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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

email: hta@hta.ac.uk
web: www.hta.ac.uk

HTA No. 13/12: Interventions to treat premature ejaculation: Protocol for systematic review short report

1. Title of the project:

Interventions to treat premature ejaculation: a systematic review short report.

2. Name of TAR team and project 'lead'

TAR Team:

School of Health and Related Research (ScHARR), The University of Sheffield.

Project Lead:

Dr Katy Cooper, Research Fellow in Evidence Synthesis

Health Economics and Decision Science, ScHARR, University of Sheffield

Regent Court, 30 Regent Street, Sheffield S1 4DA

Tel: 0114 2220773

Fax: 0114 2724095

E-mail: k.l.cooper@sheffield.ac.uk

3. Plain English summary

Premature ejaculation (PE) is a form of male sexual dysfunction. It is also referred to as early ejaculation, rapid ejaculation, rapid climax, premature climax, and (historically) ejaculation praecox. Definitions of PE consider the time to ejaculation, the inability to control or delay ejaculation, and the negative consequences of PE[1,2,3,4]. One widely used definition is the persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it[1]. PE can be either lifelong (primary) or acquired (secondary)[5]. Lifelong PE is that which has been present since the person's first sexual experiences, while acquired PE is that which begins later following normal ejaculation experiences. Guidelines on PE include the European Association of Urology (EAU) 2013 Guidelines on Male Sexual Dysfunction[6] and the British Recommendations for the Management of Premature Ejaculation, 2006[7]. PE may occur secondary to another condition such as erectile dysfunction or prostatitis, in which case guidelines recommend treating the underlying condition first or concomitantly[6,7].

Men with PE are more likely to report lower levels of sexual functioning and satisfaction, and higher levels of personal distress and interpersonal difficulty than men without PE[8]. They may also rate their overall quality of life lower than that of men without PE[8]. In addition, the partner's satisfaction with the sexual relationship has been reported to decrease with increasing severity of the man's condition[9]. Surveys in the UK, the USA and other countries suggest that PE is the most common male sexual dysfunction, with prevalence rates of 18-31%[10,11,12,13].

The treatment of PE should attempt to alleviate concern about the condition as well as increase sexual satisfaction for the patient and the partner[7]. Treatments include: behavioural techniques, anaesthetic creams and sprays, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), sildenafil (Viagra), analgesics such as tramadol, and physiotherapy (Kegel or pelvic floor exercises)[6,7]. One antidepressant (dapoxetine, an SSRI) has received approval for the treatment of PE in the UK[14]. To date, no other drug has been approved for PE in Europe or the USA and other medical treatments prescribed for PE are 'off-label' (the practice of prescribing treatments for an unapproved indication).

The aim of this review is to evaluate the effectiveness of interventions in the treatment of PE.

4. Decision problem

The aim of this assessment is to systematically review the evidence for the clinical effectiveness of behavioural, topical and systemic treatments for PE, in the form of a HTA short report.

Population and subgroups

The relevant population will include all men aged ≥ 18 years with PE, including both lifelong and acquired PE. Studies focusing specifically on men with PE secondary to another condition (such as erectile dysfunction or prostate conditions) will be excluded. Where study populations include men with PE with and without other underlying conditions, data for men with PE only will be extracted if available. If these data are not reported separately (i.e., results are only available for the whole sample), these studies will be included but will be summarised separately.

Interventions to be assessed

Treatment modalities will include: behavioural techniques, topical therapies, systemic therapies, and other therapies (e.g., physiotherapy such as pelvic floor exercises).

Relevant comparators

Comparators will include other interventions, waiting list control, placebo, or no treatment.

Key outcomes

The key outcomes for this review are: intra-vaginal ejaculation latency time; sexual satisfaction; control over ejaculation; relationship satisfaction; and self-esteem. Other outcomes include quality of life. As these outcomes in PE are assessed in the literature using different methods, and there is a lack of core validated outcome measures, we will consider any assessment method for these outcomes.

5. Review methods for synthesis of evidence of clinical effectiveness

A review of the clinical effectiveness evidence will be undertaken systematically following the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/). The review will assess the effectiveness of interventions for premature ejaculation.

Inclusion/exclusion criteria

Population

The relevant population will include all men aged ≥ 18 years with PE, including both lifelong and acquired PE. Studies focusing specifically on men with PE secondary to another condition (such as erectile dysfunction or prostate conditions) will be excluded. Where study populations include men with PE with and without other underlying conditions, data for men with PE only will be extracted if available. If these data are not reported separately (i.e., results are only available for the whole sample), these studies will be included but will be summarised separately.

As some formal definitions of PE have only recently been developed, studies will be included whether or not they use a standard definition, and all definitions used will be reported. Common definitions of PE include the following:

- Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR)[1],
- World Health Organization's International Classification of Diseases-10 (ICD-10)[2],
- The Second International Consultation on Sexual and Erectile Dysfunction[3]; or,
- The International Society for Sexual Medicine (ISSM)[4].

Included interventions

Behavioural interventions will include psychological or psychosocial interventions to develop sexual management strategies that are either validated or described by investigators as being a treatment for premature ejaculation treatment. Examples include:

- 'Stop-start' programme developed by Semans[15] – the man or his partner stimulates the penis until he feels the urge to ejaculate, then stops until the sensation passes; this is repeated a few times before allowing ejaculation to occur. The aim is to learn to recognise the feelings of arousal in order to improve control over ejaculation.
- 'Squeeze' technique, proposed by Masters and Johnson[16] – the man's partner stimulates the penis until he feels the urge to ejaculate, then squeezes the glans of the penis until the sensation passes; this is repeated before allowing ejaculation to occur.

- Sensate focus or sensate focusing[7] – the man and his partner begin by focusing on touch which excludes breasts, genitals and intercourse, to encourage body awareness while reducing performance anxiety; this is followed by gradual reintroduction of genital touching and then full intercourse.
- Self-focus (personal communication with clinical advisor) – as for sensate focus but involves the man working on increasing his own body awareness/acceptance, and learning to be aware of body sensations.
- Psychosexual or relationship counselling[6,7] – may include any of the above with additional counselling surrounding specific issues related to PE.
- Delay device / desensitising band[17,18] – a small device which the man can use together with stop-start and squeeze techniques to gradually improve control over ejaculation.

Topical treatments will include:

- Lidocaine-prilocaine, eutectic mixture of local anaesthetics (EMLA), topical eutectic mixture for premature ejaculation (TEMPE), PSD 502, dyclonine, or lidocaine. These can be in the form of either a cream or an aerosol vehicle or a gel containing a local anaesthetic (Instillagel)

Systemic treatments will include:

- Selective serotonin re-uptake-inhibitors (SSRIs) (e.g., fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine and dapoxetine). Dapoxetine is a short-acting SSRI and the only drug currently licensed for PE in UK.
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine, venlafaxine).
- Tricyclic antidepressants (TCAs) (e.g., clomipramine).
- Phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil [Viagra], vardenafil, tadalafil).
- Alpha-blockers (e.g., terazosin, alfuzosin).
- Opioid analgesics (e.g., tramadol).

Other therapies will include:

- Pelvic floor exercises specifically indicated for treating PE as opposed to those for treating erectile dysfunction.
- Acupuncture.

Combinations of therapies (for example, drug plus behavioural therapies or combinations of drug therapies).

Excluded interventions
The following interventions will be excluded:

- Severance Secret cream (SS-cream – a topical plant-based preparation comprising extracts of nine plants). Not currently available within the UK (personal communication with clinical advisor).
- Antiepileptic drugs (e.g., Gabapentin). Not currently included in the UK[7] or European[6] guidelines and not currently used in clinical practice in the UK (personal communication with clinical advisor).
- Antipsychotics (e.g., thioridazine, perphenazine, levosulpiride). Not currently included in the UK[7] or European[6] guidelines and not currently used in clinical practice in the UK (personal communication with clinical advisor).
- Anti-emetics (e.g., metoclopramide). Not currently included in the UK[7] or European[6] guidelines and not currently used in clinical practice in the UK (personal communication with clinical advisor).
- Barbiturates (e.g., Atrium 300). Not currently included in the UK[7] or European[6] guidelines and not currently used in clinical practice in the UK (personal communication with clinical advisor).
- Beta-blockers (e.g., propranolol). Not currently included in the UK[7] or European[6] guidelines and not currently used in clinical practice in the UK (personal communication with clinical advisor).

Additional interventions

If additional interventions are identified during this review, they will be included if relevant to a UK setting, following consultation with our clinical advisors.

Comparators

Comparators will include other interventions, waiting list control, placebo, or no treatment.

Outcomes

The key outcomes for this review are:

- Intra-vaginal ejaculation latency time (IELT). Studies that do not report this outcome objectively, but assess the outcome via another subjective measure such as a questionnaire, will be included. Studies that assess ejaculation latency time in a laboratory setting, i.e., not intra-vaginally, will be excluded;
- Sexual satisfaction;
- Control over ejaculation;

- Relationship satisfaction;
- Self-esteem

Other outcomes will include:

- Quality of life
- Adverse effects and patient acceptability (a brief high-level summary will be provided; see “Included study types”).

Included study types

In order to summarise the current evidence base within the time and resource constraints of this short report, information from clinical guidelines, systematic reviews and meta-analyses that include evidence from randomised controlled trials (RCTs) of any behavioural, topical or systemic treatment for PE, will be collated to produce a high-level evidence summary for the review. We will extract and summarise data for RCTs eligible for inclusion that are reported in existing systematic reviews and meta-analyses. Where reviews summarise the same RCT, we will use all available review data to extract optimum information for each RCT. As this is a short report we will not revisit the original RCT publication.

Evidence from RCTs published subsequently to existing reviews will be fully data extracted and presented. RCTs reported in abstract form only will be eligible for inclusion, provided adequate information is presented in the abstract. Studies using quasi-randomisation will be excluded (for interventions where true RCTs exist). Non-English language studies will be excluded unless sufficient data can be extracted from English-language abstracts and tables. Dissertations and theses will be excluded.

Where no RCT evidence is identified for any individual intervention, we will summarise other forms of available evidence. This will be based on non-RCT evidence reported by existing reviews and guidelines, rather than primary study reports. A brief high-level summary of adverse effects and patient acceptability of treatments will also be provided, again based on information in existing reviews and guidelines.

Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and relevant reviews.

Databases

The following electronic databases will be searched from inception for published and unpublished research evidence: MEDLINE; Embase; Cumulative Index to Nursing and Allied Health Literature (CINAHL); The Cochrane Library including the Cochrane Systematic Reviews Database (CDSR), Cochrane Controlled Trials Register (CCRT), Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database; ISI Web of Science, including Science Citation Index, and the Conference

Proceedings Citation Index-Science; U.S. Food and Drug Administration (FDA) website; European Medicines Agency (EMA) website. All citations will be imported into Reference Manager software and any duplicates deleted.

Search terms

Searches will include a combination of medical subject headings (MeSH) and free-text searches for terms around 'premature ejaculation'.

- MeSH headings will include: Ejaculation; Premature ejaculation.
- Free-text search terms will include: premature$ adj3 ejaculat$; early adj3 ejaculat$; rapid adj3 ejaculat$; rapid adj3 climax$; premature$ adj3 climax$; ejaculat$ adj3 pr?ecox.

Search filters

Study design filters will be used to restrict the search to RCTs, reviews and guidelines.

- The RCT filter will be taken from the Scottish Intercollegiate Guidelines Network (SIGN): http://www.sign.ac.uk/methodology/filters.html#random
- The reviews filter will be taken from the York Centre for Reviews and Dissemination (CRD): http://www.biomedcentral.com/1471-2288/12/51/abstract (Additional file 1)
- The filter for guidelines will be taken from the Health Evidence Bulletins Wales resource: http://hebw.cf.ac.uk/projectmethod/appendix2.htm.

Data extraction strategy

Titles and abstracts of citations identified by the searches will be screened for potentially relevant studies by one reviewer and a subset checked by a second reviewer (and a check for consistency undertaken). Full texts will be screened by two reviewers. We will extract and summarise details of studies identified for inclusion using a data extraction sheet. One reviewer will perform independent data extraction of each included study. All numerical data will be then checked against the original article by a second reviewer. Any disagreements will be resolve by a third reviewer (EK). If data to inform the review are missing from study reports we will attempt to contact the study investigator. Where studies comprise duplicate reports (parallel publications), we will use all associated reports to extract information, but will ensure that data are not duplicated in the review.

Quality assessment strategy

The methodological quality of the included review evidence will be assessed using the AMSTAR checklist. This checklist consists of 11 items and has good face and content

validity for measuring the methodological quality of systematic reviews[19]. Methodological quality of included RCTs will be assessed using the Cochrane Collaboration risk of bias assessment criteria. This tool addresses specific domains, namely: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting[20].

Methods of analysis/synthesis

Extracted data from RCTs captured in existing reviews and further RCTs eligible for inclusion will be tabulated and summarised in a narrative review. Where possible, we will pool data in a meta-analysis using data from RCTs reported in the existing reviews along with data extracted from further RCTs eligible for inclusion identified by the literature search. We will pool data using Cochrane RevMan software (version 5.2) (RevMan 2012[21]). Outcomes reported as continuous data will be estimated using a mean difference (MD) with 95% confidence interval (95%CI). Outcomes reported as dichotomous will be estimated as risk ratios (RRs) with associated 95%CI. Clinical heterogeneity across RCTs (that is the degree to which RCTs appear similar in terms of participants, intervention type and duration and outcome type) and statistical heterogeneity will be considered prior to data pooling. Where low statistical heterogeneity exists (to be defined here as $I^2 \leq 40\%$), meta-analysis will be conducted using a fixed-effect model. Where moderate statistical heterogeneity exists (I^2 40% to 75%), meta-analysis will be conducted using a random-effects model. Where high statistical heterogeneity exists ($I^2 > 75\%$), meta-analysis will not be conducted; instead, studies will be summarised separately. Methods for meta-analysis will be those described in the Cochrane Reviewers' Handbook (Deeks et al., 2011). Pooled effect estimates from meta-analyses that are undertaken will be summarised and presented figuratively.

6. Expertise in this TAR team

TAR Centre

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence. Much of this work, together with our reviews for the international Cochrane Collaboration, underpins excellence in healthcare worldwide. A list of publications can be found at: http://www.sheffield.ac.uk/scharr/sections/heds/collaborations/scharr-tag/reports.

7. Competing interests of authors

The ScHARR authors do not have any competing interests. Details of any competing interests for clinical advisors are currently being obtained.

8. Timetable/milestones

Milestone	
Draft protocol	31 July 2013
Final protocol	TBC (estimated 13 September 2013)
Progress report	15 November 2013
Assessment report	13 December 2013

9. Appendices

Draft search strategy (MEDLINE)

1. exp Ejaculation/
2. exp Premature Ejaculation/
3. (premature$ adj3 ejaculat$).ti,ab.
4. (early adj3 ejaculat$).ti,ab.
5. (rapid adj3 ejaculat$).ti,ab.
6. (rapid adj3 climax$).ti,ab.
7. (premature$ adj3 climax$).ti,ab.
8. (ejaculat$ adj3 pr?ecox).ti,ab.

9. or/1-8

Filter 1: Randomised controlled trials

10. Randomized Controlled Trials as Topic/
11. randomized controlled trial/
12. Random Allocation/
13. Double Blind Method/
14. Single Blind Method/
15. clinical trial/
16. clinical trial, phase i.pt.
17. clinical trial, phase ii.pt.
18. clinical trial, phase iii.pt.
19. clinical trial, phase iv.pt.
20. controlled clinical trial.pt.
21. randomized controlled trial.pt.
22. multicenter study.pt.
23. clinical trial.pt.
24. exp Clinical Trials as topic/
25. or/10-24
26. (clinical adj trial$).tw.
27. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
28. PLACEBOS/
29. placebo$.tw.
30. randomly allocated.tw.
31. (allocated adj2 random$).tw.
32. 26 or 27 or 28 or 29 or 30 or 31
33. 25 or 32
34. case report.tw.
35. letter/
36. historical article/
37. 34 or 35 or 36
38. 33 not 37

Filter 2: Reviews

10. review.ab.
11. review.pt.

12. meta-analysis.ab.
13. meta-analysis.pt.
14. meta-analysis.ti.
15. or/10-14
16. letter.pt.
17. comment.pt.
18. editorial.pt.
19. or/16-18
20. 15 not 19

Filter 3: Guidelines

10. guideline.pt.
11. practice guideline.pt.
12. exp Guideline/
13. health planning guidelines/
14. 10 or 11 or 12 or 13

10. Team members' contributions

Project management and systematic reviewing

Katy Cooper, Research Fellow, ScHARR. KC has extensive experience in systematic reviews of health technologies. KC will lead the project and undertake the review of effectiveness. She will co-ordinate the review process including: protocol development, co-ordinating the searches, assessing studies for eligibility, data extraction and quality assessment of included studies, data checking and analysis (where appropriate), and development of the final review.

Marrissa Martyn-St James, Research Associate, ScHARR. MMSJ has extensive experience in systematic reviews of clinical effectiveness. MMSJ will assist KC with the project and undertake systematic reviewing. She will be involved in protocol development, selecting and assessing studies for eligibility, data extraction and quality assessment of included studies, data checking and analysis (where appropriate), and development of the final review.

Eva Kaltenthaler, Reader in Health Technology Assessment and Managing Director of ScHARR-TAG. EK has extensive experience in systematic reviews of health technologies. EK will advise and comment on the systematic review. She will advise on the review process, protocol development, abstract assessment for eligibility, quality assessment of trials,

data extraction, data entry, data analysis and review development of background information and clinical effectiveness. She will also advise on disagreements in study selection.

Information specialists

Anna Cantrell, Information Specialist, ScHARR. AC has experience of undertaking literature searches for the ScHARR Technology Assessment Group systematic reviews and other external projects. AC will be involved in developing the search strategy and undertaking the electronic literature searches.

Kath Williams, Information Specialist, ScHARR. KW has experience of undertaking literature searches for a variety of research projects. KW will be involved in developing the search strategy and undertaking the electronic literature searches.

Clinical advisors

Professor Kevan Wylie, Consultant in Sexual Medicine, NHS, Sheffield. UK. KW will assist with protocol development (clinical advice), help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness.

Address: Porterbrook Clinic, 75 Osborne Road, Nether Edge Hospital, Sheffield, S11 9BF

Dr Leila Frodsham, Chair, Institute of Psychosexual Medicine. LF will act as a clinical advisor on the project.

Address: Park House, 111 Uxbridge Road, London, W5 5LB

[Additional clinical advisors to be added once confirmed.]

Clerical and administration

Gill Rooney, Project Administrator. GR will assist in the retrieval of papers and in preparing and formatting the report.

11. References

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