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Selective serotonin re-uptake inhibitors for premature ejaculation (Protocol)

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[Intervention Protocol]

Selective serotonin re-uptake inhibitors for premature ejaculation

Ruma Mian[1], Joshua A Bodie[1], Ayman Soubra[1,2], Jennifer A Lyon[3], Shahnaz Sultan[4], Philipp Dahm[2]

[1]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [2]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA. [3]Library Services, Children's Mercy Hospital, Kansas City, Missouri, USA. [4]Gastroenterology Section III-D, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact address: Ruma Mian, Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. rumamian@gmail.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the role of selective serotonin re-uptake inhibitors in the treatment of premature ejaculation.

BACKGROUND

Description of the condition

Premature ejaculation (PE) is broadly defined as a male sexual disorder in which ejaculation occurs at a time point earlier than desired by the patient or his partner, or both, usually with minimal sexual stimulation before, at the time, 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 recent definition of "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" (Althof 2014).

Four subtypes of PE have been defined (Waldinger 2007), namely lifelong, acquired, natural variable, and premature-like ejaculatory dysfunction. 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 premature ejaculation. With primary premature ejaculation, the patient has experienced premature ejaculation since the very beginning of sexual life and it occurs in the absence of organic illnesses. Men with secondary premature ejaculation experience premature ejaculation much later in their adult sexual life and had normal coital relationships previously (Carson 2006).

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 pharmacological treatment of PE, including selective serotonin re-uptake inhibitors (SSRIs), has reinforced stereotypes of 'normal' sexual conduct and thereby reinforced social norms that cause men distress (Soderfeldt 2017). Another recent systematic review raised the concern that dapoxetine may be a costly and dangerous placebo (Feys 2014).

Pathophysiology of premature ejaculation

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). The underlying issue 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, neurobiological, pharmacological, psychological, urological, and endocrine factors have all been implicated (Buvat 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 toward 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

The prevalence rate of PE has historically been estimated as between 6% and 66% (Carson 2006). However, such high prevalence rates and their variability likely reflects the lack of a standardized definition at the time these studies were conducted. Based on the International Society of Sexual Medicine's guideline for PE, the true prevalence is unlikely to exceed 4% of the general population. Globally, the prevalence rate of premature ejaculation falls somewhere between 25% and 40% across men of all age groups (Carson 2006).

Diagnosis

Premature ejaculation is usually based solely on the sexual history of the patient (Carson 2006). According to the guidelines of the American Urological Association, the most important aspect of the assessment is therefore obtaining an accurate sexual history (Montague 2004). Specifically, clinicians should ask patients how long they have had PE, how often it occurs, and whether it happens during all sexual encounters and with all partners, whether the degree of sexual stimulation matters, and lastly, 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.

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).

Lastly, 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. 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.

Treatment

Treatment approaches to PE other than SSRIs can be broadly categorized into behavioral therapy, oral agents, and topical agents (Althof 2014; Castiglione 2016). We have introduced the 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 noradrenaline and 5-hydroxytryptamine. Findings of several randomized controlled trials (RCTs) summarized in systematic reviews and meta-analyses indicate that the daily use of clomipramine increases IELT (Cooper 2015; 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 suggest that it results in an increase in IELT (Martyn-St James 2015; Safarinejad 2006; Salem 2008).

- Phosphodiesterase-5 inhibitors: the primary role of this therapy is in treating ED. However, ED is also common among

men with PE. A systematic review has shown the benefits of this therapy to be questionable (McMahon 2006).

- Alpha-blockers: this drug class is primarily used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia. At least one trial supports a potential role in treating 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 side 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 (Pu 2013; Xia 2013). Side effects include some loss of penile sensitivity, erectile dysfunction, and female genital anesthesia.

Description of the intervention

Selective serotonin re-uptake inhibitor medications are oral agents primarily used to treat depression. Their affect on delaying ejaculation was first identified as a side 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 side 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 yawning, mild nausea, excessive sweating, fatigue, and changes in bowel function (Mulhall 2012).

- Sexual side effects such as reduced libido and new onset or worsening erectile dysfunction have also been reported.

- Stopping long-term treatment of SSRIs may lead to the "SSRI discontinuation syndrome," begining one to three days after drug cessation and possibly continuing for more than a week. Symptoms include nausea, vomiting, dizziness, headache, ataxia, drowsiness, anxiety, and insomnia. It is therefore recommended that SSRI agents 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 (Mulhall 2012).

- Studies of depressed patients on SSRIs have indicated a small increase in the risk of suicide ideation or suicide attempts in youth, but not in adults (Mulhall 2012). To date, no reports indicate an increased risk in non-depressed patients with PE. Nevertheless, 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 mechanism of action of SSRIs is thought to involve the blockage of serotonin, or 5-hydroxytryptamine (5-HT), receptors at the level of the synapse and is based on the study of rats (Giuliano 2006; Waldinger 2005). According to Mulhall 2012, serotonin is released into the synapse by the presynaptic neuron, and once in the synapse binds to the receptor located on the postsynaptic membrane. Subsequently, it returns to the presynaptic neuron facilitated by serotonin transporters. The mechanism of action of SSRIs is to block these serotonin transporters, thereby inhibiting the reabsorption of serotonin into the presynaptic neuron, resulting in increased levels of serotonin in the synapse. 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. 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.

Why it is important to do this review

SSRIs are among the most widely used drugs for premature ejaculation (Althof 2014). 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. It is therefore important for clinicians to fully understand both the benefits and potential harms associated with these agents. 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), only one Cochrane Review exists, which is focused on behavioral therapy alone (Melnik 2011). The planned Cochrane Review will distinguish itself in the following ways.

- All aspects of the systematic review will be governed by a published, a priori protocol.
- We will conduct a comprehensive search of the literature not limited by publication status or language.
- The review will focus on patient-important outcomes, and we will rate the quality of evidence using the GRADE approach on a per-outcome basis.

We therefore believe the planned review will provide important, evidence-based information for patients, clinicians, guideline developers, and health policy makers.

OBJECTIVES

To assess the role of selective serotonin re-uptake inhibitors in the treatment of premature ejaculation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomized controlled clinical trials.

Types of participants

We will include studies of adult men aged ≥ 18 years with PE, both lifelong and acquired. We will exclude men with PE secondary to other known conditions such as prostatitis or PE as a medication side effect.

Diagnostic criteria for premature ejaculation

Since a standardized definition has only recently been developed, we will include studies whether or not they used a standard definition (but recording all definitions used).

Types of interventions

We plan to investigate the following comparisons of intervention versus control/comparator.

Intervention

- SSRI

Comparator

- Placebo/no treatment

Concomitant interventions will have to be the same in both the intervention and comparator groups to establish fair comparisons. If a trial includes multiple arms, we will include any arm that meets the inclusion criteria in the review.
We will not consider agents classified as serotonin-noradrenaline re-uptake inhibitors such as duloxetine.

Minimum duration of intervention and follow-up

- 4 weeks

We will define trial duration according to the number of weeks over which the interventions have been conducted and will only include trials in the analyses with interventions that lasted at least four weeks.

Exclusion criteria

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

Types of outcome measures

We will 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 are reported, we will not include this trial but provide some basic information in an Additional table.

Primary outcomes

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

1. Participant perception of change with treatment
2. Participant satisfaction with intercourse
3. Study withdrawal due to adverse events

We will assess participant perception of change using the Clinical Global Impression of Change questionnaire, which is a validated instrument that is administered after treatment (Althof 2010). We will record the number of participants describing the change as 'better' or 'much better' after treatment. No minimal clinically important difference (MCID) has been reported; we will consider a 10% difference between groups as clinically meaningful. This is a participant self reported outcome.
We will assess participant satisfaction with intercourse using the Premature Ejaculation Profile (PEP) questionnaire (Patrick 2009), a validated instrument that addresses four domains. We will record the number of participants describing their satisfaction as 'good' or 'very good' before and after treatment (for satisfaction and control). For distress and relationship difficulties, we will record the number of participants describing their distress 'a little bit' or 'not at all.' No MCID has been reported; we will consider a 10% difference between groups as clinically meaningful. All of these are participant self reported outcomes.
We will record the number of participants withdrawing from the trial due to adverse events. We will consider a 5% difference between groups as clinically meaningful. This is an investigator-assessed outcome.

Secondary outcomes

1. Perceived control over ejaculation
2. Participant distress about PE
3. Relationship difficulties
4. Adverse events
5. Intravaginal ejaculatory latency time (IELT)
6. Depression

We will also use the PEP questionnaire to assess participant satisfaction with control over ejaculation, distress about PE, and relationship difficulties (Patrick 2009). We will record the number of participants describing their satisfaction as 'good' or 'very good' before and after treatment (for satisfaction and control). For distress and relationship difficulties, we will record the number of participants describing their distress 'a little bit' or 'not at all.' No MCID has been reported; we will consider a 10% difference between groups as clinically meaningful. All of these are participant self reported outcomes.

We will further assess the cumulative number of adverse events. We will consider a 5% difference between groups as clinically meaningful. This is an investigator-assessed outcome. We will also provide descriptive information on the most common adverse events contributing to this analysis.

We will assess IELT as measured using a stopwatch in minutes (McMahon 2010). 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. No MCID has been reported in the literature. We will therefore assume a one-minute difference as the smallest difference between groups to be clinically meaningful. This will be based on the mean IELT; we will not use the geometric mean average IELT, which has been proposed as an alternative measure more robust to non-normal distributions (Waldinger 2008).

We will record the incidence of new symptoms of depression in participants. Ideally, we would seek out information using validated instruments such as the Beck Depression Inventory questionnaire (Novaretti 2002), but will also record other types of information as collected by the investigators. No MCID has been reported; we will consider a 10% difference between groups as clinically meaningful. This may either be a participant self reported or investigator-assessed outcome.

Summary of findings

We will present a 'Summary of findings' table reporting the 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. Intravaginal ejaculatory latency time (IELT)

Although we do not plan to include relationship distress and depression as outcomes in the 'Summary of findings' table (due to a limit of seven outcomes), we will nevertheless provide the same type of analysis in the Results section and rate the quality of evidence using GRADE.

Search methods for identification of studies

The Cochrane Urology Assistant Information Specialist will conduct systematic searches for RCTs and controlled clinical trials. There will be no restrictions regarding language or publication status.

Electronic searches

We will search the following sources from the inception of each database to the three months before submission for editorial review and will place no restrictions on the language of publication. Complete search strategies for each resource are available in the Appendices.

- PubMed MEDLINE (1946 -) (Appendix 1)
- Embase via Elsevier (1947 -) (Appendix 2)
- Cumulative Index of Nursing and Allied Health Literature (CINAHL) via EBSCOhost (1981 -) (Appendix 3)
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library (1996 -) (Appendix 4)
- Latin American and Caribbean Health Sciences Literature (LILACS) via BIREME-PAHO-WHO (1982 -) (Appendix 5)
- Scopus via Elsevier (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; 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 randomized trials 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 will continuously apply a PubMed (MEDLINE) email alert to identify newly published trials using the same search strategy as described for MEDLINE (see Appendix 1 for search strategy). After we submit the final review draft for editorial approval, the Information Specialist on our review team will perform a complete search update on all databases and will send the results to the review authors. Should we identify new trials for inclusion, we will evaluate these, incorporate the findings into our review, and resubmit another Cochrane Review draft.

If we detect additional relevant keywords during any electronic or other searches, we will modify the electronic search strategies to incorporate these terms and will document the changes.

Searching other resources

We will try to identify 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 will also contact authors of included trials to identify additional information on the retrieved trials and any trials that we might have missed.

We will include studies presented in abstract form only, focusing on these relevant meetings from 2014 to 2017. For these years, abstract proceedings can be searched and identified through electronic searches of the journals identified which will be captured through our electronic MEDLINE search.

- 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) will independently scan the abstract, title, or both of every record we retrieve in the literature searches, to determine which trials we should assess further. We will obtain the full text of all potentially relevant records. Any disagreements will be resolved through consensus or by recourse to a third review author (PD). If we cannot resolve a disagreement, we will categorize the trial as a 'study awaiting classification' and contact the trial authors for clarification. We will present an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009).

Data extraction and management

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

We will provide information about potentially relevant ongoing trials, including the trial identifier, in the 'Characteristics of ongoing studies' table and in a joint appendix 'Matrix of trial endpoint (publications and trial documents).' We will attempt to find the protocol for each included trial and will report primary, secondary, and other outcomes in comparison with data in publications in a joint appendix.

We will email all authors of included trials to ask if they would be willing to answer questions regarding their trials. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the trial from the primary trial author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we will maximize the information yield by collating all available data and use the most complete data set aggregated across all known publications. We will list 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 the included trial. Furthermore, we will also list 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 the excluded trial.

Data from clinical trial registers

If data of included trials are available as study results in clinical trial registers such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract the data. If there is also a

full publication of the trial, we will collate and critically appraise all available data. If an included trial is marked as a completed study in a clinical trial register but no additional information is available, we will add this trial to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

Two review authors (RM, SS) will independently assess the risk of bias of each included trial. Any disagreements will be resolved by consensus or by consulting a third review author (PD). In case of disagreement, we will consult the rest of the group and make a judgement based on consensus. If adequate information is not available from trial authors, trial protocols, or both, we will contact the trial authors for missing data on 'Risk of bias' items.
We will use the Cochrane 'Risk of bias' assessment tool and will judge 'Risk of bias' criteria as having either low, high, or unclear risk (Higgins 2011a; Higgins 2011b). We will evaluate 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 will describe 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 are adequate if an independent person performed this who was not otherwise involved in the trial. We will consider 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 judgement 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 will describe for each included trial the method used to conceal allocation to interventions prior to assignment and will assess 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 will also evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014). Chance imbalances may also affect judgements on the risk of attrition bias. In case of unadjusted analyses, we will distinguish between studies we rate as at low risk of bias on the basis of both randomization methods and baseline similarity, and studies we rate as low risk of bias on the basis of baseline similarity alone (Corbett 2014). We will re-classify judgements 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 will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self reported, investigator assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel is ensured, and it is unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is 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 does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is 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 is likely to be 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 will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self reported, investigator assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is 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 is 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 is 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 will describe the completeness of data, including attrition and exclusions from the analyses. We will state 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 will also note if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We will consider 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 is not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardized mean difference) among missing outcomes is 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 is 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 (mean difference or standardized mean difference) 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 will assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to ORBIT classification' (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting.

- Low risk of bias: the trial protocol is available and all of the trial's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is unavailable, but it is clear that the published reports include 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 are reported; one or more primary outcomes are 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 is provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review are reported incompletely so that we cannot enter them in a meta-analysis; the trial report fails 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 appears to be free of other sources of bias.
- Unclear risk of bias: there is 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 has a potential source of bias related to the specific trial design used; the trial has been claimed to have been fraudulent; or the trial had some other serious problem.

We will present a 'Risk of bias' graph and a 'Risk of bias' summary figure.
We will distinguish between self reported, investigator assessed, and adjudicated outcome measures.
We will accept 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 difficulty
- Depression

We will require the following outcomes as investigator assessed.

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

We do 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 will mark all endpoints investigated in the associated trial as high risk. Otherwise, we will 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 will assess 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 will consider 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 will incorporate into our judgements about the quality of evidence in a 'Summary of findings' table. We will define outcomes as low risk of bias when most information comes from trials at low risk of bias; unclear risk when most information comes from trials at low or unclear risk of bias; and high risk when a sufficient proportion of information comes from trials at high risk of bias.

Measures of treatment effect

When at least two included trials are available for a comparison and a given outcome, we will attempt to express dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes measured on the same scale (e.g. weight loss in kg), we will estimate the intervention effect using the mean difference (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 will calculate the standardized mean difference (SMD).

Unit of analysis issues

We will take 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 is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants do not contribute multiple times (for example 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).

Dealing with missing data

If possible, we will obtain missing data from the authors of the included trials. We will carefully evaluate important numerical data such as screened, randomly assigned participants as well as intention-to-treat, and as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals) and will critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).
In trials where the standard deviation of the outcome is not available at follow-up or cannot be re-created, we will standardize by the average of the pooled baseline standard deviation from those trials in which this information was reported.
Where included trials do not report means and standard deviations for outcomes and we are unable to obtain the required information from trial authors, we will impute these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005). We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses and will report per outcome which trials were included with imputed standard deviations.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report trial results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we will also consider the I^2 statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis. We will interpret 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 find heterogeneity, we will attempt to determine the possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

If we include 10 or more trials that investigate a particular outcome, we will use 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 methodological design (and hence bias of small trials), and publication bias. We will therefore carefully interpret the results (Sterne 2011).

Data synthesis

We plan to undertake (or display) a meta-analysis only if we judge participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across trials, we will primarily summarize data at low risk of bias using a random-effects model (Wood 2008). We will interpret 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 will use Peto's odds ratio method, provided that there is no substantial imbalance between intervention and comparator group sizes, and intervention effects are not exceptionally large. We will also perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Quality of evidence

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (RM, PD) will independently rate the quality of evidence for each outcome.

We will present a summary of the evidence in a 'Summary of findings' table, which will provide 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 will create 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 will include an appendix titled 'Checklist to aid consistency and reproducibility of GRADE assessments' to help with standardization of the 'Summary of findings' tables (Higgins 2011a; Meader 2014). Alternatively, we will use GRADEpro GDT software and present evidence profile tables as an appendix (GRADEpro GDT 2015). We will present results for the outcomes as described in the Types of outcome measures section. If meta-analysis is not possible, we will present the results in a narrative format in a 'Summary of findings' table. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review where necessary.

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and plan to carry 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).
- Among the long-acting SSRIs, comparison of individual agents (e.g. paroxetine versus fluoxetine versus sertraline versus citalopram versus fluvoxamine).
- If applicable, different dose levels (e.g. dapoxetine 30 mg versus 60 mg).

Sensitivity analysis

We plan to perform 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 to be at high risk of bias.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. 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 nore-

(*Continued*)

	pinephrine 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]
#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]

(*Continued*)

#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 2. 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

(*Continued*)

#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
#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

(*Continued*)

#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
#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

(*Continued*)

#50	#3 AND #19 AND #49

Appendix 3. 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 "serotonine 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

(*Continued*)

#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"
#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 4. 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
#14	norfluoxetine:ti,ab,kw OR norsertraline:ti,ab,kw OR omiloxetine:ti,ab,kw

(*Continued*)

#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 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

CONTRIBUTIONS OF AUTHORS

- Ruma Mian: drafted the first version of this protocol
- Joshua A Bodie: provided clinical content expertise, reviewed and revised the protocol
- Ayman Soubra: provided clinical content expertise, reviewed and revised the protocol
- Jennifer A Lyon: developed the search strategies
- Shahnaz Sultan: provided methodological expertise, reviewed and revised the protocol
- Philipp Dahm: provided guidance and oversight, reviewed and revised the protocol

All protocol authors read and approved the final protocol draft.

DECLARATIONS OF INTEREST

- Ruma Mian: none known
- Joshua A Bodie: none known
- Ayman Soubra: none known
- Jennifer A Lyon: none known
- Shahnaz Sultan: none known
- Philipp Dahm: none known

SOURCES OF SUPPORT

Internal sources

- Minneapolis VAMC, USA.

Salary support for Philipp Dahm, Ayman Soubra, and Shahnaz Sultan

- University of Minnesota, USA.

Salary support for Joshua Bodie and Ayman Soubra

External sources

- No sources of support supplied

NOTES

We have based parts of the Methods and Appendix 1 sections of this Cochrane Review protocol on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group.