxamine OR milnacipran OR moxifetin OR nefazodone OR nomelidine OR norcitalopram OR norfluoxetine OR norsertraline OR omiloxetine OR Paroxetine OR paxil OR Pexeva OR Sertraline OR zoloft OR tedatioxetine OR Trazodone OR Desyrel OR Vilazodone OR Venlafaxine OR Pristiq OR Effexor OR Cymbalta OR vortioxetine OR Zimeldine OR zimlidine OR zimelidin

Appendix 10. OCLC WorldCat Dissertations and Theses search strategy

www.worldcat.org/

Advanced Search

Keyword: ("Premature Ejaculation" OR "early ejaculation" OR "rapid ejaculation" OR "rapid climax" OR "premature climax" OR "ejaculatio praecox" OR "ejaculatio precox" OR "premature ejaculations" OR "early ejaculations" OR "premature ejaculator" OR "premature ejaculators") AND ("5-ht uptake inhibitor" OR "5-ht uptake inhibitors" OR "5-hydroxytryptamine uptake inhibitor" OR "5-hydroxytryptamine uptake inhibitors" OR "serotonin and noradrenaline re uptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitor" OR "serotonin and noradrenaline reuptake inhibitors" OR "serotonin and norepinephrine re uptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitor" OR "serotonin and norepinephrine reuptake inhibitors" OR "serotonin norepinephrine re uptake inhibitor" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitor" OR "serotonin reuptake inhibitors" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitor" OR "serotonin uptake inhibitors" OR "serotonine and noradrenaline reuptake inhibitor" OR "serotonine and noradrenaline reuptake inhibitors" OR "serotonine and norepinephrine re uptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitor" OR "serotonine and norepinephrine reuptake inhibitors" OR "serotonine norepinephrine re uptake inhibitor" OR "serotonine norepinephrine reuptake inhibitor" OR "serotonine norepinephrine reuptake inhibitors" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitor" OR "serotonine reuptake inhibitors" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitor" OR "serotonine uptake inhibitors" OR "serotonine and noradrenaline re uptake inhibitor" OR snris OR ssnris OR ssris OR snri OR ssnri OR ssri OR Cericlamine OR Citalopram OR celexa OR escitalopram OR lexapro OR Cipralex OR Dapoxetine OR Priligy OR Westoxetin OR Desvenlafaxine OR Duloxetine OR femoxetine OR Fluoxetine OR fluoxetine OR prozac OR Sarafem OR Fluvoxamine OR luvox OR hydroxynefazodone OR hyperforin OR ifoxetine OR indalpine OR liafensine OR litoxetine OR lubazodone OR medifoxamine OR milnacipran OR moxifetin OR nefazodone OR nomelidine OR norcitalopram OR norfluoxetine OR norsertraline OR omiloxetine OR Paroxetine OR paxil OR Pexeva OR Sertraline OR zoloft OR tedatioxetine OR Trazodone OR Desyrel OR Vilazodone OR Venlafaxine OR Pristiq OR Effexor OR Cymbalta OR vortioxetine OR Zimeldine OR zimlidine OR zimelidin)

Select Content: Thesis/Dissertation

HISTORY

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Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

- NS: screened studies; performed full-text review, data extraction and data analysis; and wrote the review.
- ECH: screened studies; performed full-text review, data extraction and data analysis; and revised the review.
- RM: drafted the first version of the protocol; screened studies; performed full-text review, data extraction and data analysis; and revised the review.
- JB: provided clinical content expertise, reviewed and revised the protocol/review.
- AS: provided clinical content expertise, reviewed and revised the protocol/review.
- JL: developed the search strategies; performed and updated the search; and revised the protocol/review.
- SS: provided methodologic expertise, reviewed and revised the protocol/review.
- PD: provided guidance and oversight; screened studies; performed full-text review, data extraction and data analysis; and revised the protocol/review.

DECLARATIONS OF INTEREST

- NS: none.
- ECH: none.
- RM: none.
- JB: none.
- AS: none.
- JL: none.
- SS: none.
- PD: none.

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External sources

- None, USA

N/A

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a published protocol (Mian 2017) but there are two additional authors to this review: Dr Niranjan J Sathianathen and Dr Eu Chang Hwang.

NOTES

We have based parts of the Methods and Appendix 2 sections of this Cochrane Review on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Coitus [psychology]; Confidence Intervals; Ejaculation [drug effects]; Odds Ratio; Patient Satisfaction [statistics & numerical data]; Placebos [therapeutic use]; Premature Ejaculation [*drug therapy] [psychology]; Randomized Controlled Trials as Topic; Selective Serotonin Reuptake Inhibitors [adverse effects] [*therapeutic use]

MeSH check words

Adolescent; Adult; Humans; Male; Middle Aged; Young Adult