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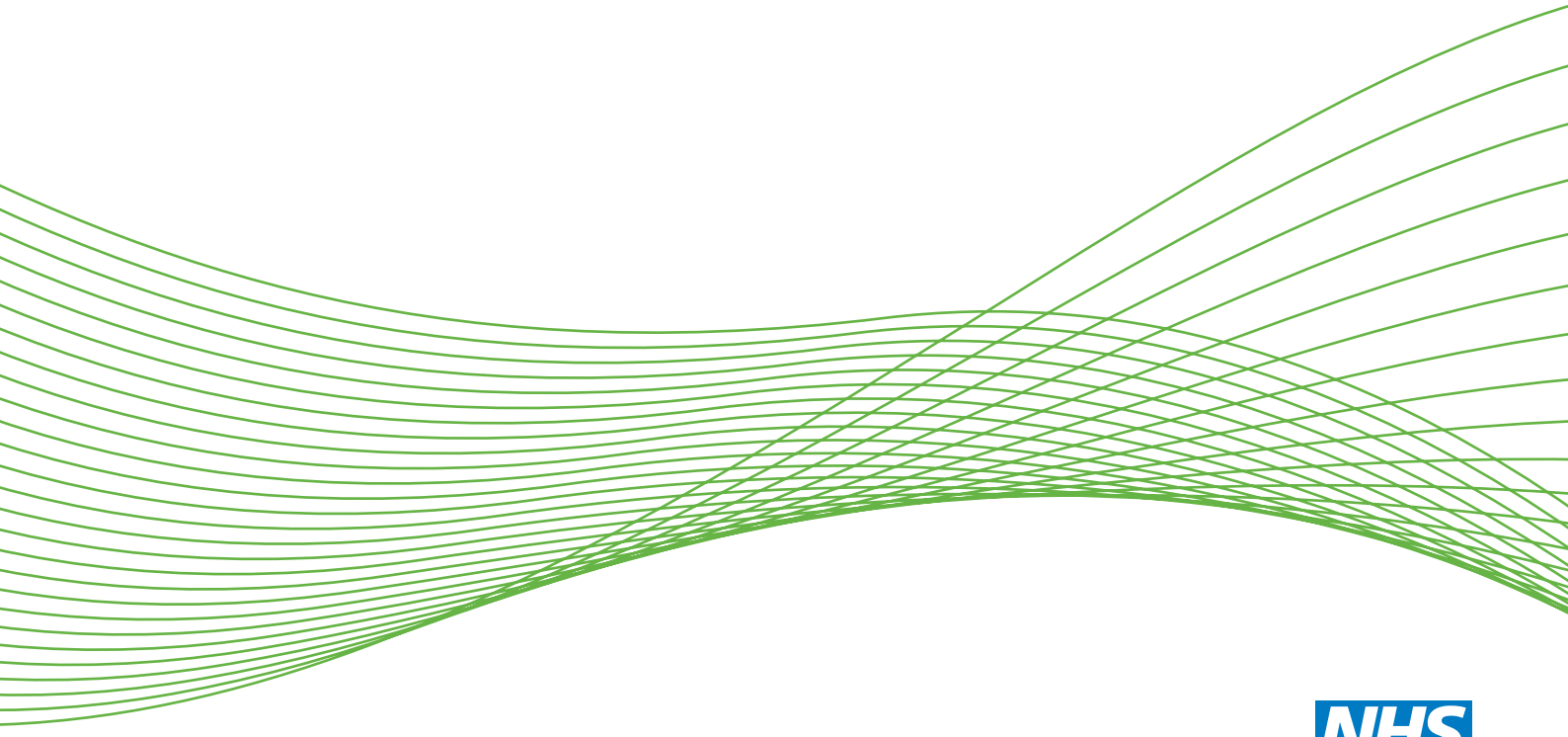

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Katy Cooper,* Marrissa Martyn-St James, Eva Kaltenthaler, Kath Dickinson and Anna Cantrell

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield, Sheffield, UK

*Corresponding author

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Editorial contact: nihredit@southampton.ac.uk

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Abstract

Interventions to treat premature ejaculation: a systematic review short report

Katy Cooper,* Marrissa Martyn-St James, Eva Kaltenthaler, Kath Dickinson and Anna Cantrell

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield, Sheffield, UK

*Corresponding author k.l.cooper@sheffield.ac.uk

Background: Premature ejaculation (PE) is commonly defined as ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it. PE can be either lifelong and present since first sexual experiences (primary), or acquired (secondary), beginning later (Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. *J Sex Marital Ther* 1989;**15**:130–4). Treatments include behavioural and pharmacological interventions.

Objective: To systematically review evidence for clinical effectiveness of behavioural, topical and systemic treatments for PE.

Data sources: The following databases were searched from inception to 6 August 2013 for published and unpublished research evidence: MEDLINE; EMBASE; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects and the *Health Technology Assessment* database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science. The US Food and Drug Administration website and the European Medicines Agency (EMA) website were also searched.

Methods: Randomised controlled trials (RCTs) in adult men with PE were eligible (or non-RCTs in the absence of RCTs). RCT data were extrapolated from review articles when available. The primary outcome was intravaginal ejaculatory latency time (IELT). Data were meta-analysed when possible. Other outcomes included sexual satisfaction, control over ejaculation, relationship satisfaction, self-esteem, quality of life, treatment acceptability and adverse events (AEs).

Results: A total of 103 studies (102 RCTs, 65 from reviews) were included. RCTs were available for all interventions except yoga. The following interventions demonstrated significant improvements ($p < 0.05$) in arithmetic mean difference in IELT compared with placebo: *topical anaesthetics* – eutectic mixture of local anaesthetics (EMLA®, AstraZeneca), topical eutectic mixture for PE (Plethora Solutions Ltd) spray; *selective serotonin reuptake inhibitors* (*SSRIs*) – citalopram (Cipramil®, Lundbeck), escitalopram (Cipralex®, Lundbeck), fluoxetine, paroxetine, sertraline, dapoxetine (Priligy®, Menarini), 30 mg or 60 mg; *serotonin–noradrenaline reuptake inhibitors* – duloxetine (Cymbalta®, Eli Lilly & Co Ltd); *tricyclic antidepressants* – inhaled clomipramine 4 mg; *phosphodiesterase-5* (*PDE5*) *inhibitors* – vardenafil (Levitra®, Bayer), tadalafil (Cialis®, Eli Lilly & Co Ltd); *opioid analgesics* – tramadol (Zydol SR®, Grünenthal). Improvements in sexual satisfaction and other outcomes compared with placebo were evident for SSRIs, PDE5 inhibitors and tramadol. Outcomes for interventions not compared with placebo were as follows: *behavioural therapies* – improvements over wait list control in IELT and other outcomes, behavioural therapy plus pharmacotherapy better than either therapy alone; *alpha blockers* – terazosin (Hytrin®, AMCO)

not significantly different to antidepressants in ejaculation control; *acupuncture* – improvements over sham acupuncture in IELT, conflicting results for comparisons with SSRIs; *Chinese medicine* – improvements over treatment as usual; *delay device* – improvements in IELT when added to stop–start technique; *yoga* – improved IELT over baseline, fluoxetine better than yoga. Treatment-related AEs were evident with most pharmacological interventions.

Limitations: Although data extraction from reviews was optimised when more than one review reported data for the same RCT, the reliability of the data extraction within these reviews cannot be guaranteed by this assessment report.

Conclusions: Several interventions significantly improved IELT. Many interventions also improved sexual satisfaction and other outcomes. However, assessment of longer-term safety and effectiveness is required to evaluate whether or not initial treatment effects are maintained long term, whether or not dose escalation is required, how soon treatment effects end following treatment cessation and whether or not treatments can be stopped and resumed at a later time. In addition, assessment of the AEs associated with long-term treatment and whether or not different doses have differing AE profiles is required.

Study registration: This study is registered as PROSPERO CRD42013005289.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Anejaculation Inability to ejaculate.

Bibliotherapy Expressive therapy that uses an individual's relationship to the content of books.

Hypoaesthesia Diminished sensitivity to pain.

Intravaginal ejaculatory latency time Time taken by a man to ejaculate during vaginal penetration.

Libido Sexual drive or desire for sexual activity.

Sensate focus A focus on the patient's own varied sense experience, rather than viewing orgasm as the sole goal of sex.

Somnolence Strong desire for sleep.

Squeeze technique Application of firm pressure with thumb and forefinger below head of penis.

Stop–start/pause technique Pausing action when approaching 'point of no return'.

List of abbreviations

AE	adverse event
AEC	Ability of Ejaculation Control
AIPE	Arabic Index of Premature Ejaculation
AMSTAR	Assessing Methodological Quality of Systematic Reviews
CBT	cognitive–behavioural therapy
CCRT	Cochrane Controlled Trials Register
CGI-I	Clinical Global Impression – Improvement
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIPE	Chinese Index of Premature Ejaculation
CIPE5	Chinese Index of Premature Ejaculation 5 premature ejaculation-related items
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition-Text Revision
EAU	European Association of Urology
EMLA®	eutectic mixture of local anaesthetics
EU	European Union
GP	general practitioner
GRISS	Golombok Rust Inventory of Sexual Satisfaction
HTA	Health Technology Assessment
ICD-10	*International Classification of Diseases*, Tenth Edition
IELT	intravaginal ejaculatory latency time
IIEF	International Index of Erectile Function
IPE	Index of Premature Ejaculation
ISSM	International Society for Sexual Medicine
MD	mean difference
MeSH	medical subject heading
NIHR	National Institute for Health Research
OSAT	overall sexual act time
PDE5	phosphodiesterase-5
PE	premature ejaculation
PEDT	Premature Ejaculation Diagnostic Tool
PEP	Premature Ejaculation Profile
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
RR	relative risk
SARI	serotonin antagonist and reuptake inhibitor
ScHARR	School of Health and Related Research
ScHARR-TAG	School of Health and Related Research Technology Assessment Group
SD	standard deviation
SNRI	serotonin–noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TEMPE	topical eutectic mixture for premature ejaculation
WHO	World Health Organization

Plain English summary

Premature ejaculation (PE) is ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it, and can cause distress for a man and his partner. Evidence from randomised controlled trials suggests that several treatments provide improvements of between 1 and 6 minutes in time to ejaculation, including drug treatments [selective serotonin inhibitors and other antidepressants, phosphodiesterase-5 inhibitors and tramadol (Zydol SR®, Grünenthal)], anaesthetic creams and behavioural therapies. Many treatments also improve sexual satisfaction and other measures. However, drug treatments and anaesthetic creams are associated with side effects. Behavioural therapy combined with drug treatment is better than behavioural therapy or drug treatment alone. Most studies of treatments for PE last 12 weeks [some that we found, e.g. for dapoxetine (Priligy®, Menarini) and tramadol, lasted 24 weeks]. Patients may have different treatment preferences related to differences in treatment administration, clinical effectiveness and side effects (e.g. drug or behavioural treatments). For this reason, maintaining a range of treatment options is a useful approach. Future research should aim to investigate the long-term safety and effectiveness of treatments (> 6 months), whether or not higher doses are required in the longer term, the effects of treatment cessation and whether or not treatments can be stopped and restarted later. This research could be undertaken by reviewing the literature for these treatments used in other conditions, in addition to further, longer-duration studies in men with PE.

Scientific summary

Background

Premature ejaculation (PE) is commonly defined as ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it. PE can be either lifelong and present since first sexual experiences (primary), or acquired (secondary), beginning later. Prevalence rates internationally are 20–30%. Treatments include behavioural techniques, anaesthetic creams and sprays, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), phosphodiesterase-5 (PDE5) inhibitors, analgesics such as tramadol (Zydol SR®, Grünenthal) and other interventions. Dapoxetine (Priligy®, Menarini) (a SSRI) is the only drug to have received approval for the treatment of PE in the UK.

Objectives

The objective was to systematically review the evidence for the clinical effectiveness of behavioural, topical and systemic treatments for PE in the form of a *Health Technology Assessment* (HTA) short report.

Data sources

The following electronic databases were searched from inception to 6 August 2013 for published and unpublished research evidence: MEDLINE; EMBASE; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects and the HTA database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science. The US Food and Drug Administration website and the European Medicines Agency website were also searched.

Methods

The systematic review included randomised controlled trials (RCTs) evaluating any intervention relevant to the UK in men with primary and/or secondary PE. Comparators included other interventions, waiting list control, placebo, or no treatment. RCTs were identified through literature searching of databases from inception to August 2013 and from existing reviews. Quality assessment was conducted for existing reviews and for further RCTs not captured in a review. For RCTs within existing reviews, data were extracted from the review and not from the original RCT publication. When no RCT evidence was identified for an intervention, other study types were considered. Outcomes included intravaginal ejaculatory latency time (IELT), sexual satisfaction, control over ejaculation, relationship satisfaction, self-esteem, quality of life, treatment acceptability and adverse events (AEs).

Results

A total of 103 studies (102 RCTs) were included (65 from reviews). The majority of RCTs not already in reviews ($n = 37$) were of unclear methodological quality.

Behavioural interventions

Twelve RCTs were identified. Behavioural therapies improved IELT and sexual satisfaction compared with waiting list control, and behavioural therapies combined with pharmacological therapies were better than either intervention alone in improving IELT, sexual satisfaction, sexual anxiety and ejaculation control. When reported, no AEs were associated with behavioural interventions alone.

Topical anaesthetics

Nine RCTs assessed treatment over 4–12 weeks. Both eutectic mixture of local anaesthetics cream and topical eutectic mixture for PE spray were significantly more effective than placebo in increasing IELT [mean difference (MD) 6.44 minutes, 95% confidence interval (CI) 6.01 to 6.87 minutes] and 3.30 minutes (95% CI 1.33 to 5.27 minutes); both $p < 0.00001$. AEs include loss of sensation and irritation (men and women) and loss of erection with applications ≥ 20 minutes.

Selective serotonin reuptake inhibitors other than dapoxetine

Forty-two RCTs assessed SSRIs, mostly taken daily, and treatment duration was 4–12 weeks. Citalopram (Cipramil®, Lundbeck) significantly increased IELT compared with placebo or no treatment [MD 0.25 minutes (95% CI –0.06 to 0.56 minutes) to 4.62 minutes (95% CI 4.21 to 5.03 minutes); $p < 0.00001$] and improved sexual satisfaction. Escitalopram (Cipralex®, Lundbeck) significantly increased IELT compared with placebo (MD 1.2 minutes, 95% CI 0.79 to 1.61 minutes; $p < 0.00001$). Fluoxetine significantly increased IELT compared with placebo (MD 2.41 minutes, 95% CI 2.10 to 2.73 minutes; $p < 0.00001$). Fluvoxamine did not significantly increase IELT compared with placebo. Paroxetine significantly increased IELT compared with placebo (MD 5.34 minutes, 95% CI 3.79 to 6.89 minutes; $p < 0.00001$) and improved sexual satisfaction. Sertraline significantly increased IELT compared with placebo (MD 2.72 minutes, 95% CI 1.77 to 3.67 minutes; $p < 0.00001$) and improved ejaculation control. AEs included nausea, headache, insomnia, dry mouth, diarrhoea, drowsiness, dizziness, somnolence, decreased libido and anejaculation.

Selective serotonin reuptake inhibitors: dapoxetine

Eight RCT reports assessed licensed doses of dapoxetine, generally taken on demand prior to intercourse. Treatment duration was 2–24 weeks. Dapoxetine 30 mg and 60 mg significantly increased IELT compared with placebo [MD 1.16 minutes (95% CI 0.94 to 1.39 minutes) and 1.66 minutes (95% CI 1.46 to 1.87 minutes); $p < 0.00001$] and dapoxetine 60 mg was more effective than 30 mg (MD 0.46 minutes, 95% CI 0.19 to 0.74 minutes; $p = 0.0009$). Similar effects are evident for ejaculatory control, sexual satisfaction, global impression of change and clinical benefit. AEs included nausea, diarrhoea, headache and dizziness and appearing to be dose dependent.

Serotonin–noradrenaline reuptake inhibitors

Three RCTs were identified. One 12-week trial indicated that duloxetine (Cymbalta®, Eli Lilly & Co Ltd) is better than placebo in increasing IELT (MD 1.52 minutes, 95% CI 0.08 to 2.24 minutes; $p < 0.00001$). Evidence from two RCTs suggests venlafaxine is not effective at increasing IELT compared with placebo. Duloxetine side effects included dry mouth and nausea. Venlafaxine caused significantly more side effects than placebo.

Tricyclic antidepressants

Thirteen RCTs were identified all evaluating clomipramine (oral or nasal). RCT evidence summarised from reviews suggests a significant increase in IELT with clomipramine compared with placebo; however, data were poorly reported. Inhaled clomipramine 4 mg appears effective at increasing IELT when compared with placebo (1.68 minutes, 95% CI 1.06 to 2.29 minutes; $p < 0.00001$). AEs were not well reported but included dry mouth and constipation. Inhaled clomipramine may cause some local irritation.

Phosphodiesterase-5 inhibitors

Twelve RCTs were identified, but IELT was poorly reported. Vardenafil (Levitra®, Bayer) and tadalafil (Cialis®, Eli Lilly & Co Ltd) significantly increased IELT compared with placebo [based on one RCT each; MD 3.80 minutes (95% CI 3.30 to 4.30 minutes) and 2.59 minutes (95% CI 1.28 to 3.90 minutes); $p = 0.006$ and $p < 0.00001$, respectively], but there was no significant difference in one RCT between sildenafil and placebo. Sexual satisfaction favoured PDE5 inhibitors over placebo. Sildenafil plus sertraline or behavioural therapy was better than sildenafil alone. AEs included flushing, headache and palpitations.

Alpha-blockers

Two RCTs were identified, neither assessing IELT. Evidence from one 8-week RCT showed improvements for terazosin (Hytrin®, AMCO) compared with placebo in ejaculation control. The current evidence base for alpha-blockers in the treatment of PE is limited.

Tramadol

Seven RCTs were identified. Treatment duration was 6–24 weeks. Tramadol significantly increased IELT compared with placebo (MD 1.35 minutes, 95% CI 0.63 to 2.07 minutes; $p = 0.0002$) and improved sexual satisfaction. Tramadol plus behavioural therapy improved IELT over behavioural therapy alone (MD 1.65 minutes, 95% CI 0.30 to 3.00 minutes; $p = 0.02$). There was no significant difference between tramadol and paroxetine. AEs included erectile dysfunction, constipation, nausea, headache, somnolence, dry mouth, dizziness, pruritus and vomiting. Addiction potential was not assessed.

Acupuncture

Two 4-week RCTs were identified. Acupuncture significantly increased IELT compared with sham acupuncture but comparisons with SSRIs were inconsistent. AEs were not well reported.

Chinese medicine

Five RCTs were identified. In one 2-week trial, Chinese medicine was more effective than treatment as usual (1.57 minutes, 95% CI 1.11 to 2.03 minutes; $p < 0.00001$). In one 4-week trial, fluoxetine improved IELT compared with Chinese medicine (0.60 minutes, 95% CI 0.19 to 1.01 minutes; $p < 0.00001$). AEs were not well reported.

Delay devices

One RCT compared a desensitising band plus stop–start technique compared with behavioural therapy plus stop–start technique (treatment duration unclear). IELT appeared improved with the desensitising band. AEs (soreness with overuse) were minimal when used as directed.

Yoga

No RCTs were identified. In one non-RCT comparing yoga with fluoxetine over 12 weeks, both yoga and fluoxetine significantly improved IELT from baseline, but fluoxetine significantly increased IELT compared with yoga. A high proportion of partners reported a good sexual satisfaction with yoga. AEs were not reported.

Discussion

Strengths

This report systematically reviews the evidence for PE treatments relevant to the UK. In contrast to many existing reviews, this review meta-analysed data across RCTs where appropriate, used appropriate outcome measures (MD) to summarise IELT, avoided double-counting of participants and considered pairwise and crossover RCT data separately. An assessment of methodological quality is also included.

Limitations and uncertainties

Owing to the large volume of evidence, data for RCTs reported in reviews were extracted from the review article and not the original RCT publication. Thus, the reliability of these data cannot be guaranteed. Similarly, the methodological quality of individual RCTs reported in existing reviews was not assessed by this assessment report.

Generalisability of findings

Most trials involved men with primary PE without a concomitant condition such as erectile dysfunction, mainly recruited from specialist sexual health settings. The effectiveness of treatments for men with secondary PE, PE concomitant to another condition, or not attending specialised clinics, is less certain. Included trials were undertaken in various European Union (EU) and non-EU countries. Variability in trial populations, PE definitions and IELT entry criteria, cultural attitudes towards PE and acceptability of treatments also limits generalisability of findings. Treatment duration among trials ranged from 2 to 24 weeks. The long-term effectiveness and safety for patients either continuing or withdrawing from treatment are unknown. Furthermore, patient adherence to and acceptability of treatments have not been fully evaluated. The improvements in IELT ranged from 1 to 6 minutes. While these effects were statistically significant, it is difficult to quantify how acceptable and meaningful these changes are for men with PE without being able to evaluate the relationship between IELT, ejaculation control, and sexual satisfaction. There is currently no consensus on what constitutes a clinically significant threshold response to interventions for PE.

Conclusions

Implications for service provision

Several interventions provided statistically significant improvements of between 1 and 6 minutes in time to ejaculation (IELT), including pharmacological interventions (SSRIs and other antidepressants, PDE5 inhibitors, tramadol), topical anaesthetics and behavioural therapies. Many interventions also demonstrated improvements in sexual satisfaction and other outcomes. Behavioural therapy combined with pharmacotherapy was better than behavioural therapy or pharmacotherapy alone. Pharmacological and topical therapies are associated with some AEs. Trial duration was a maximum of 12 weeks for most interventions (24 weeks for dapoxetine and tramadol). Different interventions have different modes of action and individual patients may have a preference for pharmacological or behavioural interventions, so maintaining a range of options (to be used individually or in combination) may remain a useful approach in the treatment of PE.

Suggested research priorities

Assessment of long-term safety and effectiveness of interventions (> 6 months) is required and should assess whether or not initial treatment effects are maintained long term, whether or not the effects end with treatment cessation, whether or not treatments require dose escalation to maintain initial treatment effects and whether or not treatments can be stopped and resumed, as well as AEs associated with long-term treatment. This could be addressed by reviewing the literature for these treatments in other conditions, supplemented by longer-term studies in PE, possibly observational studies or longer-term follow-up of RCT participants.

The current evidence base does not include sufficient direct comparisons to inform a judgement regarding the 'best treatment' in terms of either efficacy or safety as active treatments are compared with placebo/no treatment by the majority of RCTs. Future research could consider head-to-head trials or a mixed treatment comparison/network meta-analysis, as well as assessment of cost-effectiveness of the different interventions. As dapoxetine has been specifically developed for PE and has been extensively evaluation for this indication, head-to-head comparisons between this and other treatments might be informative. The effect of treatments used sequentially or in combination should also be further assessed. For behavioural therapies, further research is required to determine the components, intensity and delivery

of interventions that are most effective. However, patients may have preferences for different types of treatment (e.g. pharmacological or behavioural) and, therefore, maintaining a range of options may be a useful approach.

Future research should also consider an evaluation of clinically meaningful increases in IELT, including evaluation of the relationship between increases in IELT, ejaculatory control and sexual satisfaction, and whether or not increases of a few minutes in IELT are more meaningful to some patients than others. The trade-off between an improvement in IELT and other effectiveness outcomes compared with AEs and inconvenience should also be further evaluated.

Funding

Funding for this study was provided by the HTA programme of the National Institute for Health Research.

Chapter 1 Background

Description of health problem

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. Official definitions of PE have been set out in the *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition-Text Revision (DSM-IV-TR)[1] and in the World Health Organization's (WHO's) *International Classification of Diseases*, Tenth Edition (ICD-10).[2] The DSM-IV-TR defines the condition as persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it.[1] Other definitions have also been proposed by the Second International Consultation on Sexual and Erectile Dysfunction[3] and the International Society for Sexual Medicine (ISSM).[4] All four definitions consider time to ejaculation, inability to control or delay ejaculation and negative consequences of PE. However, there is no current consensus on quantification of the time to ejaculation, which is usually described by intravaginal ejaculatory latency time (IELT), i.e. the time taken by a man to ejaculate during vaginal penetration.[5]

Aetiology, pathology and prognosis

According to the European Association of Urology (EAU), the aetiology of PE is unknown, with few data to support suggested biological and psychological hypotheses, including anxiety, penile hypersensitivity and 5-hydroxytryptamine (5-HT) receptor dysfunction, and the pathophysiology of PE is largely unknown.[6] PE can be either lifelong (primary) or acquired (secondary).[7] 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. PE can occur secondary to another condition such as erectile dysfunction or prostatitis, in which case guidelines recommend treating the underlying condition first or concomitantly.[6,8] PE cannot be cured, but can be managed with behavioural and/or pharmacological treatment.

Epidemiology and prevalence

Epidemiological surveys in the USA and other countries suggest that PE as defined in the *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition (DSM-IV)[9] is the most common male sexual dysfunction, with prevalence rates of 20–30%.[3,10,11] The highest prevalence, 31% (among men aged 18–59 years), was found by the USA National Health and Social Life Survey study.[11] In a five-country European observational study, which included the UK, the prevalence of PE was 18%.[12]

Impact of health problem

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.[5] They may also rate their overall quality of life lower than that of men without PE.[5] In addition, the partner's satisfaction with the sexual relationship has been reported to decrease with increasing severity of the condition.[13]

Measurement of disease

Diagnosis of PE is based on the patient's medical and sexual history.[14,15] IELT can be either self-assessed or stopwatch measured. The EAU 2013 Guidelines on Male Sexual Dysfunction[6] state that the use of IELT alone is not sufficient to define PE, and the need to assess PE objectively has led to the development of several questionnaires, including two questionnaires that can discriminate between patients who have PE and those who do not. These are the Premature Ejaculation Diagnostic Tool (PEDT)[16,17] and the Arabic Index of Premature Ejaculation (AIPE).[18] Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP),[19] the Index of Premature Ejaculation (IPE)[20] and the Male Sexual Health Questionnaire Ejaculatory Dysfunction.[21]

Current service provision

Relevant national guidelines

Guidelines on PE include the EAU 2013 Guidelines on Male Sexual Dysfunction[6] and the British Recommendations for the Management of Premature Ejaculation, 2006.[8]

Management of the condition

The treatment of PE should attempt to alleviate concern about the condition as well as increase sexual satisfaction for the patient and the partner.[8] Descriptions of a recommended treatment pathway for the condition are varied. The British Association of Urological Surgeons suggest that counselling may help men with less troublesome PE but, for most men, the mainstay of long-term treatment is drugs.[22] The British Association for Sexual Health and HIV, Special Interest Group for Sexual Dysfunction, suggests that management of patients should be decided on a case-by-case basis that considers behavioural, local and systemic pharmacological treatments.[8] The EAU presents a definitive treatment pathway based on clinical diagnosis of the condition and treatment of PE based on whether or not the condition is either lifelong or acquired. There is currently no published literature that identifies a clinically significant threshold response to interventions for PE.[23]

Description of technology under assessment

Summary of interventions

Treatments include behavioural techniques, anaesthetic creams and sprays, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), phosphodiesterase-5 (PDE5) inhibitors such as sildenafil, analgesics such as tramadol (Zydol SR®, Grünenthal) and other drug and non-drug interventions.[6,8]
One antidepressant [dapoxetine (Priligy®, Menarini), a SSRI] has received approval for the treatment of PE in the UK.[24] 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).

Chapter 2 Definition of the decision problem

Decision problem

Population and subgroups

The relevant population comprised all men aged ≥ 18 years with PE, both lifelong and acquired PE. Studies focusing specifically on men with PE secondary to another condition (such as erectile dysfunction or prostate conditions) were excluded if possible; however, this information was often not reported.

Interventions assessed

Treatment modalities included behavioural techniques, topical therapies, systemic therapies and other therapies.

Relevant comparators

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

Key outcomes

The key outcomes for this review were IELT, sexual satisfaction, control over ejaculation, relationship satisfaction, self-esteem and 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, any assessment methods were permitted for these outcomes.

Overall aim and objective of assessment

The aim and objective of this assessment were to systematically review the evidence for the clinical effectiveness of interventions for management of PE, in the form of a *Health Technology Assessment* (HTA) short report.

Chapter 3 Assessment of clinical effectiveness

A systematic review of the literature was undertaken to evaluate the clinical effectiveness of interventions for men with PE. A review of the evidence was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25] The completed PRISMA checklist is presented in *Appendix 1*.

Methods for reviewing effectiveness

Identification of studies

The following electronic databases were searched from inception to 6 August 2013 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; Cochrane Controlled Trials Register (CCRT); Database of Abstracts of Reviews of Effects and the HTA database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science; The US Food and Drug Administration website and the European Medicines Agency website were also searched. All citations were imported into Reference Manager Software (version 12, Thomson ResearchSoft, Carlsbad, CA, USA) and any duplicates deleted.

Search terms were included a combination of medical subject headings (MeSHs) and free-text searches for terms around 'premature ejaculation'. These included:

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

Search filters (study design filters) were used to restrict the searches to randomised controlled trials (RCTs), reviews and guidelines. These were:

- the RCT filter available from the Scottish Intercollegiate Guidelines Network[26]
- the reviews filter available from the York Centre for Reviews and Dissemination[27]
- the filter for guidelines available from the Health Evidence Bulletins Wales resource.[28]

Details of the MEDLINE strategy are presented in *Appendix 2*. Existing reviews identified by the searches were obtained and examined for relevant RCT data. However, all bibliographic data sources were searched from inception; thus, existing reviews were not relied upon as the only source for identifying relevant RCTs.

Inclusion and exclusion criteria

Population

The relevant population included 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) were excluded; however, this information was often not reported.

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

- DSM-IV-TR[1]
- WHO's ICD-10[2]
- the Second International Consultation on Sexual and Erectile Dysfunction[4]
- ISSM.[29]

Included interventions

Behavioural interventions included psychological or psychosocial interventions to develop sexual management strategies that were either validated or described by investigators as being a treatment for PE treatment. Examples include:

- 'Stop–start' programme developed by Semans:[16] 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:[17] 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:[4] 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.

Topical treatments included:

- Lidocaine–prilocaine, eutectic mixture of local anaesthetics (EMLA®, AstraZeneca), topical eutectic mixture for PE [(TEMPE), a combination of two medicines – lidocaine and prilocaine], 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®, CliniMed).

Systemic treatments included:

- SSRIs [e.g. fluoxetine, sertraline, citalopram (Cipramil®, Lundbeck), paroxetine, fluvoxamine and dapoxetine]. Dapoxetine is a short-acting SSRI that can be taken a few hours preintercourse rather than as a daily dose and is the only drug currently licensed for PE in the UK.
- Serotonin–noradrenaline reuptake inhibitors (SNRIs) [e.g. duloxetine (Cymbalta®, Eli Lilly & Co Ltd), venlafaxine].
- TCAs (e.g. clomipramine).
- PDE5 inhibitors [e.g. sildenafil (Viagra), vardenafil (Levitra®, Bayer), tadalafil (Cialis®, Eli Lilly & Co Ltd)].
- Alpha-blockers [e.g. terazosin (Hytrin®, AMCO), alfuzosin].
- Opioid analgesics (e.g. tramadol).

Other therapies included:

- acupuncture
- Chinese medicine
- delay device/desensitising band: a small device which the man can use together with stop–start and squeeze techniques to gradually improve control over ejaculation
- yoga.

Combinations of therapies included drug plus behavioural therapies or combinations of drug therapies.

Excluded interventions

The following interventions not considered relevant to the UK setting were excluded:

- Severance Secret cream (SS cream: a topical plant-based preparation comprising extracts of nine plants). Not currently available within the UK (Professor Kevan Wylie, Porterbrook Clinic, 2013, personal communication).
- Antiepileptic drugs (e.g. gabapentin). Not currently included in the UK[30] or European[6] guidelines and not currently used in clinical practice in the UK (Professor Kevan Wylie, personal communication).
- Antipsychotics [e.g. thioridazine (Melleril, Novartis, withdrawn worldwide in 2005), perphenazine (Trilafon, Merck Sharp & Dohme), levosulpiride]. Not currently included in the UK[30] or European[6] guidelines and not currently used in clinical practice in the UK (Professor Kevan Wylie, personal communication).
- Antiemetics (e.g. metoclopramide). Not currently included in the UK[30] or European[6] guidelines and not currently used in clinical practice in the UK (Professor Kevan Wylie, personal communication).
- Barbiturates (e.g. Atrium 300). Not currently included in the UK[30] or European[6] guidelines and not currently used in clinical practice in the UK (Professor Kevan Wylie, personal communication).
- Beta-blockers (e.g. propranolol). Not currently included in the UK[30] or European[6] guidelines and not currently used in clinical practice in the UK (Professor Kevan Wylie, personal communication).

Comparators

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

Outcomes

The key outcomes for this review were:

- IELT: studies that do not report this outcome objectively, but assess the outcome via another subjective measure such as a questionnaire, were included. Studies that assess ejaculation latency time in a laboratory setting, i.e. not intravaginally, were excluded.
- Sexual satisfaction.
- Control over ejaculation.
- Relationship satisfaction.
- Self-esteem.

Other outcomes included:

- Quality of life.
- Treatment acceptability.
- Adverse events (AEs).

Included study types

Included study designs were restricted to RCTs, if available. If no RCT evidence was identified for a particular intervention, other study types (non-RCT) were considered. Owing to the time constraints of this short report, if RCTs were included in existing reviews, data were extracted from the review and not from the original RCT publication. RCTs not captured by existing reviews and those published subsequently to existing reviews were identified via the literature search and data were extracted directly from the RCT publication. RCTs reported in abstract form only were eligible for inclusion, provided adequate information was presented in the abstract. Studies using quasi-randomisation were excluded, providing other RCT evidence for the treatment of interest was available.

Non-English-language studies were excluded unless sufficient data could be extracted (from English-language abstracts and/or tables). Dissertations and theses were excluded.

Data abstraction strategy

Titles and abstracts of citations identified by the searches were screened for potentially relevant studies by one reviewer and a subset checked by a second reviewer (and a check for consistency undertaken). Full texts were screened by two reviewers. Details of studies identified for inclusion were extracted using a data extraction sheet. One reviewer performed data extraction of each included study. All numerical data were then checked against the original article by a second reviewer. Any disagreements were resolved by a third reviewer. When studies comprised duplicate reports (parallel publications), all associated reports were used to extract information.

Methods of data synthesis

When possible, data were pooled in a meta-analysis from RCTs reported in the existing reviews along with data extracted from additional RCTs not captured by the existing reviews. Meta-analysis of outcome data from all RCTs was then undertaken using Cochrane RevMan software (version 5.2, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Outcomes reported as continuous data were estimated using a mean difference (MD) with 95% confidence interval (CI). Outcomes reported as dichotomous were estimated as relative risks (RRs) with associated 95% CI. When RCTs reported AEs in sufficient detail (e.g. the number of participants who experienced at least one AE), these were analysed as dichotomous data. Data from single-arm randomised crossover design studies were considered separately in the analysis to avoid a unit-of-analysis error.[31]

Clinical heterogeneity across RCTs (the degree to which RCTs appear different in terms of participants, intervention type and duration and outcome type) and statistical heterogeneity were considered prior to data pooling. Statistical heterogeneity was assessed using the chi-squared test (p-value < 0.10 was considered to indicate statistically significant heterogeneity) in conjunction with the I-squared statistic.[32] For comparisons in which there was little apparent clinical heterogeneity and the I^2-value was $\leq 40\%$, a fixed-effects model was applied. When there was little apparent clinical heterogeneity and the I^2-value was $> 40\%$, a random-effects model was applied. Effect estimates (estimated in RevMan as z-values) were considered significant at $p < 0.05$. Data were not pooled across RCTs for which heterogeneity was very high (I^2-values of $\geq 75\%$).

Quality assessment of included studies

The methodological quality of systematic reviews used as a source of RCT data were assessed using the Assessing Methodological Quality of Systematic Reviews (AMSTAR) checklist.[33] This checklist consists of 11 items and has good face and content validity for measuring the methodological quality of systematic reviews.[33] Domain items with a 'yes' response are scored one point. 'No', 'not applicable' and 'unclear' responses score a zero. An overall score was estimated for each review by summing the total number of points. It was not possible to undertake quality assessment for RCTs for which data were extracted from existing reviews. Methodological quality of further RCTs identified from the literature search was 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.[34] We classified RCTs as being at overall 'low risk' of bias if they were rated as 'low' for each of three key domains – allocation concealment, blinding of outcome assessment and completeness of outcome data. RCTs judged as being at 'high risk' of bias for any of these domains were judged at overall 'high risk'. Similarly, RCTs judged as being at 'unclear risk' of bias for any of these domains were judged at overall 'unclear risk'.

Results

Quantity and quality of research available

The searches identified 2283 citations. Of these, 2181 citations were excluded, 2174 based on title and/or abstract information and seven that we were unable to obtain. One hundred and three (103) full-text articles were obtained as potentially relevant. Of these, 24 were excluded: eight were non-systematic reviews or treatment overviews, two were laboratory-based assessments, two were pharmacokinetic assessment studies and 12 were studies evaluating treatments not relevant to the UK setting. Details of the 24 excluded studies are presented in *Appendix 3*. In total, 78 articles from the searches were included in this assessment report comprising: 28 reviews, 47 primary study articles (relating to 38 studies) and three guideline articles (relating to two guidelines) (*Figure 1*).

From these publications, a total of 103 primary studies (102 RCTs) are summarised in this review (*Table 1*). Sixty-five RCTs were extracted from existing reviews and 38 further studies from the literature search (see *Table 1*). All 65 RCTs reported in existing reviews were also captured by the searches for this

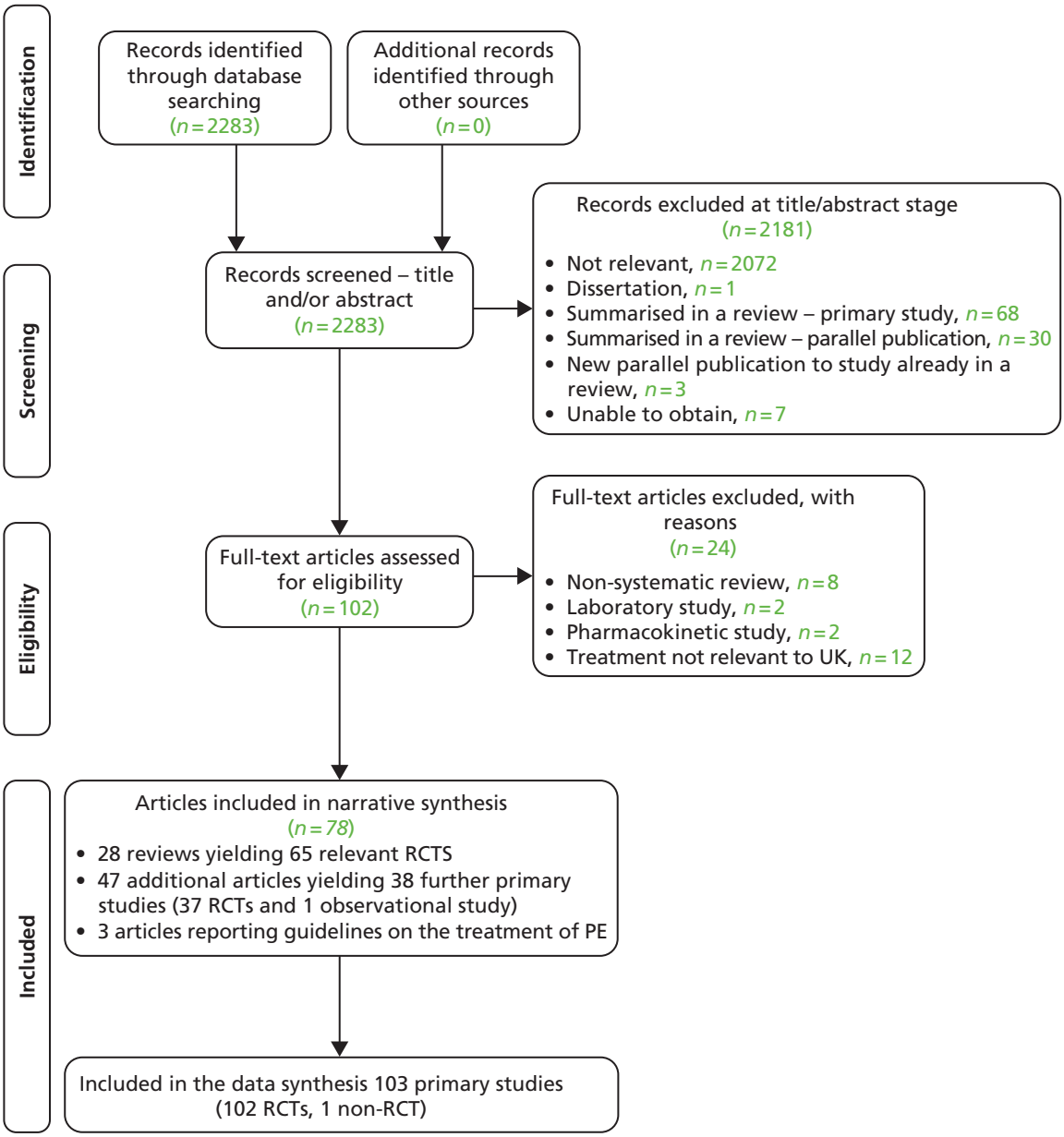

FIGURE 1 Study selection process: PRISMA flow diagram.

TABLE 1 Summary of reviews and RCTs by intervention

Intervention type	No. of reviews	No. of RCTs (extracted from reviews)	Further RCTs (not in reviews)	RCTs (total)
Behavioural therapies	4[35–38]	9[39–47]	3[48–50]	12
Topical anaesthetics	4[51–54]	7[55–61]	2[62,63]	9
SSRIs other than dapoxetine	7: • SSRIs: 4[64–67] • Various treatments: 3[52,68,69]	26: • Citalopram: 4[70–73] • Escitalopram (Cipralex®, Lundbeck): 0 • Fluoxetine: 11[41,74–83] • Fluvoxamine: 1[81] • Paroxetine: 9[39,73,81,82,84–88] • Sertraline: 9[39,76,78,81,82,84,89–91]	16: • Citalopram: 5[92–96] • Escitalopram (Cipralex®, Lundbeck): 4[94,97–99] • Fluoxetine: 5[95,97,100–102] • Fluvoxamine: 0 • Paroxetine: 4[97,103–105] • Sertraline: 4[92,102,106,107]	42: • Citalopram: 9 • Escitalopram (Cipralex®, Lundbeck): 4 • Fluoxetine: 16 • Fluvoxamine: 1 • Paroxetine: 13 • Sertraline: 13
Dapoxetine	8: • Dapoxetine: 6[68,108–112] • Various SSRIs: 2[65,67]	8[85,113–119] (one non-licensed doses; data not included here[115])	1[120]	9 (8 for licensed doses)
SNRIs	1[68]	1 (duloxetine)[121]	2 (venlafaxine)[122,123]	3
TCAs (clomipramine)	3[52,68,69]	10[39,76,124–131]	3[107,132,133]	13
PDE5	5[37,134–137]	10[39,55,138–145]	2[101,120]	12
Alpha-blockers	2 (various treatments)[52,69]	1[146]	1[107]	2
Opioid analgesics (tramadol)	3[147–149]	5[46,150–153]	2[154,155]	7
Acupuncture	0	0	2[156,157]	2
Chinese medicine	0	0	5[158–162]	5
Delay device	0	0	1[163]	1
Yoga	0	0	1[164] (non-RCT)	1 (non-RCT)

assessment report. RCT evidence was available for all of the treatments of interest for this review, bar yoga. For yoga, one observational study was included (a non-RCT). Details of the AMSTAR[33] quality assessment of included reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews are presented in *Appendix 4*.

As titles and abstracts were screened for inclusion by one reviewer, a check for consistency was undertaken. A second reviewer screened approximately 10% of the references ($n = 250$) during the initial screening stage. At this stage, references tagged as potentially relevant by reviewer 1 included 5 out of 194 (3%) references excluded by reviewer 2, and references tagged as potentially relevant by reviewer 2 included 22 out of 211 (10%) references excluded by reviewer 1. This gave a kappa statistic of 0.65, generally classed as good agreement. The discrepancies appeared to be due to the very broad inclusion criteria (in terms of study type and intervention type) that were applied at the time of initial screening. The references for which there was a discrepancy related to article types such as comment articles, news articles and uncontrolled studies that were initially tagged as potentially relevant. However, later examination revealed that none of these articles were relevant for inclusion in the final review.

Assessment of effectiveness

Overall summary of results

An overall results summary from this assessment report for outcomes of IELT, sexual satisfaction, control over ejaculation and other secondary outcomes, plus AEs, following treatment with behavioural techniques anaesthetic creams and sprays, TCAs, SSRIs including dapoxetine, PDE5 inhibitors, analgesics (tramadol) and other interventions in the management of PE is provided in *Table 2*. A detailed assessment of the effectiveness for each treatment type then follows.

TABLE 2 Summary of overall results from RCT pairwise non-crossover comparisons

Treatment	Better than	On outcomes of	Between-group difference significant	AEs with treatment
Behavioural therapies				
Behavioural therapy	Waiting list control	Duration of intercourse, sexual satisfaction, desire, self-confidence	Yes	No AE data available for behavioural therapies
Behavioural therapy plus pharmacotherapy	Pharmacotherapy alone	IELT, ejaculatory control, sexual satisfaction, sexual anxiety	Yes	
Behavioural therapy plus pharmacotherapy	Behavioural therapy alone	IELT, ejaculatory control, sexual satisfaction, sexual anxiety	Yes	
Pharmacotherapy alone	Behavioural therapy alone	IELT, sexual satisfaction	Yes	Various AEs associated with pharmacotherapy (nausea, vomiting, dry mouth, dizziness, flushing, diarrhoea)
Topical anaesthetics				
EMLA cream	Placebo	IELT	Yes	Loss of sensation, irritation and loss of erection (application ≥ 20 minutes)
TEMPE spray	Placebo	IELT ejaculatory control, sexual satisfaction and distress	Yes	
SSRIs currently not licensed for PE				
Citalopram	Placebo or no therapy	IELT, sexual satisfaction and measures of clinical improvement	Yes	
Escitalopram (Cipralex®, Lundbeck)	Placebo	IELT, sexual satisfaction	Yes	Nausea, headache, insomnia, dry mouth, diarrhoea, drowsiness, dizziness, somnolence, decreased libido and anejaculation
Fluoxetine				
Paroxetine				
Sertraline	Placebo	IELT, ejaculation control	Yes	
Clomipramine	Paroxetine	IELT	Yes	Similar to SSRIs
Fluvoxamine	Placebo	IELT	No	Not significant between fluvoxamine, fluoxetine, paroxetine and sertraline
SSRIs licensed for PE (dapoxetine)				
Dapoxetine 30 mg or 60 mg	Placebo	IELT, ejaculatory control, sexual satisfaction, patients reporting change	Yes	Similar to other SSRIs
Dapoxetine 60 mg	Dapoxetine 30 mg		Yes	

continued

TABLE 2 Summary of overall results from RCT pairwise non-crossover comparisons (*continued*)

Treatment	Better than	On outcomes of	Between-group difference significant	AEs with treatment
SNRIs				
Duloxetine	Placebo	IELT	Yes	Dry mouth and nausea; more AEs with venlafaxine than placebo
Venlafaxine	Placebo	IELT	No	Significantly more treatment-related side effects than placebo
TCAs				
Clomipramine: oral	Placebo	IELT	Yes	More AEs with clomipramine than fluoxetine or sertraline
Clomipramine: nasal (4 mg)			Yes	Local irritation associated with nasal administration
PDE5 inhibitors				
PDE5 inhibitors	Placebo	IELT	Vardenafil or tadalafil, yes; sildenafil, no	Flushing, headache and palpitations
PDE5 inhibitors	SSRIs		Sertraline, yes; fluoxetine, no	
PDE5 inhibitors plus SSRIs	SSRIs alone		Yes	
PDE5 inhibitors	Behavioural therapy		Yes	
Alpha-blockers				
Terazosin	Placebo	Ejaculation control	Yes	Headache, hypotension, drowsiness, ejaculation disorder
Opioid analgesics				
Tramadol	Placebo	IELT, various patient-reported outcomes, including sexual satisfaction	Yes	Erectile dysfunction, constipation, nausea, headache, somnolence, dry mouth, dizziness, pruritus, vomiting
Tramadol plus behavioural therapy	Behavioural therapy		Yes	
Paroxetine	Tramadol	IELT	No	
Other therapies				
Acupuncture	Sham acupuncture	IELT	Yes	No AE, data available for acupuncture, Chinese medicine or yoga
Chinese medicine	Treatment as usual		Yes	
Yoga (observational study)	Baseline	IELT	Yes	
Fluoxetine	Yoga		Yes	
Desensitising band plus stop–start technique	Stop–start technique	IELT	Yes	Appear minimal when device used as directed

Behavioural therapies

Characteristics of included studies: behavioural therapies

Behavioural therapies were evaluated by one Cochrane review[35] and two further systematic reviews of behavioural therapies.[36,38] Nine RCTs evaluating behavioural therapies were identified from these and other reviews of pharmacological therapies.[39–47] A further three RCTs of behavioural therapy were identified by the literature search:[48–50] one evaluated pelvic floor exercises compared with dapoxetine,[48] one evaluated a multicomponent behavioural therapy intervention compared with paroxetine alone or in combination with the behavioural intervention[49] and one evaluated an internet-based behavioural intervention compared with waiting list control.[50]

Reviews The Cochrane review by Melnik *et al.*[35] and the systematic review by Melnik *et al.*[38] were conducted in Brazil. The review by Berner and Gunzler[36] was undertaken in Germany. The Cochrane review by Melnik *et al.*[35] was awarded an overall AMSTAR quality score 7 out of 11. The systematic reviews by Berner and Gunzler[36] and Melnik *et al.*[38] were awarded 6 and 3 out of 11, respectively. Details of the review type, the databases searched and dates, relevant included RCTs and the AMSTAR points awarded to these reviews is presented in *Table 3*. Full details of the AMSTAR assessment for these and all other include reviews are presented in *Appendix 4*.

Randomised controlled trials included in reviews All reviews varied in terms of which RCTs they included. In total, nine RCTs of behavioural therapies[39–47] (total $n = 505$) were included in at least one systematic review. The method of IELT assessment (stopwatch) was reported for only five RCTs.[39,40,44,46,48] The duration of the RCTs included in the reviews ranged from 2 to 12 weeks. The behavioural therapies that were evaluated included the squeeze technique,[39] functional–sexological treatment involving movement of the body, speed of sexual activity and education regarding sensuality,[40] the stop–start technique plus squeeze technique,[40] behavioural psychotherapy,[42] stop–start technique alone,[43] behavioural psychotherapy,[44] 'Bibliotherapy' (consisting of introduction to PE, descriptions of squeeze technique, pause technique and sensate focusing), and sexual therapy for couples (sensate focus, stop–start technique and communication exercises).[45] The type of behavioural intervention was not specified for one RCT.[47]

In addition to the RCTs captured in reviews of behavioural therapy, one RCT evaluating the stop–start technique compared with fluoxetine or placebo[41] was captured in reviews of SSRIs (see *Selective serotonin reuptake inhibitors currently not licensed for premature ejaculation*) and one RCT evaluating a behavioural therapy that intervention was not specified compared with tramadol[46] was captured in another review of pharmacological agents (see *Opioid analgesics*). Details of the RCTs extracted from reviews are presented in *Table 4*. All RCTs in reviews were captured by the search strategy for this assessment report.

Randomised controlled trials not included in reviews The RCT by Pastore *et al.*[48] was conducted in Italy. Forty patients were randomised to pelvic floor muscle physiokinesitherapy (awareness of muscle contraction), comprising electrical stimulation of perineal floor, three 60-minute sessions per week, or to dapoxetine (30 mg or 60 mg on demand). IELT was assessed with a stopwatch. The duration was 12 weeks. The authors reported that 34 out of 40 (85%) patients completed the trial and IELT was stopwatch assessed. The RCT by Shao and Li[49] was conducted in China. A total of 120 patients were randomised to paroxetine 10 mg per day (for the first 4 weeks) combined with behavioural therapy comprising the Masters and Johnson squeeze technique,[17] sensate focus and Chinese traditional Qigong treatment (penis swinging and acupoint tapping), to paroxetine 20 mg per day, or to behavioural therapy only. The duration was 8 weeks. No objective assessment of IELT was reported. All patients (100%) were reported as completing the intervention. In the RCT by van Lankveld *et al.*,[50] an internet-based sex therapy based on the Masters and Johnson sensate focus technique was compared with waiting list control and 40 patients were randomised. The number and frequency of therapeutic contacts was left to the judgement of the therapist and the participant. No objective assessment of IELT was reported. The authors reported that 37 out of 40 (93%) patients completed the 3-month treatment programme. All three RCTs[107,132,133] were considered to be at overall unclear risk of bias.[34]

TABLE 3 Behavioural therapies: details of reviews and AMSTAR quality score

Author (country) review type	Databases searched and dates	Included RCTs relevant to this section	AMSTAR review quality assessment
Berner and Gunzler, 2012[36] (Germany) systematic review	CENTRAL, MEDLINE, CINAHL, Academic Search Premier, PsycINFO, PubMed and PSYNDEX between 1985 and 2009	de Carufel and Trudel 2006,[40] Oguzhanoglu *et al.* 2005,[43] Trudel and Proulx 1987[45]	AMSTAR score, 6/11: • a priori design reported • duplicate study selection and data extraction • comprehensive literature search • characteristics of included studies reported • study quality assessed, study quality used to informed conclusions • conflict of interest statement reported
Melnik *et al.* 2009[38] (Brazil) systematic review	MEDLINE by PubMed (1966–2009), PsycINFO (1974–2009), EMBASE (1980–2009), Latin America and Caribbean Health Sciences Literature (1982–2009) and CENTRAL (The Cochrane Library, 2009, issue 1)	Abdel-Hamid *et al.* 2001,[39] de Carufel and Trudel 2006,[40] Li *et al.* 2006,[42] Tang *et al.* 2004,[44] Trudel and Proulx 1987,[45] Yuan *et al.* 2008[47]	AMSTAR score, 3/11: • comprehensive literature search • studies included regardless of publication type • study quality assessed
Melnik *et al.* 2011[35] (Brazil) Cochrane review	MEDLINE, 1966–2010; PsycINFO, 1974–2010; EMBASE, 1980–2010; Latin America and Caribbean Health Sciences Literature, 1982–2010; and The Cochrane Library, 2010	Abdel-Hamid *et al.* 2001,[39] de Carufel and Trudel 2006,[40] Li *et al.* 2006,[42] Yuan *et al.* 2008[47]	AMSTAR score, 7/11: • a priori design reported • comprehensive literature search • studies included regardless of publication type • characteristics of included studies reported • study quality assessed • study quality used to informed conclusions • appropriate methods used to pool data • conflict of interest statement reported

CENTRAL, Cochrane Central Register of Controlled Trials.
AMSTAR review quality criteria: a priori design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; and conflict of interest statement included.

TABLE 4 Behavioural therapies: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Abdel-Hamid *et al.* 2001[39] (references to review in which the publication is included[35,37,38,52,69,134,135,137,165])	Single-arm crossover. 5 × 4-week phases each with 2-week washout	Sildenafil 50 mg 1 hour precoitus Clomipramine 25 mg 3–5 hours precoitus Sertraline 50 mg 3–5 hours precoitus Paroxetine 20 mg 3–5 hours precoitus Squeeze technique (Total $n = 31$)	IELT ≤ 2 minutes	Lifelong	Stopwatch	Modified Erectile Dysfunction Inventory of Treatment Satisfaction, Arabic Anxiety Inventory (scale 0–30)
de Carufel and Trudel 2006[40] (reviews[35,36,38])	NR	Functional-sexological treatment (education on sensuality, body movements, speed of sexual activity) Behavioural therapy (squeeze and stop–start techniques) Waiting list control (Total $n = 36$ couples)	IELT < 2 minutes	NR	Stopwatch	Perception of duration of intercourse, sexual satisfaction
Kolomaznik *et al.* 2002[41] (reviews[52])	8 weeks	Stop–start technique Fluoxetine (dose NR) Placebo (Total $n = 93$)	NR	NR	IELT not assessed	Duration of coitus, subject report
Li *et al.* 2006[42] (reviews[35,38])	6 weeks	Behavioural therapy + chlorpromazine 50 mg/day ($n = 45$) Chlorpromazine 50 mg/day ($n = 45$)	IELT < 1 minute	NR	Method NR	Self-Rating Anxiety Scale Chinese Index Premature Ejaculation

continued

TABLE 4 Behavioural therapies: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Oguzhanoglu *et al.* 2005[43] (review[36])	8 weeks	Stop–start technique ($n = 16$) Fluoxetine 20 mg/day ($n = 16$)	Ejaculation before or within several minutes	NR	Method NR	Anxiety Satisfaction with treatment
Tang *et al.* 2004[44] (reviews[35,37,38,134])	6 weeks	Behavioural psychotherapy ($n = 30$) Sildenafil 50 mg + behavioural psychotherapy ($n = 30$)	NR	NR	Stopwatch	Patient/partner sexual satisfaction (0–5-point Likert scale)
Trudel and Proulx 1987[49] (reviews[36,38])	12 weeks	Bibliotherapy (book on behavioural techniques) Bibliotherapy with therapist contact by phone Sexual therapy for couples (sensate focus, stop–start, communication) Waiting list control (Total $n = 25$ couples)	IELT $\leq$ 5 minutes	NR	Method NR	NR
Xiong *et al.* 2011[46] (reviews[148,149])	12 weeks	Behavioural modification alone (not reported which) ($n = 36$) Tramadol 50 mg 2 hours preintercourse with behavioural modification ($n = 36$)	IELT $\leq$ 2 minutes	Lifelong	Stopwatch	IIEF
Yuan *et al.* 2008[47] (reviews[35,38])	2 weeks	Behavioural therapy ($n = 32$) Citalopram 20 mg/day ($n = 32$) Behavioural therapy plus citalopram ($n = 32$)	NR	NR	Method NR	Sexual satisfaction

Further RCTs identified by searches (not captured in reviews)

RCT (country), risk of bias	Duration	Treatments, *numbers analysed/randomised (%)*	PE definition	Lifelong/acquired	IELT assessment	Other outcomes
Pastore *et al.* 2012[48] (Italy), unclear	RCT 12 weeks	Pelvic floor muscle rehabilitation and electrical stimulation, three sessions/week ($n = 19$) Dapoxetine 30 mg or 60 mg on demand ($n = 21$) *Pelvic floor musclerehabilitation, 17/19 (89%); dapoxetine, 15/21 (71%)*	ISSM definition of PE	Lifelong	Stopwatch	None
Shao and Li 2008[49] (China), unclear	RCT 8 weeks	Paroxetine 10 mg/day (for first 4 weeks only) and behavioural therapy ($n = 40$) Paroxetine 20 mg/day ($n = 40$) Behavioural therapy (squeeze technique, sensate, focus, Qigong, acupoint tapping) ($n = 40$) *Paroxetine + behavioural therapy, 40/40 (100%); paroxetine, 40/40 (100%); behavioural therapy, 40/40 (100%)*	NR	NR	CIPE5	CIPE5
van Lankveld *et al.* 2009[50] (the Netherlands), unclear	RCT 3 months	Internet-based sex therapy (sensate focus) ($n = 22$) Waiting list control ($n = 18$) *Internet-based sex therapy, 21/22 (95%); waiting list control, 16/18 (89%)*	NR	NR	GRISS PE subscale	IIEF sexual desire, overall satisfaction, erectile dysfunction SEAR self-confidence Global Endpoint Question improvement/impairment of sexual functioning

CIPE5, Chinese Index of Premature Ejaculation 5 PE-related items; GRISS, Golombok Rust Inventory of Sexual Satisfaction; IIEF, International Index of Erectile Function; NR, not reported; SEAR, Self-Esteem and Relationship.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews and the overall study quality assessment (AMSTAR[33] for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 4*.

Assessment of effectiveness: behavioural therapies – intravaginal ejaculatory latency time outcomes

The reporting of IELT outcomes for RCTs included in the reviews was varied in terms of the treatment comparisons, the reporting of the assessment method, the outcome metric that was reported and the reporting of variance estimates and *p*-values. With the exception of the crossover study by Abdel-Hamid *et al.*[39] and the RCT by Xiong *et al.*,[46] no data were suitable to either estimate between-group differences for individual trial or pool data across studies in RevMan for this assessment report.

Intravaginal ejaculatory latency time: behavioural therapy compared with waiting list control

Duration of intercourse: functional sexological treatment or behavioural therapy compared with waiting list control No variance estimates were reported for this outcome in the review by Berner and Gunzler.[36] Melnik *et al.*[35] reported that both functional sexological treatment and behavioural therapy significantly increased duration of intercourse compared with waiting list controls (functional sexological therapy: MD 6.87 minutes, 95% CI 5.10 to 8.64 minutes; behavioural therapy: MD 6.80 minutes, 95% CI 5.04 to 8.56 minutes) for one RCT.[40] *p*-values for the between-group differences were not reported. Summary results for these and across all other behavioural intervention trials are presented in *Table 5*.

Intravaginal ejaculatory latency time: bibliotherapy with/without therapist contact, sexual therapy, waiting list control Mean ejaculatory latency (minutes) post treatment in one trial[45] was reported by Berner and Gunzler[36] as follows: bibliotherapy without therapist contact, 11.05 minutes (change from baseline, $p < 0.01$); bibliotherapy with therapist contact by phone, 9.23 minutes (change from baseline, $p < 0.01$); sexual therapy for couples, 10.78 minutes (change from baseline, $p < 0.01$); and waiting list control, 1.94 minutes (improvement not significant, *p*-value not reported).

Golombok Rust Inventory of Sexual Satisfaction premature ejaculation subscale score: internet-based behavioural therapy compared with waiting list control The between-group MD in the Golombok Rust Inventory of Sexual Satisfaction (GRISS) PE subscale score at 3 months based on one RCT[50] ($n = 37$) was –0.20 minutes (fixed effect; 95% CI –1.75 to 1.35 minutes; $p = 0.80$) (*Figure 2*).

Intravaginal ejaculatory latency time: behavioural therapy with pharmacotherapy compared with pharmacotherapy alone

Intravaginal ejaculatory latency time: behavioural therapy plus chlorpromazine compared with chlorpromazine Melnik *et al.*[35] reported that behavioural therapy plus chlorpromazine was superior to chlorpromazine alone in increasing IELT (minutes) after treatment in one RCT[42] (MD 1.11 minutes, 95% CI 0.82 to 1.40 minutes). A *p*-value for the between-group difference was not reported.

Intravaginal ejaculatory latency time: behavioural therapy plus citalopram compared with citalopram Melnik *et al.*[35] reported that, in one trial,[47] citalopram combined with behavioural therapy compared with citalopram alone favoured the combined approach therapy (no data reported). *p*-values were not reported.

TABLE 5 Behavioural therapies: results summary

Comparison	Outcome	No. of RCTs[a]	No. of participants	Meta-analysis	Effect estimate (95% CI)	Favours	*p*-value
IELT							
BT compared with waiting list control	IELT (minutes)	2[40,45]	36	N/A	MD (two types BT vs. WL), 6.80, 6.87 (both significant)[35,40]	BT	NR
			25		MD (three types BT vs. WL), 7.29, 8.84, 9.11[36,45]	BT	NR
BT with pharmacotherapy compared with pharmacotherapy alone	IELT	1[42]	90	N/A	MD 1.11 (0.82 to 1.40)[35]	BT + chlorpromazine	NR
		1[47]	96		NR	BT + citalopram	NR
	CIPE5 ejaculatory latency score	1[49]	80	N/A	MD 0.40 (0.18 to 0.62)	BT + paroxetine	0.0003
BT with pharmacotherapy compared with BT alone	IELT	1[44]	32	N/A	MD 1.81 (NR)	BT + sildenafil	< 0.001
		1[46]	72		MD 1.65 (0.30 to 3.00)	BT + tramadol	0.02
	CIPE5 ejaculatory latency score	1[49]	80	N/A	MD 0.60 (0.40 to 0.80)	BT + paroxetine	< 0.00001
BT compared with pharmacotherapy	IELT	1[48]	32	N/A	MD 1.22 (0.79 to 1.65)	Dapoxetine	< 0.00001
		1[47]	96		RR 0.52 (0.34 to 0.78)[35]	Citalopram[35]	NR[35]
		1[39] crossover	31		NS for clomipramine, sertraline and paroxetine	Sildenafil; NS for clomipramine, sertraline, paroxetine	< 0.00001; NS
	CIPE5 ejaculatory latency score	1[49]	80	N/A	MD 0.20 (0.00 to 0.40)	Paroxetine	0.05

continued

TABLE 5 Behavioural therapies: results summary (*continued*)

Comparison	Outcome	No. of RCTs[a]	No. of participants	Meta-analysis	Effect estimate (95% CI)	Favours	*p*-value
Other outcomes							
BT vs. waiting list control	Sexual satisfaction, desire, self-confidence	2[40,50]	Varies	N/A		BT	< 0.05[40,50]
BT with pharmacotherapy vs. pharmacotherapy alone	Ejaculatory control, sexual satisfaction and sexual anxiety	4[42,44,47,49]	Varies	N/A		BT with pharmacotherapy (citalopram, chlorpromazine, sildenafil, paroxetine[49])	< 0.01[49]; others NR
BT with pharmacotherapy vs. BT alone	Ejaculatory control, sexual satisfaction and sexual anxiety	2[46,49]	Varies	N/A		BT with pharmacotherapy (paroxetine,[49] tramadol[46])	< 0.01;[49] < 0.05[46]
BT vs. pharmacotherapy	Ejaculatory control	1[49]	80	N/A		Paroxetine[49]	< 0.01[49]
	Sexual satisfaction	1[49]	80			BT[49]	< 0.01[49]
		1[47]	96			Citalopram	NR

BT, behavioural therapy; CIPE5, Chinese Index of Premature Ejaculation 5 PE-related items; N/A, not applicable; NR, not reported; NS, not significant; WL, waiting list control.
a Crossover indicates that the estimate is from a crossover RCT.

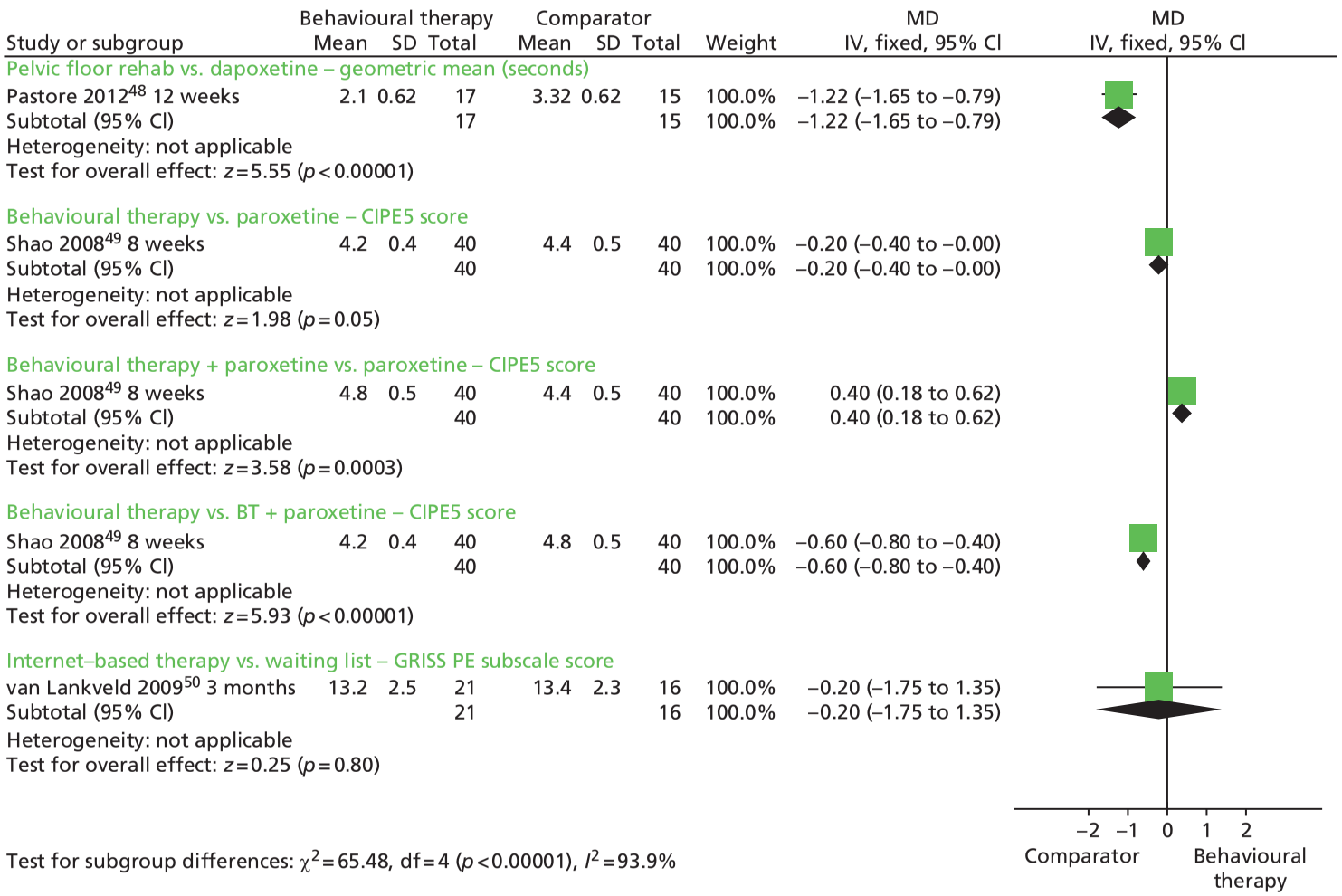

FIGURE 2 Behavioural therapies compared with comparator: forest plot of IELT outcomes. CIPE5, Chinese Index of Premature Ejaculation 5 premature ejaculation-related items; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Chinese Index of Premature Ejaculation 5 premature ejaculation-related items ejaculatory latency score: behavioural therapy plus paroxetine compared with paroxetine The between-group difference in the Chinese Index of Premature Ejaculation 5 PE-related items (CIPE5) ejaculatory latency score at 8 weeks based on one RCT[49] ($n = 80$) was 0.40 minutes in favour of behavioural therapy combined with paroxetine 20 mg compared with paroxetine 20 mg alone [MD (fixed effect), 95% CI 0.18 to 0.62 minutes; $p = 0.0003$] (see *Figure 2*).

Intravaginal ejaculatory latency time: behavioural therapy with pharmacotherapy compared with behavioural therapy alone

Intravaginal ejaculatory latency time: behavioural therapy plus sildenafil compared with behavioural therapy Mean values (minutes) at week 6 for one trial[44] were reported as 3.63 minutes for cognitive–behavioural therapy (CBT) plus sildenafil compared with 1.82 minutes for behavioural therapy alone. The *p*-value for between-group difference was reported as $p < 0.001$ in favour of behavioural therapy with sildenafil.

Intravaginal ejaculatory latency time: behavioural therapy plus tramadol vs. behavioural therapy The between-group difference in mean IELT (minutes) at 12 weeks, based on one RCT[46] ($n = 72$), was 1.65 minutes, significantly favouring tramadol with behavioural therapy compared with behavioural therapy alone (95% CI 0.30 to 3.00 minutes; $p = 0.02$). The forest plot for this analysis is presented as *Figure 18* in the *Opioid analgesics* section of this assessment report.

Chinese Index of Premature Ejaculation 5 premature ejaculation-related items ejaculatory latency score – behavioural therapy plus paroxetine compared with behavioural therapy The between-group difference in the CIPE5 ejaculatory latency score at 8 weeks based on one RCT[49] ($n = 80$) was 0.60 minutes in favour of behavioural therapy combined with paroxetine 20 mg compared with behavioural therapy alone [MD (fixed effect), 95% CI 0.40 to 0.80 minutes; $p < 0.00001$] (see *Figure 2*).

Intravaginal ejaculatory latency time: behavioural therapy compared with pharmacotherapy

Intravaginal ejaculatory latency time: pelvic floor rehabilitation compared with dapoxetine The between-group difference in geometric mean IELT (minutes) at 12 weeks based on one RCT[48] ($n = 32$) was 1.22 minutes in favour of dapoxetine 30 mg or 60 mg compared with pelvic floor rehabilitation [MD (fixed effect) 95% CI 0.79 to 1.65 minutes; $p < 0.0001$] (see *Figure 2*).

Intravaginal ejaculatory latency time: behavioural therapy compared with citalopram Melnik *et al.*[35] reported that, in one trial,[47] citalopram significantly improved IELT compared with behavioural therapy (RR 0.52, 95% CI 0.34 to 0.78). *p*-values were not reported.

Intravaginal ejaculatory latency time: stop–start technique compared with fluoxetine The review by Berner and Gunzler[36] reported that no outcome data were available for the one RCT evaluating this treatment comparison.[43]

Intravaginal ejaculatory latency time: squeeze technique compared with selective serotonin reuptake inhibitors or tricyclic antidepressants The between-group difference in mean IELT change (minutes) following a 4-week randomised crossover comparison[39] was 12.00 minutes in favour of sildenafil compared with squeeze technique [MD (fixed effect) 95% CI 8.06 to 15.94 minutes; $p < 0.00001$]. Comparisons of squeeze technique with clomipramine, sertraline and paroxetine were not significant (*Figure 3*). A paired analysis could not be undertaken for approximation purposes for this study. Data from this trial were not pooled with other RCTs in any meta-analysis in this assessment report.

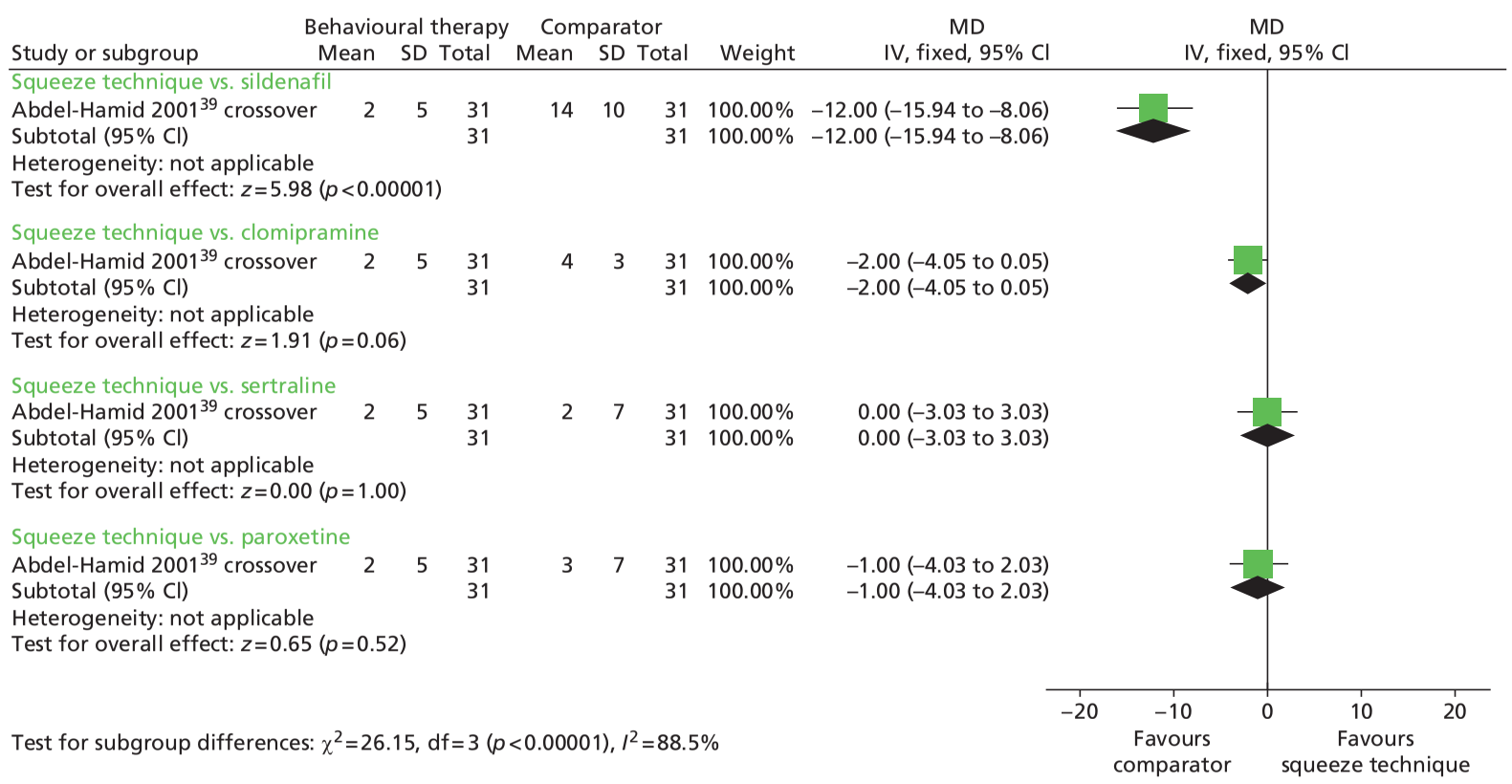

FIGURE 3 Behavioural therapies, squeeze technique vs. SSRIs or TCAs – forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Chinese Index of Premature Ejaculation 5 premature ejaculation-related items ejaculatory latency score: behavioural therapy compared with paroxetine The between-group difference in the CIPE5 ejaculatory latency score at 8 weeks based on one RCT[49] ($n = 80$) was 0.20 in favour of paroxetine 20 mg compared with behavioural therapy [MD (fixed effect), 95% CI 0.00 to 0.40 minutes; $p = 0.05$] (see *Figure 2*).

Assessment of effectiveness – behavioural therapies: other outcomes

With the exception of the RCTs by Pastore *et al.*[48] and Trudel and Proulx[45] all of the included trials were reported as evaluating one or more other outcomes. However, these were diverse across the included trials and were often not reported in sufficient detail to permit any pooling across trials (*Table 6*).

Other outcomes: behavioural therapy compared with waiting list control Male perceptions of the duration of intercourse and couples' sexual satisfaction were significantly improved with either functional sexological treatment (sensual education) or behavioural therapy (stop–start technique and squeeze technique) compared with waiting list control in one RCT.[40] One RCT[50] reported a significant increase from baseline in International Index of Erectile Function (IIEF) measures of sexual satisfaction and desire, and on a measure of self-confidence associated with internet-based sex therapy based on a sensate focus technique compared with waiting list control. No difference was evident on an improvement/impairment of sexual functioning measure.

Other outcomes: behavioural therapy with pharmacotherapy compared with pharmacotherapy alone Behavioural psychotherapy combined with chlorpromazine was reported by one RCT as being more effective than chlorpromazine alone on a self-rated measure of anxiety and Chinese Index of Premature Ejaculation (CIPE) measures of sexual anxiety, sexual satisfaction and ejaculatory control.[42] Shao *et al.*[49] reported that CIPE measures of ejaculation control, patient/partner satisfaction and sexual anxiety were all significantly improved following treatment with behavioural therapy comprising squeeze technique, sensate focus and Chinese traditional treatment plus paroxetine compared with paroxetine alone. Yuan *et al.*[47] reported that behavioural therapy combined with citalopram was more effective at improving sexual satisfaction than citalopram alone.

Other outcomes: behavioural therapy with pharmacotherapy compared with behavioural therapy alone Shao *et al.*[49] reported that CIPE measures of ejaculation control, patient/partner satisfaction and sexual anxiety were all significantly improved following treatment with behavioural therapy comprising squeeze technique, sensate focus and Chinese traditional treatment plus paroxetine compared with behavioural therapy alone. In one RCT,[44] more patients receiving behavioural therapy plus sildenafil than patients receiving behavioural therapy alone reported 'satisfied' on a measure of sexual satisfaction. Xiong *et al.*[46] reported a between-group difference at 8 weeks of $p < 0.05$ on the IIEF favouring the tramadol plus behavioural therapy group compared with behavioural therapy alone.

Other outcomes: behavioural therapy compared with pharmacotherapy Shao *et al.*[49] reported that paroxetine was significantly better than behavioural therapy on CIPE assessed ejaculation control. However, patient/partner satisfaction was significantly better following behavioural therapy than following paroxetine. No significant between-group difference was observed for sexual anxiety. Yuan *et al.*[47] reported that citalopram significantly increased the number of couples satisfied with their sex life compared with behavioural therapy alone. Oguzhanoglu *et al.*[43] reported no statistically significant between-group difference in satisfaction with treatment for stop–start technique compared with fluoxetine.

Assessment of safety: behavioural therapies – adverse events

Adverse event data were available for only 4 of the 12 included RCTs. Abdel-Hamid *et al.*[39] reported that the incidence of side effects was similar among groups and included headache, flushing and nasal congestion in 18% of the patients who received sildenafil. Pastore *et al.*[48] reported that dapoxetine was associated with nausea and diarrhoea whereas no AEs were reported for the pelvic floor rehabilitation group.

TABLE 6 Behavioural therapies: outcomes other than IELT and AEs

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
BT compared with waiting list control					
de Carufel and Trudel 2006,[40] NR	Functional sexological treatment	Perception of duration of intercourse	Perception of duration of intercourse improved significantly in both treatments, but not in the waiting-list group ($p < 0.05$)	Yes	NR
	BT	Couples' sexual satisfaction	Both treatment groups had significant improvements over waiting list for couples' sexual satisfaction	Yes	
	Waiting list control				
	(Total $n = 36$ couples)				
Trudel and Proulx 1987,[45] 12 weeks	Bibliotherapy	NR	NR	NR	Different and high dropout rates across groups. No further data reported
	Bibliotherapy with therapist contact				
	Sexual therapy for couples				
	Waiting list control				
	(Total $n = 25$ couples)				
van Lankveld *et al.* 2009,[50] treatment duration was 3 months, follow-up at 3 and 6 months post treatment	Internet-based sex therapy ($n = 22$)	IIEF sexual desire, overall satisfaction, erectile dysfunction	IIEF overall satisfaction and IIEF sexual desire: *p*-values for change from baseline for internet-based sex therapy of $p < 0.05$	Yes (from baseline)	NR
	Waiting list control ($n = 18$)	SEAR self-confidence	SEAR self-confidence score: *p*-value of 0.05 for change from 3-month to 6-month follow-up	Yes (at one time point)	
		GEQ improvement/ impairment of sexual functioning	GEQ: no significant between-group difference ($p > 0.05$)	No	

continued

TABLE 6 Behavioural therapies: outcomes other than IELT and AEs (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Combined therapies compared with monotherapy					
Li *et al.* 2006,[42] 6 weeks	BT + chlorpromazine ($n = 45$) Chlorpromazine ($n = 45$)	Self-Rating Anxiety Scale CIPE	Chlorpromazine + BT was superior to chlorpromazine alone for Self-Rating Anxiety Scale and for some CIPE questions ('anxiety in sexual activity', 'partner sexual satisfaction', 'patient sexual satisfaction', 'control ejaculatory reflex' and 'ejaculatory latency')	Yes	NR
Shao and Li 2008,[49] 8 weeks	BT + paroxetine ($n = 40$) Paroxetine 20 mg per day ($n = 40$) BT ($n = 40$)	CIPE5	Ejaculation control: BT + paroxetine better than paroxetine, $p < 0.01$; or BT, $p < 0.01$; paroxetine better than BT, $p < 0.01$ Patient satisfaction: BT + paroxetine better than paroxetine, $p < 0.01$; or BT, $p < 0.05$; BT better than paroxetine, $p < 0.01$ Partner satisfaction: BT + paroxetine better than paroxetine, $p < 0.01$; or BT, $p < 0.05$; BT better than paroxetine, $p < 0.01$ Sexual anxiety: BT + paroxetine better than paroxetine, $p < 0.01$; or BT, $p < 0.01$; BT vs. paroxetine, NS	Yes	Four AEs (10%) in the paroxetine + BT group and 16 (40%) in the paroxetine group. No further details reported
Tang *et al.* 2004,[44] 6 weeks	BT ($n = 30$) Sildenafil + BT ($n = 30$)	Patient/partner sexual satisfaction (0–5-point Likert scale)	BT, 19/30 'satisfied'; BT + sildenafil, 26/30 'satisfied'. NR what point(s) of scale = 'satisfied'. *p*-value for between-group difference, NR	Unclear	NR

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Combined therapies compared with monotherapy					
Xiong *et al.* 2011,[46] 12 weeks	Behaviour modification ($n = 36$) Tramadol + behaviour modification ($n = 36$)	IIEF	Tramadol + behaviour modification: mean change 4 Behaviour modification alone: mean change 2 Between-groups $p < 0.05$	Yes	Any AE: • Tramadol: 28% • Behavioural: 0% • Tramadol: nausea (11.1%), vomiting (2.8%), dry mouth (5.6%), dizziness (8.3%)
Yuan *et al.* 2008,[47] 2 weeks	Behavioural – therapy ($n = 32$) Citalopram ($n = 32$) BT plus citalopram ($n = 32$)	Sexual satisfaction	Citalopram significantly improved the number of couples satisfied with their sex life vs. BT Citalopram + BT vs. citalopram favoured combined approach for satisfaction with sex life	Yes	NR
BT compared with pharmacotherapy					
Abdel-Hamid *et al.* 2001,[39] 5 × 4 week phases each separated by a 2-week washout	Squeeze technique Sildenafil 50 mg – Clomipramine Sertraline Paroxetine (Total $n = 31$)	Erectile Dysfunction Inventory of Treatment Satisfaction scale 0–5: sexual satisfaction score Arabic Anxiety Inventory (scale 0–30)	Clomipramine, 11; sertraline, 11; sildenafil, 30; paroxetine, 9; squeeze technique, 6 Clomipramine, 11; sertraline, 10; sildenafil, 15; paroxetine, 12; squeeze technique, 3 (Unclear if means or medians; no SD or *p*-values reported)	NR NR	Headache, flushing, and nasal congestion: sildenafil, 18% The incidence of side effects was similar among groups (numbers NR)

continued

TABLE 6 Behavioural therapies: outcomes other than IELT and AEs (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Kolomaznik *et al.* 2002,[41] 8 weeks	Stop–start technique Fluoxetine Placebo Total $n = 93$	Duration of coitus, subject report	NR	NR	NR
BT compared with pharmacotherapy					
Oguzhanoglu *et al.* 2005,[43] 8 weeks	Stop–start technique ($n = 16$) Fluoxetine ($n = 16$)	Anxiety	State Anxiety change from baseline: • BT, $p < 0.05$; fluoxetine, $p < 0.05$ Trait Anxiety change from baseline: • BT, $p < 0.05$; fluoxetine, $p < 0.05$	No No	NR
		Satisfaction with treatment	Satisfaction with treatment: $p > 0.05$ between groups		
Pastore *et al.* 2012,[48] 12 weeks	Pelvic floor muscle rehabilitation ($n = 19$) Dapoxetine 30 or 60 mg ($n = 21$)	None	–	–	Pelvic floor muscle rehabilitation, no side effects Dapoxetine: 30 mg nausea 1/8 (12.5%); 60 mg nausea, 2/7 (28.5%), diarrhoea 1/7 (14.0%) No severe AEs, no discontinuations due to AEs

BT, behavioural therapy; CIPE, Chinese Index of Premature Ejaculation; GEQ, Global Endpoint Question; IIEF, International Index of Erectile Function; NR, not reported; NS, not significant; SD, standard deviation; SEAR, Self-Esteem and Relationship.

In the RCT by Shao *et al.*,[49] the incidence of AEs was reported in the paroxetine group and the behavioural therapy combined with paroxetine group. However, the types of AEs were not reported. AEs for the behavioural therapy-only group were not reported. For one RCT,[46] the between-group difference in relative risk (RR) at 12 weeks was 21.00 experiencing AEs [RR (random effects), 95% CI 1.28 to 345.41; $p = 0.03$] in favour of behavioural therapy alone compared with tramadol (lower risk). The forest plot for this analysis is presented as *Figure 20* in the *Opioid analgesics* section of this assessment report.

Assessment of effectiveness: behavioural therapies – evidence summary

The current evidence base for behavioural therapy in the treatment of PE comprises 12 RCTs, nine captured in three low to good methodological quality systematic reviews and three further RCTs which are at overall unclear risk of bias. The quality of IELT outcome reporting across these trials is limited and does not facilitate any meaningful pooling across trials to be undertaken. However, individual trial results suggest that behavioural therapies are better than waiting list control in improving IELT, that behavioural therapies combined with pharmacological therapies are better than pharmacological agents alone (chlorpromazine, citalopram or paroxetine) and that behavioural therapies combined with pharmacological therapies (sildenafil, paroxetine or tramadol) are better than behavioural therapy alone in improving IELT in men with PE.

Various assessment methods in terms of ejaculation control, patients'/partners' sexual satisfaction, anxiety and other patient-reported outcomes have been used across RCTs to measure the effectiveness of behavioural therapies. There is, however, some evidence to suggest that behavioural therapies combined with pharmacological therapies (paroxetine or tramadol) are better than behavioural therapy alone and that behavioural therapies combined with pharmacological therapies are better than pharmacotherapy alone (paroxetine, chlorpromazine, sildenafil or citalopram) in improving outcomes other than IELT. AE reporting across RCTs evaluating behavioural interventions is limited and AEs are often reported only for an adjuvant pharmacological agent or a pharmacological comparator. Adjuvant therapies to behavioural interventions that include SSRIs (dapoxetine, paroxetine) and PDE5 inhibitors (sildenafil) are reported to be associated with headache, flushing, nausea and diarrhoea.

Behavioural therapy alone appears to be more effective than no treatment in the treatment of PE. Behavioural therapy combined with pharmacological therapy appears more effective than behavioural therapy or pharmacological therapy alone. Comparisons between behavioural therapy and pharmacological therapies generally favour the pharmacological intervention for improvement in IELT, but are uncertain for other outcomes. AEs may be associated with adjuvant pharmacotherapy. The long-term efficacy of behavioural therapy in the treatment of PE is not evaluated in the current evidence base.

Topical anaesthetics

Characteristics of included studies: topical anaesthetics

Topical anaesthetics were evaluated by two systematic reviews[51,53] and one 'mini review'.[54] Two of these systematic reviews pooled data in a meta-analysis.[51,53] Trials of topical treatments were also included in one other review of pharmacological therapies.[52] A further two RCTs were identified, one of which evaluated EMLA (lidocaine and prilocaine) cream compared with electrical stimulation or placebo,[62] while the other evaluated a lidocaine spray (Premjact, Boots Pharmaceuticals) compared with paroxetine.[63]

Reviews One of the reviews of topical anaesthetics was conducted in the USA.[54] The two systematic reviews that pooled data in a meta-analysis were both undertaken in China.[51,53] The overall AMSTAR quality score of one of the reviews was 1 out of 11.[54] The two systematic reviews with a meta-analysis were scored as 4 out of 11[51] and 5 out of 11.[53] Details of the review type, the databases searched and dates, relevant included RCTs and the AMSTAR points awarded to these reviews are presented in *Table 7*. Full details of the AMSTAR assessment for these and all other include reviews are presented in *Appendix 4*.

TABLE 7 Topical anaesthetics: details of reviews and AMSTAR quality score

Author (country), review type	Databases searched and dates	Included RCTs relevant to this section	AMSTAR review quality assessment
Morales *et al.* 2007[54] (USA), mini-review	MEDLINE 1966 to January 2004	Atan *et al.* 2006,[55] Atikeler *et al.* 2002,[56] Busato and Galindo 2004,[57] Dinsmore *et al.* 2007,[59] Gittelman *et al.* 2006[61]	AMSTAR score, 1/11: • conflict of interest statement reported
Pu *et al.* 2013[51] (China), systematic and meta-analysis	Cochrane Central Register of Controlled Trials, PubMed (from 1980 to June 2012), and EMBASE (from 1980 to June 2012)	Atan *et al.* 2006,[55] Atikeler *et al.* 2002,[56] Busato and Galindo 2004,[57] Carson *et al.* 2010,[58] Dinsmore *et al.* 2007,[59] Dinsmore and Wyllie 2009[60]	AMSTAR score, 4/11: • comprehensive literature search • studies included regardless of publication type • characteristics of included studies reported • study quality assessed
Xia *et al.* 2013[53] (China), systematic and meta-analysis	The Cochrane Library, PubMed and EMBASE to October 2012	Atikeler *et al.* 2002,[56] Busato and Galindo 2004,[57] Carson *et al.* 2010,[58] Dinsmore *et al.* 2007,[59] Dinsmore and Wyllie 2009[60]	AMSTAR score, 5/11: • duplicate study selection extraction • characteristics of included studies reported • study quality assessed • appropriate methods used to pool data • conflict of interest statement reported

AMSTAR review quality criteria: a priori design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; and conflict of interest statement included.

The search methodology and inclusion criteria varied across these reviews. Pu *et al.*[51] pooled secondary outcome data from different domains of the same instrument in an overall summary effect estimate, in effect counting participants twice in the analysis. In the review by Xia *et al.*,[53] the authors pooled IELT effect estimates across studies using a standardised MD.

Randomised controlled trials included in reviews The reviews above varied in terms of which RCTs they included. In total, seven RCTs (total $n = 675$) were included in at least one of these reviews.[55–61] IELT was reported as being assessed using a stopwatch in four RCTs[57–60] and by patient self-report in one RCT.[56] The method of IELT assessment was not reported for two RCTs.[55,61] With the exception of the RCTs by Atikeler *et al.*[56] that evaluated the effects after more than five applications of treatment, and one trial reported as a crossover RCT,[61] duration across trials ranged from 4 to 12 weeks. The topical anaesthetics evaluated included EMLA cream, TEMPE spray (containing lidocaine and prilocaine) and other topical anaesthetic creams (dyclonine cream and alprostadil cream). All of the RCTs compared topical anaesthetics with placebo. In addition, one RCT was identified that compared EMLA cream with sildenafil or EMLA cream combined with sildenafil.[55] This RCT is also evaluated in the section *Phosphodiesterase-5 inhibitors* of this assessment report. All RCTs in reviews were captured by the search strategy for this assessment report.

Randomised controlled trials not included in reviews The RCT by Mallat *et al.*[62] was conducted in Tunisia. Patients were randomised, 30 per group, to EMLA, electrical stimulation or placebo. The trial was reported in abstract form only and the full details each treatment were not reported. The authors reported that 90 out of 90 (100%) patients completed the 12-week follow-up. The assessment method of IELT was

not reported. The RCT by Steggall *et al.*[63] was conducted in the UK. Sixty patients were recruited to the trial and were randomised to either a lidocaine spray (Premjact) 10 minutes preintercourse or paroxetine 20 mg daily. Treatment duration was 2 months and the authors reported that 44 out of 60 (70%) patients completed the intervention. Both of these trials were considered to be at overall unclear risk of bias.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews, and the overall study quality assessment (AMSTAR[33] for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 8*.

Assessment of effectiveness: topical anaesthetics – intravaginal ejaculatory latency time outcomes

With the exception of the RCT by Atan *et al.*,[55] IELT outcomes were reported for all of the RCTs identified from existing reviews. The review by Morales *et al.*[54] reported that there was no statistical advantage in adding sildenafil to topical prilocaine-lidocaine treatment in the RCT by Atan *et al.*[55] No data or *p*-value were reported. The two further RCTs identified for inclusion in this assessment report both reported IELT outcomes, but without any variance estimates. Mallat *et al.*[62] reported a *p*-value for IELT of $p < 0.001$, but it was unclear if this was across or between groups, or whether this was for end of study values or change from baseline. Steggall *et al.*[63] reported a *p*-value for median IELT change from baseline of $p = 0.038$ for lidocaine spray and $p < 0.0005$ for paroxetine. These trials were therefore not included in any IELT meta-analysis in this assessment report.

Intravaginal ejaculatory latency time: EMLA cream compared with placebo Meta-analysis of mean IELT (minutes) following an application of EMLA cream < 20 minutes preintercourse, based on two RCT study group comparisons ($n = 49$), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 6.44 minutes, significantly favouring EMLA [MD (fixed effect); 95% CI 6.01 to 6.87 minutes; $p < 0.00001$]. The forest plot for this analysis is presented in *Figure 4*. Summary results for these and all other meta-analyses are presented in *Table 9*.

Intravaginal ejaculatory latency time: TEMPE spray compared with placebo The between-group difference in mean IELT (minutes) based on one RCT ($n = 54$) was 3.30 minutes, significantly favouring TEMPE spray [MD (fixed effect); 95% CI 1.33 to 5.27 minutes; $p = 0.001$]. Meta-analysis of geometric mean IELT (minutes), based on two RCT study group comparisons ($n = 49$), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 2.10 minutes, significantly favouring TEMPE spray [MD (fixed effect); 95% CI 1.27 to 2.93 minutes; $p < 0.00001$]. The forest plot for this analysis is presented in *Figure 4*.

Intravaginal ejaculatory latency time: other topical anaesthetics compared with placebo
One single-arm randomised crossover trial ($n = 30$) evaluated three different topical anaesthetics.[61] The between-group differences in mean IELT (minutes) were 0.87 minutes in favour of dyclonine cream compared with placebo (95% CI 0.71 to 1.03 minutes; $p < 0.00001$); 1.41 minutes in favour of alprostadil cream compared with placebo (95% CI 1.24 to 1.58 minutes; $p < 0.00001$); and 1.74 minutes in favour of dyclonine/alprostadil cream compared with placebo (95% CI 1.58 to 1.90 minutes; $p < 0.00001$). The forest plot for this analysis is presented in *Figure 5*. A paired analysis could not be undertaken for approximation purposes for this study. Data from this trial were not pooled with other RCTs in any meta-analysis in this assessment report.

Assessment of effectiveness: topical anaesthetics – other outcomes

Three RCTs did not report any effectiveness outcomes other than IELT.[55,56,63] Amongst the other RCTs, outcomes other than IELT were diverse across the included trials (*Table 10*).

TABLE 8 Topical anaesthetics: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Atan *et al.* 2006[55] (reviews[51,54])	8 weeks	EMLA 15 minutes precoitus ($n = 22$) Sildenafil 50 mg 45 minutes precoitus ($n = 20$) EMLA + sildenafil ($n = 22$) Placebo ($n = 20$) All patients analysed	DSM-IV	NR	IELT not assessed	NR
Atikeler *et al.* 2002[56] (reviews[152–154])	≥ 5 applications	EMLA 2.5 g with condom: • 20 minutes precoitus ($n = 10$) • 30 minutes precoitus ($n = 10$) • 45 minutes precoitus ($n = 10$) Placebo ($n = 10$)	IELT < 1 minute	Lifelong	Subject report	NR
Busato and Galindo 2004[57] (reviews[51,53,54])	4–8 weeks	EMLA 2.5 g with condom 10–20 minutes precoitus ($n = 24$) Placebo ($n = 18$) (16 and 13 completed)	DSM-IV	Lifelong and acquired	Stopwatch	Sexual satisfaction (method NR)
Carson and Wyllie 2010[58] (reviews[51,53])	12 weeks	TEMPE spray 3 actuations (each 7.5 mg lidocaine, 2.5 mg prilocaine) 5 minutes precoitus ($n = 167$) Placebo ($n = 82$)	DSM-IV and ISSM	Lifelong and acquired	Stopwatch	IPE PEP

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Dinsmore *et al.* 2007[59] (reviews[51,53,54])	4 weeks	TEMPE 3 actuations (each 7.5 mg lidocaine, 2.5 mg prilocaine) 15 minutes precoitus ($n = 27$) Placebo ($n = 28$) (20 and 23 analysed)	DSM-IV	Lifelong	Stopwatch	IEC SQoL
Dinsmore and Wyllie 2009[60] (reviews[51,53])	12 weeks	TEMPE 3 actuations (each 7.5 mg lidocaine, 2.5 mg prilocaine) 5 minutes precoitus ($n = 200$) Placebo ($n = 100$) (191 and 99 analysed)	DSM-IV and ISSM	Lifelong and acquired	Stopwatch	IPE PEP
Gittelman *et al.* 2006[61] (reviews[54])	Single–arm crossover: duration NR	5–20 minutes preintercourse: • 1% dyclonine cream • 0.4% alprostadil cream • 0.5% dyclonine/ 0.4% alprostadil • placebo cream (Total $n = 30$)	NR	NR	Method NR	Sexual satisfaction – yes or no in 'PSQ diary'[a]

continued

TABLE 8 Topical anaesthetics: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Further RCTs identified by searches (not captured in reviews)						
RCT (country), risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Mallat *et al.* 2012[62] (Tunisia), unclear	12 weeks	EMLA ($n = 30$) Electric stimulation ($n = 30$) Placebo ($n = 30$) No details of treatments reported *All groups (100%)*	NR	NR	Method NR	IIEF
Steggall *et al.* 2008[63] (UK), unclear	2 months	Lidocaine 3–8 sprays 10 minutes precoitus Paroxetine 20 mg per day (Total $n = 60$) *Total* n *44/60 (70%),* n *per group NR*	DSM-IV diagnosis plus IELT ≤ 3 minutes	Lifelong and acquired	Stopwatch	IIEF number of acts of coitus per week IIEF intercourse satisfaction

IEC, Index of Ejaculatory Control; NR, not reported; SQoL, sexual quality of life.
a The original article did not report what 'PSQ diary' is.

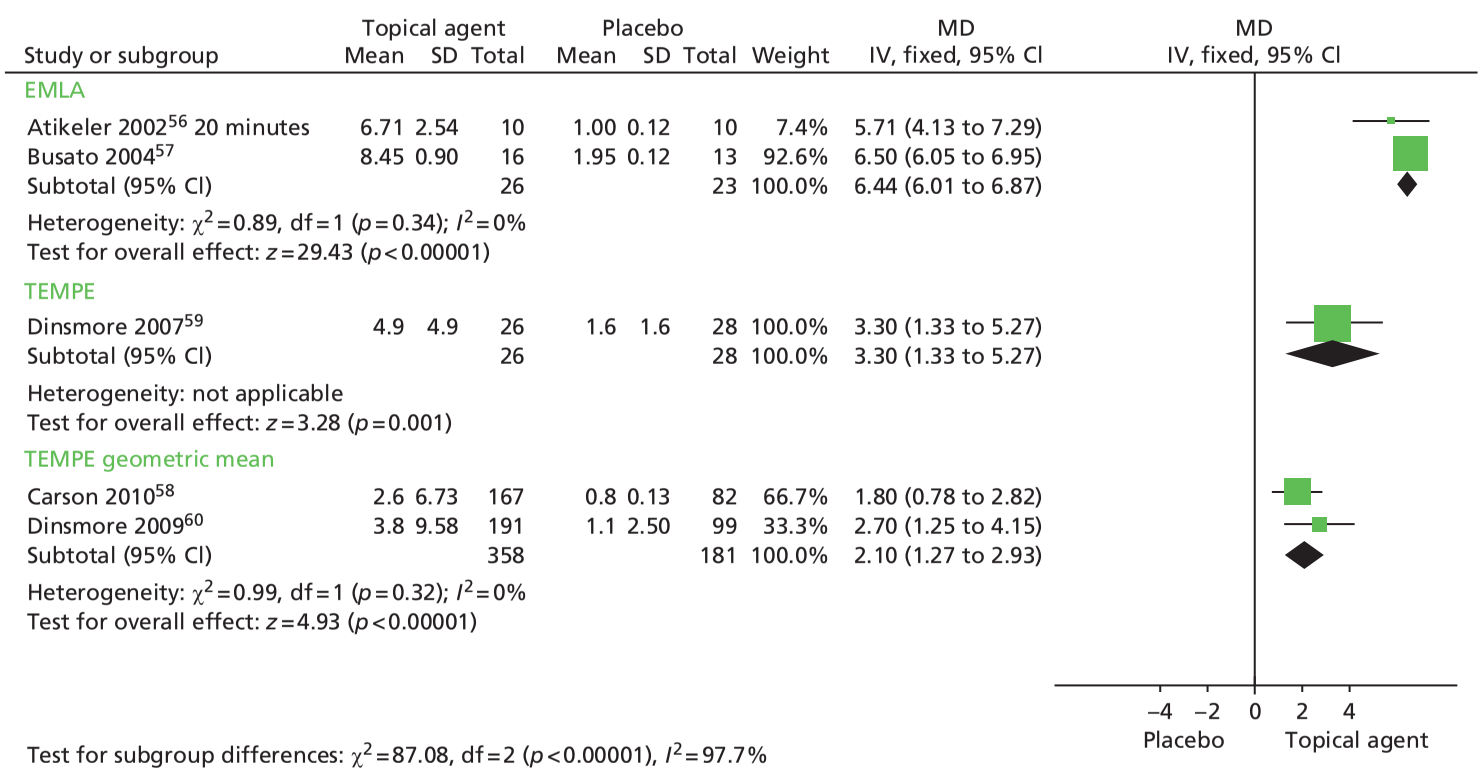

FIGURE 4 Topical anaesthetics, EMLA cream or TEMPE spray compared with placebo: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

TABLE 9 Topical anaesthetics: results summary

Comparison	Outcome	No. of RCTs[a]	No. of participants	I^2	Model	Effect estimate in minutes (95% CI)	Favours	*p*-value
IELT								
EMLA cream vs. placebo	IELT (minutes)	2[56,57]	49	0%	Fixed effect	MD 6.44 (6.01 to 6.87)	EMLA cream	< 0.00001
TEMPE spray vs. placebo	IELT (minutes)	1[59]	54	N/A	N/A	MD 3.30 (1.33 to 5.27)	TEMPE spray	0.001
TEMPE spray vs. placebo – geometric mean	IELT (minutes)	2[58,60]	539	0%	Fixed effect	MD 2.10 (1.27 to 2.93)	TEMPE spray	< 0.00001
Dyclonine cream vs. placebo	IELT (minutes)	1[55] crossover	60	N/A	N/A	MD 0.87 (0.71 to 1.03)	Dyclonine cream	< 0.00001
Alprostadil cream vs. placebo	IELT (minutes)	1[55] crossover	60	N/A	N/A	MD 1.41 (1.24 to 1.58)	Alprostadil cream	< 0.00001
Dyclonine/alprostadil cream vs. placebo	IELT (minutes)	1[55] crossover	60	N/A	N/A	MD 1.74 (1.58 to 1.90)	Alprostadil cream	< 0.00001
Other outcomes								
EMLA cream vs. placebo	Other outcomes (various)	2[57,62]	119	Two RCTs reported significant differences at 12 weeks in IPE ejaculatory control, sexual satisfaction and distress, and in PEP scores.[58,60]				
TEMPE spray vs. placebo	Other outcomes (various)	3[58–60]	594	Two RCTs reported significant differences at 12 weeks in IPE ejaculatory control, sexual satisfaction and distress and in PEP scores.[58,59] One RCT reported no significant differences in Index of Ejaculatory Control and SQoL at 4 weeks[60]				
AEs								
Topical anaesthetics (EMLA or TEMPE) vs. placebo	AEs	6[55–60]	704	0%	Fixed effect	RR 3.58 (1.71 to 7.48)	Placebo (fewer AEs)	0.0007
EMLA cream (applied ≤ 20 minutes) vs. placebo	AEs	3[55–57]	111	N/A	Fixed effect	RR 9.06 (0.55 to 150.06)	NS	0.12
TEMPE spray vs. placebo	AEs	3[58–60]	593	0%	Fixed effect	RR 3.25 (1.50 to 7.02)	Placebo (fewer AEs)	0.003

N/A, not applicable; NS, not significant; SQoL, sexual quality of life.
a Crossover indicates that the estimate is from a crossover RCT.

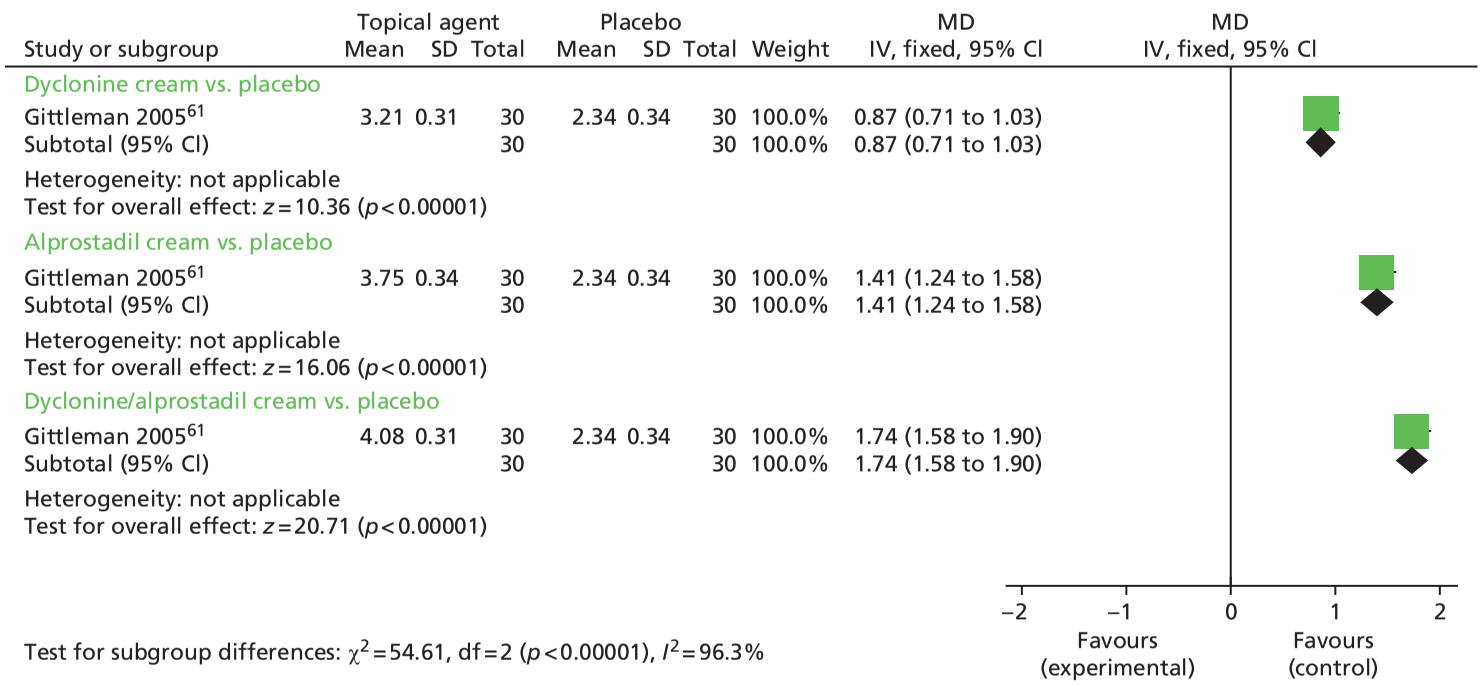

FIGURE 5 Topical anaesthetics vs. placebo – forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

TABLE 10 Topical anaesthetics: outcomes other than IELT and AEs

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Atan *et al.* 2006,[55] 8 weeks	EMLA ($n = 22$) Sildenafil ($n = 20$) EMLA + Sildenafil ($n = 15$) Placebo ($n = 20$)	NR	NR	NR	*n/N* (%) experiencing AEs: EMLA, 0/22 (0%); placebo, 0/20 (0%) (sildenafil and sildenafil + EMLA arms NR)
Atikeler *et al.* 2002,[56] ≥ 5 applications	EMLA: • 20 minutes precoitus ($n = 10$) • 30 minutes precoitus ($n = 10$) • 45 minutes precoitus ($n = 10$) Placebo ($n = 10$)	NR	NR	NR	*n/N* (%) experiencing AEs: EMLA 20 minutes, 0/10 (0%); placebo, 0/10 (0%). Erection loss or numbness: 30-minute group, 6/10; 45-minute group, 10/10
Busato and Galindo 2004,[57] 4–8 weeks	EMLA ($n = 21$)	Sexual satisfaction (method NR)	Sexual satisfaction: EMLA, 8.7; placebo, 4; $p = 0.001$	Yes	*n/N* (%) experiencing AEs: EMLA, 5/16 (34%); placebo, 0/13 (0%)
	Placebo ($n = 21$)		*n/N* reporting 'great' or 'excellent' satisfaction: EMLA, 6/16; 5/16; placebo, 3/13; 0/13	Yes	EMLA-associated AEs: men, 2/29 retarded ejaculation, 2/29 loss of sensitivity, 2/29 penile irritation; women 1/29 decreased sensitivity
Carson and Wyllie 2010,[58] 12 weeks	TEMPE spray ($n = 167$)	IPE	Ejaculatory control (IPE): TEMPE, 11.6; placebo, 6.5	Yes	*n/N* (%) experiencing AEs: TEMPE, 17/167 (10%); placebo, 1/82 (< 1%)
	Placebo ($n = 82$)		Sexual satisfaction (IPE): TEMPE, 13.4; placebo, 8.6	Yes	
			Distress (IPE): TEMPE, 6.1; placebo, 3.7	Yes	
		PEP	PEP ≥ 1 point improvement: $p < 0.0001$ (unclear if between groups or baseline)	Yes	

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Dinsmore *et al.* 2007,[59] 4 weeks	TEMPE spray ($n = 27$)	IEC	Ejaculatory control (IEC) change: TEMPE, 6.7; placebo, 3.0; $p = 0.12$	No	*n*/N (%) experiencing AEs: TEMPE, 6/26 (23%); placebo, 4/28 (14%)
	Placebo ($n = 28$)	SQoL	SQoL change: TEMPE, men 7.0, women 3.3. Placebo, men 5.5, women 1.8. *p*-value men, 0.48; women, 0.56	No	Assume with TEMPE: hypoaesthesia, 3/26; erectile dysfunction, 1/26. Women: mild burning 1/26
Dinsmore and Wyllie 2009,[60] 12 weeks	TEMPE spray ($n = 191$)	IPE	Ejaculatory control (IPE): TEMPE, 14.3; placebo, 7.4	Yes	*n/N* (%) experiencing AEs: TEMPE, 18/191 (9%); placebo 3/99 (3%)
	Placebo ($n = 99$)		Sexual satisfaction (IPE): TEMPE, 14.8; placebo, 9.1	Yes	
			Distress (IPE): TEMPE, 7.1; placebo, 4.5	Yes	
		PEP	PEP ≥ 1 point improvement: $p < 0.001$ (unclear if between groups or baseline)	Yes	
Gittelman *et al.* 2006,[61] NR (crossover)	Dyclonine cream	Sexual satisfaction – yes or no in 'PSQ diary'[a]	% reporting 'yes': dyclonine cream, 73.3%; alprostadil cream, 83.3%; dyclonine/alprostadil cream, 86.7%; placebo cream, 66.7%	Unclear	Proportion experiencing AEs: dyclonine cream, 17.5%; alprostadil cream, 20%; dyclonine/alprostadil cream, 17.5%; placebo cream, 5%. Type not reported
	Alprostadil cream				
	Dyclon/alpro cream				
	Placebo cream				
	(Total $n = 30$)				
Mallat *et al.* 2012,[62] 12 weeks	EMLA ($n = 30$)	Number of coitus per week	Number of coitus: EMLA, 1.4; electric stimulation, 2.3; placebo, 1.3	Unclear	No withdrawals caused by AEs across all treatments, but more AEs were associated with EMLA. No further details reported
	Electric stimulation ($n = 30$)	IIEF intercourse satisfaction	IIEF satisfaction: EMLA, 10; electric stimulation, 14; placebo, 10	Unclear	
	Placebo ($n = 30$)				
Steggall *et al.* 2008,[63] 8 weeks	Lidocaine spray	NR	NR	NR	NR
	Paroxetine				
	(Total $n = 60$)				

IEC, Index of Ejaculatory Control; SQoL, sexual quality of life; NR, not reported.
a The original article did not report what 'PSQ diary' is.

Other outcomes: EMLA cream compared with placebo A statistically significant between-group difference in sexual satisfaction in favour of EMLA cream after 2 months was reported by Busato and Galindo.[57] There appeared to be no difference between EMLA cream and placebo on the IIEF. Number of coitus per week and sexual satisfaction values were reported by one RCT.[62]

Other outcomes: TEMPE spray compared with placebo The between-group differences on the Index of Ejaculatory Control and Sexual Quality of Life for both men and women were reported as being not statistically significant at 4 weeks in one RCT.[59] However, two RCTs reported that TEMPE spray was significantly more effective than placebo at 12 weeks on the IPE measures including ejaculatory control, sexual satisfaction and distress and on the PEP.[58,60]

Other outcomes: other topical creams compared with placebo In one crossover RCT, > 70% of patients allocated to receive a cream containing either dyclonine, alprostadil or both agents reported 'yes' for sexual satisfaction.[61] However, 66.7% in the placebo group also reported 'yes'. A *p*-value for between-group difference was not reported.

Assessment of safety: topical anaesthetics – adverse events

Adverse events were not reported for one RCT.[63] When reported, AEs associated with topical anaesthetics included erectile dysfunction/loss of erection, loss of sensitivity/numbness (men and women) and irritation/burning (men and women).

Adverse events: topical anaesthetics compared with placebo Meta-analysis of patient numbers experiencing AEs following treatment with topical anaesthetics displayed low heterogeneity ($I^2 = 0\%$). The between-group difference in EMLA cream applied for ≥ 20 minutes compared with placebo was not statistically significant [RR 9.06 (fixed effect), 95% CI 0.55 to 150.06; $p = 0.12$]. However, Atikeler *et al.*[56] reported that EMLA cream caused 6 out of 10 men in the 30-minute application group and 10 out of 10 men in the 45-minute application group to report erection loss or numbness.

The pooled RR across three trials comparing TEMPE spray with placebo (593 participants) was 3.25 [RR (fixed effect); 95% CI 1.50 to 7.02; $p = 0.003$] in favour of placebo (lower risk). The forest plot for this analysis is presented in *Figure 6*. Results for these and all other meta-analyses are presented in *Table 10*.

Assessment of effectiveness: topical anaesthetics – evidence summary

The current evidence base for topical anaesthetics in the treatment of PE comprises nine RCTs,[54–63] seven[55–61] captured in three low methodological quality systematic reviews[51,53,54] and two further RCTs[62,63] which are at overall unclear risk of bias. The pooled evidence across two RCTs[56,57] comprising 49 participants suggests that EMLA cream is effective in significantly increasing IELT in men with PE compared with placebo (MD 6.44 minutes, 95% CI 6.01 to 6.87 minutes; $p < 0.00001$). Evidence from one RCT[59] (54 participants) suggests that TEMPE spray is effective in significantly increasing IELT in men with PE compared with placebo (MD 3.30 minutes, 95% CI 1.33 to 5.27 minutes; $p < 0.00001$). Evidence from one crossover RCT[61] suggests that creams containing dyclonine, alprostadil or both agents are more significantly more effective than placebo.

Various assessment methods in terms patient/partners sexual satisfaction and other outcomes have been used across RCTs to measure the effectiveness of topical anaesthetics. Evidence from three RCTs[58–60] suggests significant improvements in sexual satisfaction with topical anaesthetics compared with placebo. However, two other RCTs that assessed the effects of topical anaesthetics or placebo suggests there is no difference in sexual satisfaction or intercourse frequency,[57] or ejaculatory control and sexual quality of life.[58] Pooled evidence across trials suggests that topical anaesthetics are associated with significantly more AEs than placebo. AEs associated with topical anaesthetics include loss of sensitivity/numbness and irritation/burning for both men and women. Erectile dysfunction and loss of erection are also reported by men and appear to be related to treatment applications ≥ 20 minutes preintercourse.

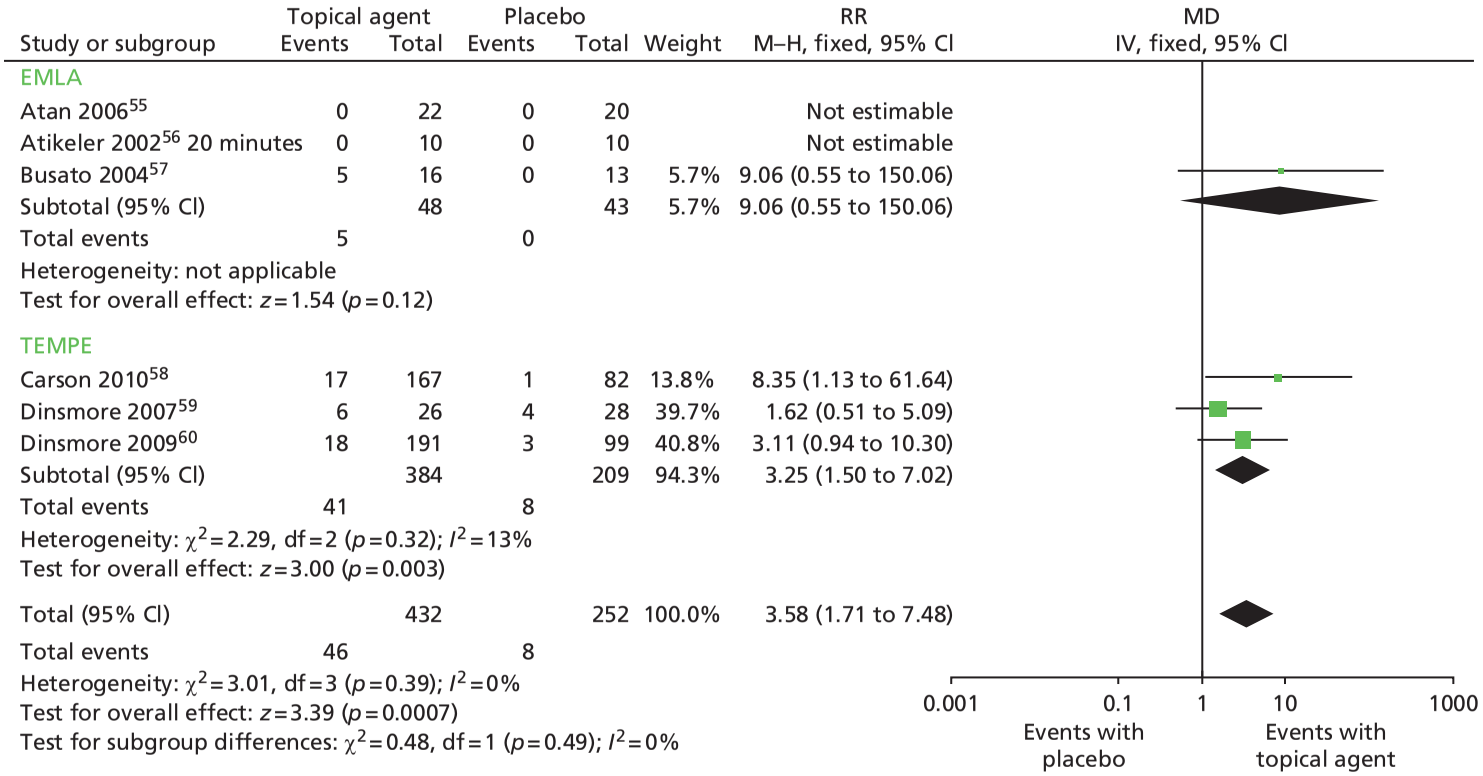

FIGURE 6 Topical anaesthetics compared with placebo: forest plot of AEs. df, degrees of freedom; IV, inverse variance.

Topical anaesthetics appear more effective than placebo in the treatment of PE. Loss of sensation and irritation are common AEs in both men and women, and there is more reporting of AEs associated with TEMPE spray than EMLA cream. Application of topical anaesthetics ≥ 20 minutes preintercourse is associated with erection loss. However, these findings should be interpreted with caution given the methodological quality of the available evidence. In addition, patient acceptability of this treatment modality (topical application) for PE has not been evaluated in the current evidence base.

Selective serotonin reuptake inhibitors currently not licensed for premature ejaculation

Characteristics of included studies: selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors were evaluated by seven systematic reviews.[52,64–69] Four reviews focused specifically on SSRIs,[64–67] while the others evaluated various treatments for PE including SSRIs. One review of SSRIs pooled data from RCTs comparing fluoxetine with placebo in a meta-analysis,[64] and one pooled data from RCTs comparing citalopram, dapoxetine, fluoxetine, fluvoxamine and sertraline with placebo in a meta-analysis.[65] Details of the review type, the databases searched and dates, relevant included RCTs and the AMSTAR points awarded to these reviews is presented in *Table 11*.

Reviews Three of the systematic reviews were conducted in China.[64,65,67] One review was conducted in Australia,[68] one in the Netherlands,[52] one in the USA[66] and one in the UK.[69] The overall AMSTAR quality score was 1 out of 11 in three of the reviews,[52,65,69] 2 out of 11 in one review[68] and 3 out of 11 in one review.[64] Two reviews scored 0 out of 11.[66,67] The review by Huang *et al.*[65] was the most comprehensive in terms of included RCTs evaluating SSRIs. However, the reviewers pooled data from single-arm crossover studies with separate treatment arm studies in a meta-analysis. Full details of the AMSTAR assessment for these and all other included reviews are presented in *Appendix 4*. The search methodology and inclusion criteria for studies were varied across these reviews. All RCTs in reviews were captured by the search strategy for this assessment report.

Randomised controlled trials (included in reviews and further randomised controlled trials) Twenty-six RCTs of SSRIs were evaluated across the seven reviews.[39,41,70–91,141,166] A further 16 RCTs additional to those already included reviews were identified for inclusion,[92–107] resulting in a total of 42 RCTs that evaluated SSRIs. Fourteen of the 16 additional RCTs identified by the literature search were considered to be at overall unclear risk of bias.[92–94,96–102,104–107] Two were considered to be at overall high risk of bias.[95,103] The 16 additional RCTs were undertaken in China, Egypt, Georgia, Italy, the Islamic Republic of Iran, the Republic of Korea, the Netherlands, Saudi Arabia and Turkey. Across the 42 included RCTs:

- Citalopram was assessed in nine RCTs.[70–73,92–96] Four RCTs were identified from reviews[70–73] and five from the literature search.[92–96] Across these RCTS treatment doses ranged from 20 mg to 60 mg. Comparators included placebo, no therapy and other SSRIs. Duration ranged from 4 to 12 weeks.
- Escitalopram (Cipralex®, Lundbeck) was evaluated in four RCTs, all identified from the literature search.[94,97–98] All prescribed daily dose of 10 mg. Comparators included placebo and other SSRIs. Duration ranged from 4 to 12 weeks.
- Fluoxetine was assessed in 16 RCTs.[41,74–81,83,95,97,100–102,141] Eleven RCTs were identified from reviews[41,74–83] and five from the literature search.[95,97,100–102] The doses evaluated were 10, 20 or 40 mg per day or 90 mg once weekly. Comparators included placebo, other SSRIs, clomipramine, fluoxetine plus tadalafil, and behavioural therapies (stop–start/squeeze technique). Duration ranged from 4 to 12 weeks.
- Fluvoxamine was assessed in one RCT at a dose of 20 mg for 6 weeks, compared with placebo and other SSRIs (Waldinger *et al.*,[81] identified from a review).

TABLE 11 Selective serotonin reuptake inhibitors currently not licensed for PE: details of reviews and AMSTAR quality score

Author (country), review type	Databases searched and dates	Included RCTs relevant to this section	AMSTAR review quality assessment
Cong *et al.* 2012,[64] (China), systematic review and meta-analysis	MEDLINE, EMBASE, PubMed, Ovid, CENTRAL, CBM and CNKI database July 1996 to May 2012	Kara *et al.* 1996,[75] Kim and Seo 1998,[76] Mattos *et al.* 2008,[141] Panshou and Xie 2004,[80] Waldinger *et al.* 1998,[81] Yilmaz *et al.* 1999[83]	AMSTAR score, 3/11: • comprehensive literature search • study quality assessed • publication bias assessed
Huang *et al.* 2009[65] (China), systematic review and meta-analysis	MEDLINE, January 1950 to March 2008; EMBASE, January 1950 to March 2008; The Cochrane Library, Issue I 2008; and CNKI, January 1979 to March 2008	Atmaca *et al.* 2002,[70] Atmaca *et al.* 2003,[71] Biri *et al.* 1998,[89] Kara *et al.* 1996,[75] Kim and Seo 1998,[76] Mattos *et al.* 2008,[141] McMahon and Touma 1999,[84] Mendels *et al.* 1995,[90] Novaretti *et al.* 2002,[79] Panshou and Xie 2004,[80] Safarinejad and Hosseini 2006,[72] Safarinejad 2006,[85] Waldinger *et al.* 1998,[81] Yilmaz *et al.* 1999,[83] Zhou 2007[91]	AMSTAR score, 1/11: • study quality assessed
McMahon and Porst 2011[68] (Australia), systematic review	PubMed 2004	Atmaca *et al.* 2002,[70] Kara *et al.* 1996,[75] Mattos *et al.* 2008,[141] Novaretti *et al.* 2002,[79] Waldinger *et al.* 1998,[81] Waldinger *et al.* 2001[82]	AMSTAR score, 2/11: • characteristics of included studies reported • conflict of interest statement reported
Moreland and Makela 2005[66] (USA), described as a 'mini review'	NR	Atmaca *et al.* 2002,[70] Biri *et al.* 1998,[89] Kim and Seo 1998,[76] Manasia *et al.* 2003,[77] McMahon and Touma 1999,[84] Mendels *et al.* 1995,[90] Waldinger *et al.* 1997,[87] Waldinger *et al.* 1998,[81] Waldinger *et al.* 2001,[73] Waldinger *et al.* 2001[82]	AMSTAR score, 0/11
Richardson *et al.* 2005[69] (UK), systematic review	MEDLINE, 1966 to January 2003 and PsycINFO, 1872 to January 2003	Abdel-Hamid *et al.* 2001,[39] Kara *et al.* 1996,[75] Kim and Seo 1998,[76] McMahon and Touma 1999,[84] Waldinger *et al.* 1997,[87] Waldinger *et al.* 1998,[81] Waldinger *et al.* 2001,[82] Waldinger *et al.* 2001,[73] Yilmaz *et al.* 1999[83]	AMSTAR score, 1/11: • characteristics of included studies reported
Waldinger *et al.* 2004[52] (the Netherlands), systematic review	MEDLINE (1966–2002), Web of Science, PICA, a and EMBASE (1980–2002)	Biri *et al.* 1998,[89] Abdel-Hamid *et al.* 2001,[39] Atmaca *et al.* 2002,[70] Haensel *et al.* 1998,[74] Kara *et al.* 1996,[75] Kim and Seo 1998,[76] Kolomaznik *et al.* 2002,[41] McMahon and Touma 1999,[84] Novaretti *et al.* 2002,[79] Waldinger *et al.* 1994,[86] Waldinger *et al.* 1997,[87] Waldinger *et al.* 1998,[81] Waldinger *et al.* 2001,[73] Waldinger *et al.* 2001,[82] Waldinger *et al.* 2003,[88] Yilmaz *et al.* 1999[83]	AMSTAR score, 1/11: • characteristics of included studies reported
Wang *et al.* 2007[67] (China), systematic review	MEDLINE 1 January 1996 to 1 August 2006	Atmaca *et al.* 2003,[71] McMahon 1998,[166] McMahon and Touma 1999,[84] Murat Basar *et al.* 1999,[78] Safarinejad and Hosseini 2006,[72] Waldinger *et al.* 2001,[82] Waldinger *et al.* 2001,[73] Waldinger *et al.* 2003,[88] Yilmaz *et al.* 1999[83]	AMSTAR score, 0/11

CBM, Chinese Biomedical Literature database; CENTRAL, Cochrane Central Register of Controlled Trials; CNKI, China National Knowledge Infrastructure; NR, not reported.
a Acronym not defined in original study.
AMSTAR review quality criteria: a priori design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; and conflict of interest statement included.

- Paroxetine was assessed in 13 RCTs.[39,73,81,82,84–88,97,103,104,105] Nine RCTs were identified from reviews[39,73,81,82,84–88] and four from the literature search.[97,103,104,105] Doses were 20 mg or 40 mg (usually 20 mg as a daily dose). Comparators included placebo, other SSRIs, clomipramine, sildenafil, mirtazapine, nefazodone (Serzone, Bristol-Myers Squibb, discontinued 2005) and the squeeze technique. Duration ranged from 4 to 12 weeks.
- Sertraline was assessed in 13 RCTs.[39,76,78,81,82,89–92,102,106,107,166] Nine RCTs were identified from reviews[39,76,78,81,82,89–91,166] and four from the literature search.[92,102,106,107] Doses ranged from 50 mg to 200 mg (usually 50 mg as a daily dose). Comparators included placebo, other SSRIs, clomipramine, sildenafil, terazosin, mirtazapine, PDE5 inhibitors and behavioural therapies.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews, and the overall study quality assessment (AMSTAR for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 12*.

Assessment of effectiveness: selective serotonin reuptake inhibitors – intravaginal ejaculatory latency time outcomes

Previous reviews have pooled data from single-arm crossover studies with separate treatment arm studies in a meta-analysis.[64,65] Data from these trials[39,74,76,79,84] have not been included in any meta-analysis of SSRIs in this assessment report.

Intravaginal ejaculatory latency time – selective serotonin reuptake inhibitors compared with placebo or no treatment

Intravaginal ejaculatory latency time: citalopram compared with placebo or no treatment Mean IELT data with variance estimates were available for four RCTs.[70–72,96] A high level of heterogeneity was observed across these trials ($I^2 = 99\%$, meta-analysis not undertaken). Three of the four trials[70,72,96] demonstrated a significant improvement in IELT for citalopram compared with placebo after 8–12 weeks (all $p < 0.00001$). The *p*-value for the between-group difference for one trial comparing citalopram with no therapy[71] was $p < 0.00001$ (*Figure 7*). Summary results for these, and all other meta-analyses, are presented in *Table 13*.

Intravaginal ejaculatory latency time: escitalopram compared with placebo The between-group difference in IELT in favour of escitalopram compared with placebo was significant for one RCT reporting end of study mean values[98] and one reporting geometric mean fold increase[99] (both $p < 0.0001$) (see *Figure 7*).

Intravaginal ejaculatory latency time: fluoxetine compared with placebo Meta-analysis of mean IELT (minutes) at 3–12 weeks' follow-up, based on six RCT comparisons of fluoxetine at 20 mg or 40 mg daily, or 90 mg weekly ($n = 170$), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 2.41 minutes, significantly favouring fluoxetine [MD (fixed effect); 95% CI 2.10 to 2.73 minutes; $p < 0.00001$] (*Figure 8*). Fluoxetine at 90 mg weekly was compared with 20 mg daily in one RCT.[77] IELT outcomes were reported without variance estimates or *p*-values. The between-group difference was reported as non-significant. For the comparison of fluoxetine alone compared with fluoxetine plus PDE inhibitor (tadalafil) reported in one RCT,[141] refer to the section *Phosphodiesterase-5 inhibitors*.

Intravaginal ejaculatory latency time: fluvoxamine compared with placebo The between-group difference in change from baseline values after 6 weeks of treatment for one RCT comparing fluvoxamine with placebo[81] was not significant ($p = 0.98$) (see *Figure 7*).

TABLE 12 Selective serotonin reuptake inhibitors are currently not licensed for PE: characteristics of RCTs included reviews and additional RCTs not captured in reviews

Citalopram: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Atmaca *et al.* 2002[70] (reviews[52,65,66,68])	8 weeks	Citalopram 20–60 mg/day ($n = 13$) Placebo ($n = 13$)	Partially ISSM: DSM-III R[167]	NR	Stopwatch	CGI-I, YSFI-II
Atmaca *et al.* 2003[71] (reviews[65,67])	8 weeks	Citalopram 20–60 mg (n=15) No therapy (n=15)	NR	NR	Method NR	NR
Safarinejad and Hosseini 2006[72] (reviews[65,67])	12 weeks	Citalopram 20 mg ($n = 26$) Placebo ($n = 25$)	NR	NR	Method NR	IIEF: intercourse satisfaction, coitus per week
Citalopram: further RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *number analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Farnia *et al.* 2008[93] (the Islamic Republic of Iran) unclear risk	4 weeks	Citalopram 20 mg 4 h precoitus ($n = 49$) Placebo ($n = 43$) *Completers: citalopram, 42/49 (86%); placebo, 38/43 (88%)*	DSM-IV-TR diagnosis	NR	Stopwatch	CIPE
Shang *et al.* 2012[96] (China) unclear risk	Duration NR, 2-week follow-up and 4-week follow-up post treatment	Citalopram 20 mg/day ($n = 40$) Placebo ($n = 40$) *NR*	NR	NR	Treatment druation NR	Sexual satisfaction

continued

TABLE 12 Selective serotonin reuptake inhibitors are currently not licensed for PE: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Escitalopram: RCTs identified by searches (not captured in reviews)						
Nada *et al.* 2009[98] (Egypt) unclear risk	4 weeks (and further 2 months follow-up)	Escitalopram 10 mg/day ($n = 15$) Placebo ($n = 15$) *NR*	NR	NR	CIPE	NR
Safarinejad 2007[99] (the Islamic Republic of Iran) unclear risk	12 weeks (then 3 and 6 months follow-up)	Escitalopram 10 mg/day ($n = 138$) Placebo ($n = 138$) *Escitalopram, 128/138 (93%)* *Placebo, 126/138 (91%)*	IELT < 2 minutes on 90% occasions	Lifelong, 82% Acquired, 18%	Stopwatch	IIEF intercourse satisfaction Weekly coitus episodes
Fluoxetine: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Haensel *et al.* 1998[74] (reviews[52])	Crossover, 4 weeks per treatment	Fluoxetine 5 mg/day (2 weeks), then 10 mg/day (2 weeks) Placebo ($n = 15$)	DSM-IV	NR	Ejaculatory latency questionnaire	NR
Kara *et al.* 1996[75] (reviews[52,64,68,69])	4 weeks	Fluoxetine 20 mg/day for 1 week then 40 mg/day ($n = 9$) Placebo ($n = 8$)	DSM-III[168]	NR	Stopwatch	Hamilton Depression Scale
Kolomaznik *et al.* 2002[41] (reviews[52])	8 weeks	Fluoxetine (dose NR) Stop–start technique Placebo ($n = 93$)	NR	NR	IELT not assessed	Duration of coitus, subject report
Manasia *et al.* 2003[77] (reviews[66])	Duration NR	Fluoxetine 90 mg/week ($n = 40$) Fluoxetine 20 mg/day ($n = 40$)	NR	NR	Method NR	Sexual satisfaction ratings

Fluoxetine: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Mattos *et al.* 2008[141] (reviews[64,65,68])	12 weeks	Fluoxetine 90 mg/week ($n = 15$) Tadalafil 20 mg 1–3 hours precoitus + fluoxetine 90 mg ($n = 15$) Tadalafil ($n = 15$) Placebo ($n = 15$)	DSM-IV + IELT ≤ 1.5 minutes	Lifelong	Stopwatch	NR
Novaretti *et al.* 2002[79] (reviews[52,65,68])	Crossover, 8 weeks	Fluoxetine 20 mg/d Placebo ($n = 50$)	NR	NR	Stopwatch	Hamilton Anxiety and Depression Scale; Beck Depression Inventory
Panshou and Xie 2004[80] (reviews[64,65])	12 weeks	Fluoxetine 20 mg/day ($n = 24$) Placebo ($n = 20$)	DSM-IV	NR	Method NR	NR
Yilmaz *et al.* 1999[83] (reviews[52,64,65,68,69])	RCT, 4 weeks	Fluoxetine 20 mg/day ($n = 20$) Placebo ($n = 20$)	DSM-IV	NR	Self-report	Penile vibratory threshold and evoked potentials
Fluoxetine: further RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *number analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Ahn *et al.* 1996[100] (the Republic of Korea) unclear risk	6 weeks	Fluoxetine 20 mg/day (for 1 week) then 40 mg/day ($n = 12$) Placebo ($n = 11$) *Fluoxetine, 12/12 (100%)* *Placebo, 11/11 (100%)*	NR	Lifelong	IELT assessed with questionnaire	Questionnaire assessing number of thrusts before ejaculation, frequency of coitus, libido and side effects of treatment
Culba *et al.* 2008[101] (Turkey) unclear risk	10 weeks	Fluoxetine 20 mg/day Fluoxetine 20 mg/day + tadalafil 20 mg twice weekly Placebo ($n = 180$) *Total 158/180 (88%)*	NR	NR	IELT via visual scale, ELTQ, IIEF	IIEC PE question of CMASH questionnaire

continued

TABLE 12 Selective serotonin reuptake inhibitors are currently not licensed for PE: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Paroxetine: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
McMahon and Touma 1999[84] (reviews[52,65–67,69])	2 × RCTs –crossover. Duration unclear	Study I: • Paroxetine 20 mg 3–4 hours precoitus • Placebo ($n = 26$) Study II: • Paroxetine 10 mg 3 weeks, 20 mg precoitus • Placebo ($n = 42$)	NR	NR	Stopwatch	NR NR NR NR NR NR NR
Waldinger *et al.* 1994[86] (reviews[52])	6 weeks	Paroxetine (dose NR) Placebo ($n = 14$)	NR	NR	Questionnaire	NR
Waldinger *et al.* 1997[87] (reviews[52,66,69])	8 weeks	Paroxetine 20 mg Paroxetine 40 mg ($n = 34$)	IELT ≤ 1 minute > 50% of time	Lifelong	Clock with a second hand	NR
Waldinger *et al.* 2003[88] (reviews[52,67])	6 weeks	Paroxetine ($n = 12$) Mirtazapine ($n = 12$)	IELT ≤ 1 minute	Lifelong	Stopwatch	NR

Paroxetine: RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Giammusso *et al.* 1997[103] (Italy) high risk	6 months (and further 3 months follow-up)	Paroxetine 20 mg/day ($n = 28$) Paroxetine 20 mg/day (for 2 weeks) then 10 mg/day ($n = 34$) *Paroxetine 20 mg, 27/28 (96%)* *Paroxetine 10 mg, 16/34 (47%)*	NR	Lifelong	No objective assessment of IELT	Self-report control over ejaculation
Khelaia *et al.* 2012[104] (Georgia) unclear risk	4 weeks	Paroxetine 20 mg/day ($n = 26$) Paroxetine 20 mg 2–3 hours precoitus ($n = 28$) Placebo ($n = 24$) *NR*	NR	NR	Method NR	IIEF: intercourse and overall satisfaction
Sertraline: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Biri *et al.* 1998[89] (reviews[52,65–67])	4 weeks	Sertraline 50 mg ($n = 22$) Placebo ($n = 15$)	NR	NR	Ejaculatory latency questionnaire	NR
McMahon *et al.* 1998[166] (reviews[52,65,67,69])	4 weeks	Sertraline 50 mg ($n = 19$) Placebo ($n = 18$)	IELT < 1 minute	NR	Stopwatch	NR
Mendels *et al.* 1995[90] (reviews[52,65,66])	8 weeks	Sertraline 50–200 mg ($n = 22$) Placebo ($n = 22$)	NR	NR	Self-report	Patient and partner satisfaction via scale
Zhou *et al.* 2007[91] (reviews[65])	4 weeks	Sertraline ($n = 24$) Placebo ($n = 22$)	NR	NR	Method NR	NR

continued

TABLE 12 Selective serotonin reuptake inhibitors are currently not licensed for PE: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Sertraline: RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Arafa and Shamloul 2007[106] (Egypt and Saudi Arabia) unclear risk	RCT (crossover), 4 weeks each (4-week washout) and 6-month follow-up	Sertraline 50 mg/day ($n = 77$) Placebo ($n = 70$) *AIPE scores reported for 147/147 (100%)*	IELT ≤ 2 minutes; < 31 on AIPE	Lifelong 11% Acquired 89%	Stopwatch	AIPE frequency of intercourse (method NR)
Tuncel *et al.* 2008[107] (Turkey) unclear risk	2 months, assessment 'after eight sexual attempts'	Sertraline 50 mg/day ($n = 20$) Clomipramine 25 mg/day ($n = 23$) Terazosin 5 mg/day ($n = 25$) Placebo ($n = 22$) *All 100%*	WHO ICD-10	NR	Not assessed	Clinical responses (assume control of ejaculation) self-assessed
More than one SSRI: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Abdel-Hamid *et al.* 2001[39] (reviews[37,134,135,137])	RCT crossover, 4 weeks each 2-week washout	Sildenafil 50 mg 1 hour precoitus Clomipramine 25 mg 3–5 hours precoitus Sertraline 50 mg 3–5 hours precoitus Paroxetine 20 mg 3–5 hours precoitus Squeeze technique (total $n = 31$)	IELT ≤ 2 minutes	Lifelong	Stopwatch	Modified Erectile Dysfunction Inventory of Treatment Satisfaction, Arabic Anxiety Inventory (scale 0–30)
Kim *et al.* 1998[76] (reviews[52,64–66,69])	RCT crossover, 4 weeks each 1-week washout	Fluoxetine 40 mg Sertraline 100 mg Clomipramine 50 mg Placebo (total $n = 36$)	DSM-III	NR	Method NR	Patient self-reported questionnaire for patient and partner sexual satisfaction

More than one SSRI: RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Murat Basar *et al.* 1999[78] (reviews[67])	4 and 8 weeks	Fluoxetine 20 mg for one week then 40 mg ($n = 26$) Sertraline 50 mg ($n = 31$)	NR	NR	Method NR	Results classified as unsuccessful, improvement and cure
Safarinejad 2006[85] (reviews[65])	12 weeks	Paroxetine 20mg ($n = 113$) Dapoxetine 60mg ($n = 115$) Placebo ($n = 112$)	NR	NR	IELT not assessed	Sexual satisfaction
Waldinger *et al.* 1998[81] (reviews[52,64–66,68,69])	6 weeks	Fluoxetine 20 mg/day ($n = 12$) Fluvoxamine 100 mg/day ($n = 12$) Paroxetine 20 mg/day ($n = 12$) Sertraline 50 mg/day ($n = 12$) Placebo ($n = 12$)	IELT ≤ 1 minute	Lifelong	Stopwatch	Libido, erection hardness (questionnaire)
Waldinger *et al.* 2001[82] (reviews[52,66–69])	6 weeks	Paroxetine 20 mg/day ($n = 12$) Sertraline 50 mg/day ($n = 12$) Nefazodone 400 mg/day ($n = 12$) Placebo ($n = 12$)	IELT ≤ 1 minute	Lifelong	Stopwatch	NR
Waldinger *et al.* 2001[73] (reviews[52,66,67,69])	6 weeks	Paroxetine 20 mg (n=15) Citalopram 20 mg (n=15)	IELT ≤ 1 minute	Lifelong	Stopwatch	NR

continued

TABLE 12 Selective serotonin reuptake inhibitors are currently not licensed for PE: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

More than one SSRI: RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *number analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Akgül *et al.* 2008[92] (Turkey) unclear risk	8 weeks	Citalopram 20 mg/day ($n = 40$) Sertraline 50 mg/day ($n = 40$) *Citalopram, 40/40 (100%)* *Sertraline, 40/40 (100%)*	IELT ≤ 2 minutes 75% of attempts	NR	IELT not assessed	IPE
Arafa and Shamloul 2007[97] (Egypt and Saudi Arabia) unclear risk	4 weeks	Fluoxetine 20 mg/day ($n = 33$) Escitalopram 10 mg/day ($n = 37$) Paroxetine 20 mg/day ($n = 30$) *All 100%*	IELT ≤ 2 minutes; < 31 on AIPE	All acquired	Stopwatch	AIPE frequency of intercourse (method NR)
Nada *et al.* 2012[94] (Egypt) unclear risk	6 weeks (and further 3 months follow-up)	Escitalopram 10 mg/day ($n = 30$) Citalopram 20 mg/day ($n = 30$) *NR*	NR	NR	IELT not assessed	CIPE overall
Rezakhaniha and Sirosbakht 2010[95] (the Islamic Republic of Iran) high risk	4 weeks	Fluoxetine 40 mg/day Citalopram 40 mg/day (total $n = 110$) *Fluoxetine, 43; Citalopram, 34* *In total 7/110 (70%)*	NR	NR	Stopwatch	NR
Waldinger *et al.* 2004[105] (the Netherlands) unclear risk	4 weeks	Paroxetine 20 mg/day ($n = 15$) Clomipramine 25 mg/day ($n = 15$) *Paroxetine, 15/15 (100%)* *Clomipramine, 15/15 (100%)*	IELT ≤ 1 minute on > 90% occasions	Lifelong	Stopwatch	Questionnaire Symptom Checklist-90 (SCL-90) Dutch translation of UK side effect scale

More than one SSRI: RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *number analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Weixing *et al.* 2012[102] (China) unclear risk	6 and 12 weeks	Fluoxetine 20 mg Fluoxetine 30 mg Sertraline 50 mg Sertraline 100 mg Squeeze technique (total $n = 190$) *104/190 (55%) completed*	NR	NR	Self-report	Sexual satisfaction

CGI-I, Clinical Global Impression – Improvement; CMASH, Center for Marital and Sexual Health; DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*-Third Edition; DSM-III R, *Diagnostic and Statistical Manual of Mental Disorders*-Third Edition Revision; ELTQ, ejaculatory latency time questionnaire; IIEC, International Index of Ejaculatory Control; NR, not reported YSFI-II, Yonsei Sexual Function Inventory-II.

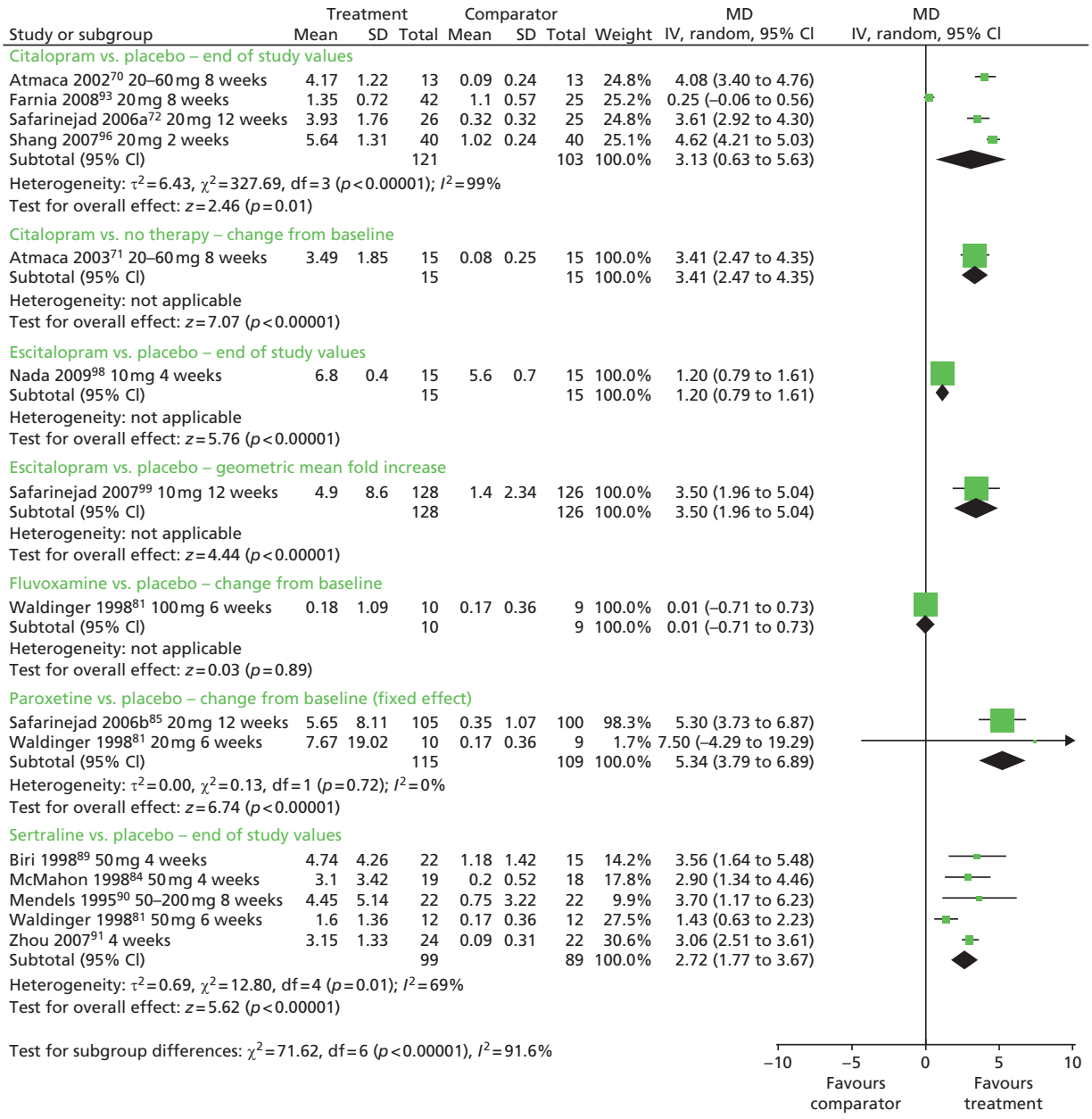

FIGURE 7 Selective serotonin reuptake inhibitors compared with placebo or no treatment: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; M–H, Mantel–Haenzel; SD, standard deviation.

TABLE 13 Selective serotonin reuptake inhibitors currently not licensed for PE: results summary

Comparison	Outcome	Study duration	No. of RCTs	No. of participants	I^2	Meta-analysis (model)	Effect estimate (MD) (95% CI)	Favours	*p*-value
IELT									
Citalopram vs. placebo	IELT (minutes) – end of study values	2–12 weeks	4[70,72,93,96]	224	99%	Data not pooled	4.08 (3.40 to 4.76)	Citalopram	< 0.00001
							0.25 (–0.06 to 0.56)	NS	0.12
							3.76 (3.07 to 4.45)	Citalopram	< 0.00001
							4.62 (4.21 to 5.03)	Citalopram	< 0.00001
Citalopram vs. no therapy	IELT (minutes) – change from baseline	8 weeks	1[71]	30	N/A	N/A	3.41 (2.47 to 4.35)	Citalopram	< 0.00001
Escitalopram vs. placebo	IELT (minutes) – end of study values	4 weeks	1[98]	30	N/A	N/A	1.20 (0.79 to 1.61)	Escitalopram	< 0.00001
Escitalopram vs. placebo	IELT (minutes) – geometric mean fold increase	12 weeks	1[99]	254	N/A	N/A	3.50 (1.96 to 5.04)	Escitalopram	< 0.00001
Fluoxetine vs. placebo	IELT (minutes) – end of study values	4–12 weeks	6[75,80,81,83,100,141]	170	N/A	Yes (fixed)	2.41 (2.10 to 2.73)	Fluoxetine	< 0.00001
Fluvoxamine vs. placebo	IELT (minutes) – change from baseline	6 weeks	1[81]	19	N/A	N/A	0.01 (–0.71 to 0.73)	NS	0.98
Paroxetine vs. placebo	IELT (minutes) – change from baseline	6–12 weeks	2[81,85]	70	0%	Yes (fixed)	5.34 (3.79 to 6.89)	Paroxetine	< 0.00001
Paroxetine vs. clomipramine	IELT (minutes) – geometric mean fold increase	4 weeks	1[105]	30	N/A	N/A	–2.29 (–2.97 to –1.61)	Clomipramine	< 0.00001
Sertraline vs. placebo	IELT (minutes) – end of study values	4–8 weeks	5[81,84,89–91]	188	69%	Yes (random)	2.72 (1.77 to 3.67)	Sertraline	< 0.00001

continued

TABLE 13 Selective serotonin reuptake inhibitors currently not licensed for PE: results summary (*continued*)

Comparison	Outcome	Study duration	No. of RCTs	Participants	Favours
Other outcomes					
Citalopram vs. placebo	Other effectiveness outcomes (various)	4–12 weeks	4[70,72,93,96]	Varies	Evidence from four RCTs suggests that sexual satisfaction and measures of clinical improvement are improved with citalopram
Escitalopram vs. placebo	Other effectiveness outcomes (various)	6–12 weeks	2[94,99]	Varies	Evidence from one RCT[99] suggests improved sexual satisfaction with escitalopram over placebo while another RCT[94] suggests no difference from placebo on the Chinese Index of Sexual Function for PE scores
Fluoxetine vs. placebo	Other effectiveness outcomes (various)	6–8 weeks	2[76,79,102]	Varies	Evidence from one crossover RCT[79] suggests that sexual satisfaction is improved with fluoxetine over placebo, while evidence from another crossover and a RCT suggests improvements over sertraline and the squeeze technique[76,102]
Paroxetine vs. placebo	Other effectiveness outcomes (various)	4–12 weeks	2[85,104]	Varies	Two RCTs indicate that sexual satisfaction appears improved with paroxetine compared with placebo (significance levels unclear)
Sertraline vs. placebo	Other effectiveness outcomes (various)	4–8 weeks	3[92,106,107]	Varies	Evidence from one RCT[106] suggests significant improvement over placebo on AIPE; another reports improvements in ejaculation control.[107] One RCT suggests no difference between sertraline and citalopram on IPE[92]

N/A, not applicable; NS, not significant.

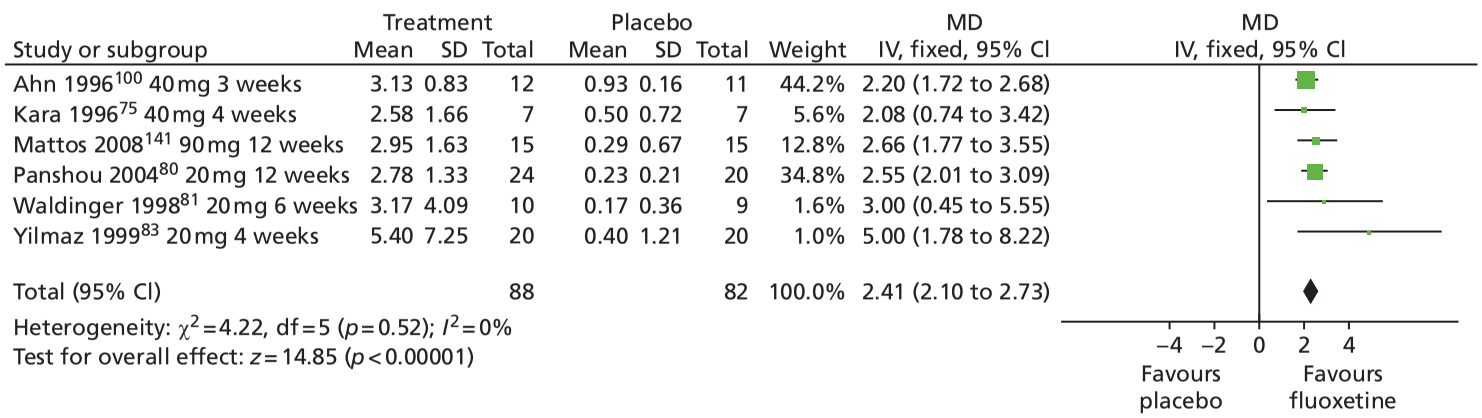

FIGURE 8 Selective serotonin reuptake inhibitors, fluoxetine compared with placebo: forest plot of IELT outcomes for end of study values. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Intravaginal ejaculatory latency time: paroxetine compared with placebo Meta-analysis of mean change from baseline IELT (minutes) at 6 or 12 weeks' follow-up, based on two RCT comparisons of paroxetine at 20 mg ($n = 70$), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 5.34 minutes, significantly favouring paroxetine [MD (fixed effect); 95% CI 3.79 to 6.89 minutes; $p < 0.00001$] (see *Figure 7*).

Intravaginal ejaculatory latency time: sertraline compared with placebo Meta-analysis of mean IELT (minutes) at 4, 6 or 8 weeks' follow-up, based on five RCT comparisons of sertraline at 50 mg to 200 mg ($n = 164$), displayed moderate heterogeneity ($I^2 = 64\%$). The pooled MD in IELT was 2.72 minutes [MD (random effects); 95% CI 1.77 to 3.67 minutes; $p < 0.00001$] (see *Figure 7*).

Intravaginal ejaculatory latency time: selective serotonin reuptake inhibitors compared with other selective serotonin reuptake inhibitors or other treatments

Intravaginal ejaculatory latency time: paroxetine compared with citalopram Waldinger *et al.*[73] reported a fold increase in IELT for paroxetine 20 mg of 8.9-fold and for citalopram 20 mg of 1.8-fold. The fold was reported to be statistically significant increase for paroxetine ($p < 0.001$), but not for citalopram ($p = 0.07$). No variance estimates were reported.

Intravaginal ejaculatory latency time: paroxetine compared with clomipramine The *p*-value for the between-group difference for one trial comparing a geometric mean fold increase between paroxetine and clomipramine[105] was 2.29-fold [MD (random effects); 95% CI 1.61 to 2.97; $p < 0.00001$] in favour of clomipramine (figure not presented).

Assessment of effectiveness: selective serotonin reuptake inhibitors – other outcomes

Outcomes other than IELT were reported across the RCTs using a diversity of instruments (which were sometimes not reported) and outcome data. In a large proportion of the RCTs, a variance estimate for the outcome was not reported. Either *p*-values were not available or it was unclear if reported *p*-values were for between- or across-group comparisons (*Table 14*).

Citalopram Sexual satisfaction and intercourse satisfaction appeared improved in two RCTs compared with placebo.[92,96] The number of intercourse episodes per week also improved after treatment with citalopram in one RCT.[72] The proportion of patients reported as 'much improved' and 'very much improved' on a subjective measure of clinical improvement was greater with citalopram than placebo in one RCT.[70] One trial reported a significant between-group difference in favour of citalopram compared with placebo on the CIPE[93] (see *Table 14*).

Escitalopram There was no between-group difference in escitalopram compared with placebo on the CIPE overall score at weeks 2, 4 or 6 in one RCT.[98] Intercourse satisfaction was reported as significantly improved at 3 and 6 months with escitalopram in one RCT[99] (see *Table 14*).

Fluoxetine The number of thrusts before ejaculation appeared greater with fluoxetine than placebo in one RCT.[100] Sexual satisfaction appeared improved with fluoxetine in two crossover RCTs compared with placebo.[78,79] There was no apparent between-group difference in sexual satisfaction between fluoxetine 20 mg daily or 90 mg weekly.[77] One RCT suggested an improvement in sexual satisfaction with fluoxetine 30 mg, compared with 20 mg, sertraline at 50 mg or 100 mg, or the squeeze technique.[102] One RCT suggested that there is no difference in change on the AIPE between fluoxetine and escitalopram[97] (see *Table 14*).

Fluvoxamine No data were available.

Paroxetine Sexual satisfaction and IIEF satisfaction scores appeared improved with paroxetine when compared with placebo in two RCTs[85,104] (see *Table 14*).

TABLE 14 Selective serotonin reuptake inhibitors currently not licensed for PE: outcomes other than IELT

RCT, duration	Treatment	Outcome measure	Results	Between-group difference significant
Citalopram vs. placebo or no therapy				
Atmaca *et al.* 2002,[70] 8 weeks	Citalopram 20–60 mg/day ($n = 13$)	CGI-I	Citalopram 'much improved', 4/13; (30.8%); 'very much improved', 5/13 (38.5%). Placebo 'much improved', 1/13 (7.7%)	Unclear
	Placebo ($n = 13$)	YSFI-II	Improved significantly with citalopram, compared with placebo (p-value NR)	Yes
		Sexual satisfaction	*n/N* 'yes': citalopram 9/13, placebo 1/13	Unclear
Farnia *et al.* 2008,[93] 4 weeks	Citalopram 20 mg 4 hours precoitus ($n = 49$)	CIPE	CIPE between-group difference in IELT change from baseline at week 4, $p = 0.002$	Yes
	Placebo ($n = 43$)			
Safarinejad and Hosseini 2006,[72] 12 weeks	Citalopram 20 mg ($n = 26$)	IIEF: intercourse satisfaction domain	*n/N* 'yes': citalopram 23/26 (88.4%), placebo 10/25 (40.0%)	Yes
	Placebo ($n = 25$)	Intercourse episodes per week	Significantly improved, citalopram (no p-value)	
Shang *et al.* 2012,[96] duration NR	Citalopram 20 mg/day ($n = 40$)	Sexual satisfaction	Mean (assume SD): citalopram – week 2, $p < 0.01$; week 4, $p < 0.01$	Yes
	Placebo ($n = 40$)		Placebo – week 2, p-value NR; week 4, $p > 0.05$	
Escitalopram vs. placebo				
Nada *et al.* 2012,[94] 2, 4 and 6 weeks' treatment	Escitalopram 10 mg ($n = 30$)	CIPE overall score	Between-group difference: week 2, $p = 0.51$; week 4, $p = 0.27$; week 6, $p = 0.32$; 3-month post-treatment follow-up, $p = 0.10$	No
	Citalopram 20 mg ($n = 30$)			
Safarinejad 2007,[99] 12 weeks	Escitalopram 10 mg/day ($n = 138$)	Weekly coitus episodes	NR	
	Placebo ($n = 138$)	IIEF intercourse satisfaction	Escitalopram: 12 weeks $p = 0.01$; 3 months $p = 0.01$; 6 months $p = 0.01$. Placebo: 12 weeks $p =$ NS; 3 months $p =$ NS; 6 months $p =$ NS	Yes
		Sexual satisfaction	Between-groups: 'satisfied', $p \leq 0.001$; 'moderately satisfied', $p =$ NS; 'dissatisfied', $p \leq 0.001$	Yes

continued

TABLE 14 Selective serotonin reuptake inhibitors currently not licensed for PE: outcomes other than IELT (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference significant
Fluoxetine vs. placebo				
Ahn *et al.* 1996,[100] 6 weeks	Fluoxetine 40 mg/day ($n = 12$) Placebo ($n = 11$)	Questionnaire assessing number of thrusts before ejaculation, frequency of coitus, libido and side effects of treatment	Number of patients with $< 30/\geq 30$ thrusts before ejaculation: fluoxetine, from baseline at 3 and at 6 weeks $p < 0.05$. Placebo change from baseline at 3 and at 6 weeks $p > 0.05$	Yes
Novaretti *et al.* 2002,[79] crossover 8 weeks	Fluoxetine 20 mg once daily Placebo once daily Total $n = 50$	Sexual satisfaction Hamilton Anxiety and Depression Scale; Beck Depression Inventory	*n/N* 'yes': fluoxetine 34/50 (68%), placebo 5/50 (10%) *p*-value between groups NR NR	Unclear
Fluoxetine vs. other treatments				
Arafa and Shamloul 2007,[97] 4 weeks	Fluoxetine 20 mg ($n = 33$) Escitalopram 10 mg ($n = 37$) Paroxetine 20 mg ($n = 30$)	AIPE Frequency of intercourse	AIPE domains with change from baseline $p < 0.05$ all groups NR	Unclear
Culba *et al.* 2008,[101] 10 weeks	Fluoxetine 20 mg/day Tadalafil + fluoxetine Tadalafil 20 mg 2/weeks Placebo (Total $n = 180$)	IIEC PE question of CMASH questionnaire	Patients who were treated with fluoxetine + tadalafil had better scores with both questionnaires Difference was NS compared with fluoxetine group. No data reported	Unclear
Kim and Seo 1998,[76] each agent for 4 weeks, with 1-week washout	Fluoxetine 40 mg Sertraline 100 mg Clomipramine 50 mg Placebo Total $n = 36$	Patient and partner sexual satisfaction: patient self-reported questionnaire	*n/N* 'yes': fluoxetine 23/36 (88.4%); sertraline 28/36 (77.7%); placebo 17/36 (47.2%); greater with clomipramine (NR) *p*-value between groups NR	Unclear
Murat Basar 1999,[78] 4 and 8 weeks	Fluoxetine 40 mg ($n = 26$) Sertraline 50 mg ($n = 31$)	The results were classified as unsuccessful, improvement and cure	Fluoxetine and sertraline, had the same efficacy. No data or *p*-value reported	Unclear

TABLE 14 Selective serotonin reuptake inhibitors currently not licensed for PE: outcomes other than IELT (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference significant
Weixing *et al.* 2012,[102] 6 and 12 weeks	Fluoxetine 20 or 30 mg Sertraline 50 or 100 mg Squeeze technique Total $n = 104$	Sexual satisfaction	Sexual satisfaction was increased significantly in fluoxetine 30 mg. *p*-value NR	Unclear
Fluoxetine different doses				
Manasia *et al.* 2003,[77] Duration NR	Fluoxetine 90 mg weekly ($n = 40$) Fluoxetine 20 mg daily ($n = 40$)	Sexual satisfaction ratings	Sexual satisfaction ratings did not significantly differ between the two groups. No data or *p*-value reported	Unclear
Paroxetine vs. placebo				
Khelaia *et al.* 2012,[104] 4 weeks	Paroxetine 20 mg/day ($n = 26$) Paroxetine 20 mg 2–3 hours precoitus ($n = 28$) Placebo ($n = 24$)	IIEF, intercourse satisfaction, overall satisfaction	Mean IIEF intercourse satisfaction scores Mean IIEF overall satisfaction scores: $p < 0.001$, but unclear if change from baseline or for which group comparison	Unclear
Safarinejad 2006,[85] 12 weeks	Paroxetine 20 mg ($n = 113$) Placebo ($n = 112$) Dapoxetine 60 mg ($n = 115$)	Sexual satisfaction	Sexual satisfaction assume *n/N* 'yes': paroxetine 97/105, placebo 30/100 *p*-value for between-group difference NR	Unclear
Sertraline vs. placebo				
Arafa and Shamloul 2007,[106] crossover 4 weeks per treatment	Sertraline 50 mg/day	AIPE	Sertraline vs. baseline or placebo, $p < 0.05$	Yes
	Placebo	Frequency of intercourse – assessment method NR	Between-group (sertraline vs. placebo) difference in overall AIPE score, $p < 0.001$	Yes
	Total $n = 77$		Between-group (sertraline vs. placebo), change from other study phases, $p > 0.05$	
Mendels *et al.* 1995,[90] 8 weeks	Sertraline 50–200 mg ($n = 22$) Placebo ($n = 22$)	Patient and partner satisfaction measured using a numbered scale	Improved during the treatment period in the sertraline group. No data or *p*-value reported	Unclear

continued

TABLE 14 Selective serotonin reuptake inhibitors currently not licensed for PE: outcomes other than IELT (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference significant
Sertraline vs. other treatments				
Abdel-Hamid *et al.* 2001,[39] 4 weeks	Sertraline 50 mg	EDITS (scale 0–5): sexual satisfaction score	Unclear if reported values are means or medians. No variance estimates or *p*-values reported	Unclear
	Paroxetine 20 mg Clomipramine 25 mg Sildenafil 50 mg Squeeze technique Total $n = 31$	Arabic Anxiety Inventory (scale 0–30)	Unclear if reported values are means or medians. No variance estimates or *p*-values reported	
Akgül *et al.* 2008[92]	Sertraline 50 mg/day ($n = 40$)	IPE	Between-group difference at 8 weeks: $p = 0.50$	No
	Citalopram 20 mg/day ($n = 40$)			
Tuncel *et al.* 2008,[107] treatment was for 2 months	Sertraline 50 mg/day ($n = 23$)	Clinical responses (assume control of ejaculation), self-assessed	Patients reporting 'no change', 'improvement', 'under control'. All three treatments 'superior to placebo': $p = 0.001$	Yes compared with placebo
	Clomipramine 25 mg/day ($n = 20$)		No significant difference in efficacy between 'medical treatments': $p = 0.537$	
	Terazosin 5 mg/day ($n = 25$)			
	Placebo ($n = 22$)			

Studies with no data on other outcomes reported	
RCT	**Treatments**
Citalopram	
Atmaca *et al.* 2003[71]	Citalopram, no therapy
Escitalopram	
Nada *et al.* 2009[98]	Escitalopram, placebo
Fluoxetine	
Haensel *et al.* 1998[74]	Fluoxetine, placebo
Kara *et al.* 1996,[75] Panshou and Xie 2004,[80] Yilmaz *et al.* 1999[83]	Fluoxetine, stop–start, placebo
Kolomaznik *et al.* 2002[41]	Fluoxetine, tadalafil, fluoxetine + tadalafil, placebo
Mattos *et al.* 2008[141]	Fluoxetine, citalopram
Fluvoxamine	
Rezakhaniha *et al.* 2010[95]	Fluvoxamine, fluoxetine, paroxetine, sertraline, placebo

TABLE 14 Selective serotonin reuptake inhibitors currently not licensed for PE: outcomes other than IELT (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference significant
Paroxetine				
Waldinger *et al.* 1997[87]			Paroxetine 20 mg, paroxetine 40 mg	
Waldinger *et al.* 1998[81]			Paroxetine, placebo	
McMahon and Touma 1999,[84] Waldinger *et al.* 1994[86]			Paroxetine, clomipramine	
Waldinger *et al.* 2004[105]			Paroxetine, citalopram	
Waldinger *et al.* 2001[73]			Paroxetine, sertraline, nefazodone, placebo	
Waldinger *et al.* 2001[82]			Paroxetine, mirtazapine	
Waldinger *et al.* 2003[86]			Paroxetine different doses	
Sertraline				
Giammusso *et al.* 1997,[103] Waldinger *et al.* 1997,[87] Biri *et al.* 1998,[89] McMahon 1998,[166] Zhou 2007[91]			Sertraline, placebo	

CGI-I, Clinical Global Impression – Improvement; CMASH, Center for Marital and Sexual Health; IIEC, International Index of Ejaculatory Control; NR, not reported; NS, not significant; SD, standard deviation; YSFI-II, Yonsei Sexual Function Inventory-II.

Sertraline A significant between-group difference between sertraline and placebo on the AIPE and the frequency of intercourse was reported in one crossover study.[106] Patient and partner satisfaction improved during the treatment period in the sertraline group in one RCT.[90] A significant difference between sertraline and placebo on ejaculation control was reported by one RCT.[107] The same RCT reported that sertraline was comparable to both clomipramine and terazosin on this outcome. One RCT reported no significant between-group difference in sertraline or citalopram on the IPE[92] (see *Table 14*).

Assessment of safety: selective serotonin reuptake inhibitors – adverse events summarised by existing reviews

The systematic review by Huang *et al.*[65] reported a summary table of the incidence of AEs for citalopram, fluoxetine, paroxetine and sertraline across the included studies. These data are adapted in *Table 15*. From these data, AEs affecting > 5% of patients appear to be:

- *citalopram*: insomnia and nausea
- *fluoxetine*: headache, insomnia, nausea, somnolence, erectile dysfunction, libido decrease
- *paroxetine*: nausea and diarrhoea
- *sertraline*: headache, dry mouth, dizziness, insomnia, nausea, somnolence, diarrhoea, anejaculation.

However, these data were reported by Huang *et al.*[65] as the overall number of incidents across included studies by AE as opposed to being reported for each included study. Therefore, it is unclear which of the included RCTs and single-arm randomised crossover trials contribute to the numbers in each AE. Thus, the differences in event rates may reflect the differences across the studies included by Huang *et al.*[65]

Assessment of safety: selective serotonin reuptake inhibitors – adverse events for individual randomised controlled trials

Adverse event data were not available for 14[41,71,72,74,84–88,90,91,94,96,98] out of the 42[39,41,70–107,141,166] included RCTs evaluating SSRIs (*Table 16*). When AE data were reported, it was often unclear how many patients suffered AEs, what the AEs were or which group the AEs related to. Reporting of how many patients withdrew owing to AEs was limited across trials.

TABLE 15 Selective serotonin reuptake inhibitors currently not licensed for PE: AEs summary from one existing systematic review. Adapted from Huang *et al.*[65]

	AE									
Treatment	Headache, *n/N* (%)	Dry mouth, *n/N* (%)	Dizziness, *n/N* (%)	Insomnia, *n/N* (%)	Nausea *n/N* (%)	Somnolence, *n/N* (%)	Diarrhoea, *n/N* (%)	Erectile dysfunction, *n/N* (%)	Anejaculation, *n/N* (%)	Libido decrease, *n/N* (%)
Citalopram	6/167 (3.6)	7/167 (4.2)	–	3/44 (6.8)	14/167 (8.4)	–	5/138 (3.6)	0/167 (0.0)	0/29 (0.0)	–
Fluoxetine	8/59 (13.6)	3/86 (3.5)	1/50 (2.0)	4/59 (6.8)	7/60 (11.7)	24/101 (23.8)	–	3/36 (8.3)	2/44 (4.5)	5/70 (7.1)
Paroxetine	2/147 (1.4)	–	2/105 (1.9)	0/105 (0.0)	8/105 (7.6)	–	8/105 (7.6)	1/147 (0.7)	3/147 (2.0)	5/147 (3.4)
Sertraline	9/48 (18.8)	10/84 (11.9)	3/26 (11.5)	3/26 (11.5)	5/62 (8.1)	15/121 (12.4)	9/48 (18.8)	4/99 (4.0)	8/89 (9.0)	0/37 (0.0)

TABLE 16 Selective serotonin reuptake inhibitors currently not licensed for PE: AE data from individual studies

RCT, duration	Treatment	AEs
Citalopram vs. placebo or no therapy		
Atmaca *et al.* 2002,[70] 8 weeks	*Citalopram* 20–60 mg ($n = 13$)	Nausea and headache were reported in three subjects. Unclear which group
	Placebo ($n = 13$)	
Atmaca *et al.* 2003,[71] 8 weeks	Citalopram 20–60 mg ($n = 15$)	NR
	No therapy ($n = 15$)	
Farnia *et al.* 2008,[93] 4 weeks	Citalopram 20 mg ($n = 49$)	Twelve patients overall left the study (seven citalopram, five placebo). Five owing to headache and nausea (n by group NR). No other AE data reported
	Placebo ($n = 43$)	
Safarinejad and Hosseini 2006[72]	Citalopram vs. placebo	NR
Shang *et al.* 2012[96]	Citalopram vs. placebo	Treatment duration NR
Escitalopram vs. placebo		
Nada *et al.* 2009,[98] 1 month	Escitalopram 10 mg ($n = 15$)	NR
	Placebo ($n = 15$)	
Nada *et al.* 2012,[94] 2, 4 and 6 weeks' treatment	Escitalopram 10 mg ($n = 30$)	NR
	Citalopram 20 mg ($n = 30$)	
Safarinejad 2007,[99] 12 weeks	Escitalopram 10 mg ($n = 138$)	Escitalopram – 12/128 (9.4%) treatment-related AEs: nausea, 6/128 (4.7%); headache, 5/128 (3.9%); dry mouth, 4/128 (3.1%); diarrhoea, 4/128 (3.1%). Insomnia, drowsiness and dizziness were reported by < 1%. Four patients (3.1%) withdrew because of AEs (nausea, two; diarrhoea, one; headache, one)
	Placebo ($n = 138$)	Placebo – 7/128 (5.5%) treatment-related AEs. Erectile dysfunction, 3/126 (2%). Two (1.6%) withdrew
		More AEs with escitalopram ($p = 0.04$)
Fluoxetine vs. placebo		
Ahn *et al.* 1996,[100] 6 weeks	Fluoxetine 40 mg (n=12)	n/N (%) patients experiencing AEs: mild fatigue or yawning, 3/12 (25%); severe fatigue, 2/12 (16.7%); gastrointestinal discomfort, 0/12 (0%)
	Placebo ($n = 11$)	n/N (%) patients experiencing AEs: mild fatigue or yawning, 0/11 (0%); severe fatigue, 1/11 (9.1%); gastrointestinal discomfort, 1/11 (9.1%)
Haensel *et al.* 1998,[74] 4-week periods	Fluoxetine 10 mg	NR
	Placebo (total $n = 15$)	
Kara *et al.* 1996,[75] 4 weeks	Fluoxetine 40 mg ($n = 9$)	Two patients stopped because of side effects. Side effects were not described and it was unclear to which group these patients belonged
	Placebo ($n = 8$)	
Novaretti *et al.* 2002,[79] crossover 8 weeks	Fluoxetine 20 mg once daily	Drowsiness (30%), headache (14%), insomnia (6%), decreased libido (4%), dry mouth (2%), dizziness (2%). Unclear if number of events or patients. Significant differences from placebo were noted
	Placebo once daily (total $n = 50$)	

continued

TABLE 16 Selective serotonin reuptake inhibitors currently not licensed for PE: AE data from individual studies (*continued*)

RCT, duration	Treatment	AEs
Panshou and Xie 2004,[80] 12 weeks	*Fluoxetine* 20 mg ($n = 24$)	*n/N* experiencing AEs: fluoxetine, 7/24 (29%); placebo, 0/20 (0%)
	Placebo ($n = 20$)	
Yilmaz *et al.* 1999,[83]	Fluoxetine 20 mg d ($n = 20$)	*n/N* experiencing AEs: fluoxetine, 10/20 (50%); placebo, 1/20 (5%)
	Placebo ($n = 20$)	
Fluoxetine vs. other treatments		
Arafa and Shamloul 2007,[97] 4 weeks	Fluoxetine 20 mg ($n = 33$)	Drowsiness, anorexia and insomnia occurred in three patients on fluoxetine and three patients on escitalopram. Five patients on paroxetine complained of somnolence
	Escitalopram 10 mg ($n = 37$)	
	Paroxetine 20 mg ($n = 30$)	
Culba *et al.* 2008,[101] 10 weeks	Fluoxetine	Minor side effects due to tadalafil and fluoxetine were temporary. No data reported
	Tadalafil + fluoxetine	
	Tadalafil	
	Placebo (total $n = 180$)	
Kim and Seo 1998,[76] each agent 4 weeks, 1-week washout	Fluoxetine 40 mg	Percentage experiencing AEs: fluoxetine 40 mg, 13%; sertraline 100 mg, 12%; clomipramine 50 mg, 23%; placebo, NR. *p*-value for clomipramine compared with sertraline and fluoxetine, $p < 0.05$. No other *p*-values reported
	Sertraline 100 mg	
	Clomipramine 50 mg	
	Placebo (total $n = 36$)	
Fluoxetine vs. other treatments		
Kolomaznik *et al.* 2002,[41] 8 weeks	Fluoxetine	NR
	Stop–start technique	
	Placebo (total $n = 93$)	
Mattos *et al.* 2008,[141] 4 weeks	Fluoxetine 90 mg/week ($n = 15$)	Fluoxetine: yawning and somnolence (three patients), asthenia (three patients), nausea (one patient)
	Tadalafil 20 mg daily + fluoxetine 90 mg ($n = 15$)	Fluoxetine + tadalafil: yawning and somnolence (three patients), nausea (two patients) palpitation (one patient), muscle soreness (one patient)
	Tadalafil ($n = 15$)	Tadalafil: headache (three patients), facial redness (two patients), palpitations (two patients)
	Placebo ($n = 15$)	
Murat Basar *et al.* 1999,[78] 4 and 8 weeks	Fluoxetine 40 mg ($n = 26$)	Sertraline, fluoxetine had the same side effects. No data or *p*-value reported
	Sertraline 50 mg ($n = 31$)	
Rezakhaniha and Sirosbakht 2010,[95] 4 weeks	Fluoxetine 40 mg	Five patients withdrew owing to drug side effects such as headache, dizziness, insomnia and diarrhoea (NR which group)
	Citalopram 40 mg d	
Weixing *et al.* 2012,[102] 6 and 12 weeks	Fluoxetine 20 mg	AEs with fluoxetine and sertraline were drowsiness, headache, insomnia and diarrhoea. No data or *p*-values reported
	Fluoxetine 30 mg	
	Sertraline 50 mg	
	Sertraline 100 mg	
	Squeeze technique (total $n = 104$)	

TABLE 16 Selective serotonin reuptake inhibitors currently not licensed for PE: AE data from individual studies (*continued*)

RCT, duration	Treatment	AEs
Fluoxetine different doses		
Manasia *et al.* 2003,[77] duration NR	Fluoxetine 90 mg weekly ($n = 40$)	The occurrence of AEs did not significantly differ between the two groups. No data or *p*-value reported
	Fluoxetine 20 mg daily ($n = 40$)	
Mattos *et al.* 2008,[141] 4 weeks	Fluoxetine 90 mg/week ($n = 15$)	Fluoxetine: yawning and somnolence (three patients), asthenia (three patients), nausea (one patient)
	Tadalafil 20 mg daily + fluoxetine 90 mg ($n = 15$)	Fluoxetine + tadalafil: yawning and somnolence (three patients), nausea (two patients) palpitation (one patient), muscle soreness (one patient)
	Tadalafil ($n = 15$)	Tadalafil: headache (three patients), facial redness (two patients), palpitations (two patients)
	Placebo ($n = 15$)	
Fluvoxamine vs. other treatments		
Waldinger *et al.* 1998[81]	Fluoxetine 20 mg ($n = 12$)	There were no statistically significant differences between the active treatment groups and the placebo group with respect to non-sexual side effects, including nausea and headache. No data or *p*-value reported
	Fluvoxamine 100 mg ($n = 12$)	
	Paroxetine 20 mg ($n = 12$)	
	Sertraline 50 mg ($n = 12$)	
	Placebo ($n = 12$) (all once daily)	
Paroxetine vs. placebo		
Khelaia *et al.* 2012,[104] 4 weeks	Paroxetine 20 mg ($n = 26$)	'Drug related side effects' were headache, drowsiness, nausea and dry mouth, but were mild an self-limited – *n* by group NR. Decreased libido was reported by four patients in the paroxetine daily group
	Paroxetine on demand 20 mg ($n = 28$)	
	Placebo ($n = 24$)	
McMahon and Touma 1999,[84] crossover (single-arm), duration unclear	Study I: paroxetine 20 mg vs. placebo (total $n = 26$)	No AEs reported with paroxetine
	Study II: paroxetine 20 mg vs. placebo (total $n = 42$)	
Safarinejad 2006[85]	Paroxetine vs. dapoxetine vs. placebo	NR
Waldinger *et al.* 1994[86]	Paroxetine vs. placebo	NR
Paroxetine vs. other treatments		
Waldinger *et al.* 2001[73]	Paroxetine 20 mg ($n = 15$)	AEs were not significantly different between the treatment groups. No data or *p*-value reported
	Citalopram 20 mg ($n = 15$)	One patient discontinued on each treatment (two in total)
Waldinger *et al.* 2001[82]	Paroxetine 20 mg ($n = 12$)	There were no statistically significant differences between the active treatment groups and the placebo group with respect to non-sexual side effects. No data or *p*-value reported
	Sertraline 50 mg ($n = 12$)	Five did not complete because of side effects (paroxetine, three; sertraline, one; nefazodone, one)
	Nefazodone 400 mg ($n = 12$)	
	Placebo ($n = 12$)	

continued

TABLE 16 Selective serotonin reuptake inhibitors currently not licensed for PE: AE data from individual studies (*continued*)

RCT, duration	Treatment	AEs
Paroxetine vs. other treatments		
Waldinger *et al.* 2003[88]	Paroxetine ($n = 12$)	NR
	Mirtazapine ($n = 12$)	
Waldinger *et al.* 2004,[105] 4 weeks	Paroxetine 20 mg ($n = 15$)	Difficulty concentrating, fatigue, sleepiness, restless, yawning, tremor, dry mouth, nausea, vomiting, loose stools, constipation, dizziness, perspiration, headache, decreased libido, difficulty attaining and maintaining erection. Six (20%) did not complete study: three owing to side effects (one on paroxetine, two on clomipramine) and three for non-medical/logistic reasons. Two drop-outs in first week, four in second week. Significant between-group differences in non-sexual side effects of treatment: day 1 sleepiness (more with paroxetine), $p < 0.005$; day one yawning (more with paroxetine), $p < 0.05$; day 2 nausea (more with clomipramine), $p < 0.05$
	Clomipramine 25 mg ($n = 15$)	
Paroxetine different doses		
Giammusso *et al.* 1997,[103] 3, 6 and 9 months	Paroxetine 20 mg ($n = 28$)	Paroxetine 20 mg – one patient withdrew from study owing to AEs (reported as 'asentia', unclear)
	Paroxetine 20 mg 10 mg ($n = 34$)	Paroxetine 10 mg – non-serious AEs: nausea, sweating, reduced libido, drowsiness (*n* NR)
Waldinger *et al.* 1997[87]	*Paroxetine* 20 mg vs. 40 mg	NR
Sertraline vs. placebo		
Arafa and Shamloul 2007,[106] crossover 4 weeks per treatment	Sertraline 50 mg	The authors report that sertraline was generally well tolerated. Most side effects were minor and none prompted withdrawal from the study. Drowsiness and anorexia occurred in one patient out of 47 (0.7%) patient. Two patients (1.4%) experienced minor gastrointestinal upset
	Placebo (total $n = 77$)	
Biri *et al.* 1998,[89] 8 weeks	Sertraline 50 mg ($n = 22$)	AEs not significantly different between groups. No data or *p*-value reported. After treatment with sertraline was discontinued, PE returned in 86.36% of patients
	Placebo ($n = 15$)	
McMahon and Touma 1999[84]	Sertraline vs. placebo	NR
Mendels *et al.* 1995[90]	Sertraline vs. placebo	NR
Zhou 2007[91]	Sertraline vs. placebo	NR
Sertraline vs. other treatments		
Abdel-Hamid *et al.* 2001,[39] 4 weeks	Sertraline 50 mg	Headache, flushing and nasal congestion: 18% of participants in the sildenafil group (*n* NR). The incidence of side effects was similar among groups
	Paroxetine 20 mg	
	Clomipramine 25 mg	
	Sildenafil 50 mg	
	Squeeze technique (total $n = 31$)	
Akgül *et al.* 2008,[92] 8 weeks	Sertraline 50 mg ($n = 40$)	No serious AEs were detected in any of the patients. 3/40 patients (7.5%) in the citalopram group and 2/40 (5.0%) in the sertraline group had mild nausea at the beginning of the treatment
	Citalopram 20 mg ($n = 40$)	

TABLE 16 Selective serotonin reuptake inhibitors currently not licensed for PE: AE data from individual studies (*continued*)

RCT, duration	Treatment	AEs
Tuncel *et al.* 2008,[107] 2 months	Sertraline 50 mg (*n*=23) Clomipramine 25 mg (*n*=20) Terazosin 5 mg (*n* = 25) Placebo (*n* = 22)	*n*/*N* (%) reporting AEs were as follows. Clomipramine – headache, 8/23 (34.8%); hypotension, 1/23 (4%); drowsiness, 2/23 (8.6%); ejaculation disorder, 0/23 (0%). Sertraline – headache, 5/20 (25%); hypotension, 0/20 (0%); drowsiness, 3/20 (15%); ejaculation disorder, 0/20 (0%). Terazosin – headache, 5/25 (20%); hypotension, 3/25 (12%); drowsiness, 0/25 (0%); ejaculation disorder, 2/25 (8%). Placebo – headache, 2/22 (9.1%); hypotension, 0/22 (0%); drowsiness, 0/22 (0%); ejaculation disorder, 0/22 (0%). No significant differences between the 'medical treatment groups' in AEs – $p = 0.204$

NR, not reported.

Citalopram Nausea and headache were reported in two RCTs evaluating citalopram.[70,91] However, between-group differences with placebo groups were unclear.

Escitalopram One RCT reported that escitalopram was associated with nausea, headache, dry mouth, diarrhoea, insomnia, drowsiness and dizziness and that significantly more AEs were experienced with escitalopram than with placebo.[99]

Fluoxetine A significant between-group difference compared with placebo in drowsiness, headache, insomnia, decreased libido, dry mouth and dizziness were reported by one crossover trial.[79] In one RCT,[100] more patients treated with fluoxetine than with placebo experienced mild/severe fatigue and yawning. One crossover RCT reported that significantly more AEs were experienced with clomipramine than fluoxetine,[76] and one RCT reported that both fluoxetine and sertraline caused the same type of AEs.[78]

Fluvoxamine One trial reported that there were no statistically significant differences between fluvoxamine, fluoxetine, paroxetine and sertraline in non-sexual side effects, including nausea and headache.[81]

Paroxetine One RCT reported paroxetine-associated AEs of headache, drowsiness, nausea and dry mouth,[104] one reported that AEs were not significantly different between paroxetine and citalopram,[73] one reported that AEs were not significantly different between paroxetine and sertraline,[82] and one reported patients on paroxetine experiencing sleepiness and yawning early in treatment, whereas more patients on clomipramine experienced nausea.[105]

Sertraline One RCT reported that sertraline was well tolerated and that drowsiness and anorexia were minor.[106] Tuncel *et al.*[107] reported no significant differences between sertraline, clomipramine or terazosin in the occurrence of headache, hypotension, drowsiness and ejaculation disorder.

Assessment of effectiveness: selective serotonin reuptake inhibitors – evidence summary

The current evidence base for SSRIs in the treatment of PE comprises 26 RCTs[39,41,70–91,141,166] captured in seven[52,64–69] low methodological quality systematic reviews and 16 further RCTs,[92–107] two[95,103] of which are at high risk of bias and 14[92–94,96–102,104–107] care onsidered at unclear risk of bias.

Citalopram Evidence from three[70,72,96] out of four[70,72,93,96] separate RCTs suggests that citalopram is significantly more effective than placebo in increasing IELT [MD 0.25 minutes (95% CI –0.06 to 0.56 minutes) to 4.62 minutes (95% CI 4.21 to 5.03 minutes); $p < 0.00001$]. However, a high level of heterogeneity is evident across these four trials. Citalopram is significantly more effective than no therapy (one RCT,[71] 30 participants). Evidence from four separate RCTs suggests that sexual satisfaction and

measures of clinical improvement are improved with citalopram.[70,72,93,96] AEs with citalopram appear to be nausea, headache, insomnia and dry mouth although the magnitude and severity are unclear.

Escitalopram Evidence from one RCT[98] reporting end of study mean values (30 participants) and one RCT[99] reporting fold increase (i.e. by how many 'fold' the value in minutes at baseline had increased) (254 participants) indicates that escitalopram is significantly more effective than placebo in increasing IELT [MD 1.20 minutes (95% CI 0.79 to 1.61 minutes), $p < 0.00001$; geometric mean 3.50 minutes (95% CI 1.96 to 5.04 minutes), $p < 0.00001$]. Evidence from one RCT[99] suggests that sexual satisfaction is improved with escitalopram. Evidence from one RCT suggests that there is no significant between-group difference for escitalopram compared with placebo on the Chinese Index of Sexual Function for PE scores.[94] Evidence from one RCT[99] indicates that nausea, headache, dry mouth, diarrhoea, insomnia, drowsiness and dizziness are reported more with escitalopram than with placebo.

Fluoxetine Pooled effects across six RCTs[75,80,81,83,100,141] (170 participants) demonstrates that fluoxetine daily or weekly is significantly more effective than placebo at increasing IELT over 4–12 weeks [MD 2.41 minutes (95% CI 2.10 to 2.73 minutes); $p < 0.00001$]. Evidence from one RCT suggests that sexual satisfaction is improved with fluoxetine compared with placebo.[79] One RCT[102] suggests that sexual satisfaction is improved with fluoxetine 30 mg compared with either fluoxetine 20 mg, sertraline at 50 mg or 100 mg, or the squeeze technique. There is evidence from one RCT[77] that there is no apparent between-group difference in sexual satisfaction between fluoxetine 20 mg daily and 90 mg weekly. Evidence from one crossover[79] indicates that fluoxetine is associated with more drowsiness, headache, insomnia, decreased libido, dry mouth and dizziness than placebo. Another crossover RCT[78] indicates that both fluoxetine and sertraline cause the same AEs, and a further crossover RCT indicates that more AEs are experienced with clomipramine than with fluoxetine[76] but that satisfaction ratings are greater with clomipramine. Evidence summarised by one systematic review[65] suggests that > 5% patients treated with fluoxetine report headache, insomnia, nausea, somnolence, erectile dysfunction and libido decrease. However, the review is of overall low methodological quality.

Fluvoxamine Evidence from one RCT[95] (19 participants) indicates that there is no significant difference between fluvoxamine and placebo in increase in IELT and that there is no significant differences between fluvoxamine, fluoxetine, paroxetine and sertraline in non-sexual side effects, including nausea and headache.

Paroxetine Pooled evidence across two RCTs[81,85] (70 participants) demonstrates that paroxetine 20 mg is significantly more effective than placebo at increasing IELT over 6–12 weeks [MD 5.34 minutes (95% CI 3.79 to 6.89 minutes); $p < 0.00001$]. However, evidence from one RCT[105] (30 participants) indicates that clomipramine is significantly more effective than paroxetine [2.29 minutes (95% CI 1.61 to 2.97 minutes); $p < 0.00001$]. Two RCTs[85,104] indicate that sexual satisfaction and IIEF satisfaction scores appear improved with paroxetine compared with placebo. Paroxetine-associated AEs include headache, drowsiness, nausea and dry mouth. One RCT[82] indicates that there is no significant difference in the occurrence of these events between paroxetine and sertraline. One RCT[105] suggests that more patients on clomipramine than those on paroxetine experience nausea early in treatment.

Sertraline Pooled effects across five RCTs[79,81,84,89,90] (188 participants) suggest that sertraline 50 mg is significantly more effective than placebo at increasing IELT over 4–8 weeks [MD 2.72 minutes (95% CI 1.77 to 3.67 minutes); $p < 0.00001$]. However, a moderate level of heterogeneity is evident across these trials. Evidence from one RCT[107] suggests a significant improvement in ejaculation control with sertraline compared with placebo. Evidence from one RCT[106] also suggests a significant improvement over placebo on the AIPE. One RCT[106] suggests that there is no significant difference between sertraline or citalopram on the IPE. One RCT[90] suggests that both patient and partner satisfaction improved are improved with sertraline. One RCT[107] indicates no significant differences between sertraline, clomipramine and terazosin in AEs including headache, hypotension, drowsiness and ejaculation disorder. Evidence summarised by one systematic review[65] suggests that > 5% patients treated with sertraline report headache, dry mouth,

insomnia, nausea, somnolence, diarrhoea and anejaculation. However, the review is of overall low methodological quality.

Selective serotonin reuptake inhibitors: evidence summary

There is evidence which suggests that, with the exception of fluvoxamine, SSRIs are more effective than placebo at increasing IELT in men with PE. Sexual satisfaction measures and other secondary outcomes also appear improved. However, the current evidence base comprises studies captured in low methodological quality reviews and further RCTs that are of unclear and high risk of bias. In addition, the evidence base is limited in terms of assessing the benefits of one SSRI compared with another SSRI in treating PE. AE data suggest that SSRIs are associated with a number of AEs. However, the choice of an appropriate SSRI for the treatment of PE in terms of a safety profile is unclear. Furthermore, long-term treatment effects and AE outcomes in the treatment of men with PE are not fully evaluated in the current literature. The RCTs evaluating SSRIs identified for inclusion in this assessment report evaluated treatments over 4 to 12 weeks and none reported a long-term follow-up or the effects when treatment with SSRIs is withdrawn. This, coupled with the limited treatment comparisons evaluated by RCTs assessing SSRIs (mainly placebo), prohibits any definitive conclusions regarding an appropriate choice of SSRI in terms of efficacy and safety for the treatment of men with PE.

Selective serotonin reuptake inhibitors licensed for premature ejaculation (dapoxetine)

Characteristics of included studies: dapoxetine

Dapoxetine as the primary treatment of investigation was evaluated by four systematic reviews of effectiveness,[108–110,169] two of which pooled data in a meta-analysis.[108,110] One systematic review evaluated the risk–benefit assessment of dapoxetine including withdrawal data from Phase III trials,[111] one review evaluated dapoxetine Phase II trials including pharmacokinetic and safety data[112] and two further effectiveness reviews of SSRIs included studies of dapoxetine and other SSRIs.[65,67] One further RCT was identified that evaluated dapoxetine and dapoxetine plus a PDE5 inhibitor (mirodenafil).[120]

Reviews Of four systematic reviews of effectiveness of dapoxetine, one was undertaken in Australia,[169] one was undertaken in Ireland[109] and two were undertaken in China.[108,110] The overall AMSTAR quality score was 1 out of 11 in one of the reviews,[108] 2 out of 11 in two of the reviews,[109,110] and 4 out of 11 in one review.[167] Details of the review type, the databases searched and dates, included RCTs and the AMSTAR points awarded to these reviews of effectiveness are presented in *Table 17*. The two reviews of SRRIs that included some of the dapoxetine trials both scored 0 out of 11.[65,67] Details of these reviews are presented in *Table 11* in the *Characteristics of included studies: selective serotonin reuptake inhibitors* section of this assessment report. Full details of the AMSTAR assessment for these and all other include reviews are presented in *Appendix 4*. The search methodology and inclusion criteria for studies varied across these. The two reviews including a meta-analysis[108,110] both included different dosing arms from studies separately in the meta-analysis, but included the comparator arm (placebo) against each dosing arm, in effect counting participants twice in the analysis.

Randomised controlled trials included in reviews The reviews above varied in terms of which RCTs they included. In total, eight RCT[85,113–116,118,119,170] reports (one[118] integrating data from two RCTs) (total $n = 6968$) were included in at least one review of effectiveness. Seven RCTs were reported as being Phase III RCTs,[85,113,116,118,119,170] (Pryor *et al.*[118] is an integrated analysis of two RCTs) and two RCTs as Phase II studies.[114,115] The IELT assessment method within the RCTs was not reported by any of the reviews. Duration of the RCTs included in these reviews was 2–4 weeks for the two Phase II trials and 9–24 weeks for the Phase III trials. The majority of the RCTs included within the reviews evaluated one or more dose level of dapoxetine compared with placebo. Only one RCT also evaluated paroxetine;[85] however, no data for this comparison were reported in any review. This trial is also evaluated in the section *Characteristics of included studies: selective serotonin reuptake inhibitors*. Across the reviews, the dapoxetine doses evaluated were 20 mg, 30 mg, 40 mg, 60 mg and 100 mg on demand. As dapoxetine at 30 mg and 60 mg

TABLE 17 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): details of reviews and AMSTAR quality score

Author (country), review type	Databases searched and dates	Included RCTs relevant to this section	AMSTAR review quality assessment
Luo *et al.* 2012[108] (China), systematic and meta-analysis	PubMed, BIOSIS Previews (now part of the Web of Knowledge), The Cochrane Library, CNKI, Wangfang Database searched to 2011	Buvat *et al.* 2009,[113] Kaufman *et al.* 2009,[116] McMahon *et al.* 2010,[170] Pryor *et al.* 2006[118]	AMSTAR score, 1/11: • study quality assessed
McCarty and Dinsmore 2012[109] (Ireland), systematic review	PubMed, the Cochrane Database of Systematic Reviews, NHS Evidence and NICE to August 2011. Start date not reported	Buvat *et al.* 2009,[113] Kaufman *et al.* 2009,[116] McMahon *et al.* 2010,[170] Safarinejad 2008[119]	AMSTAR score, 2/11: • characteristics of included studies reported • conflict of interest statement reported
McMahon 2012[169] (Australia), systematic review	MEDLINE, Web of Science, PICA and EMBASE 1993 to April 2012	Phase II studies: Hellstrom *et al.* 2004,[114] Hellstrom *et al.* 2005[115] Phase III studies: Buvat *et al.* 2009,[113] Kaufman *et al.* 2009,[116] McMahon *et al.* 2010,[170] Pryor *et al.* 2006[118]	AMSTAR score, 4/11: • comprehensive literature search • studies included regardless of publication type • characteristics of included studies reported • conflict of interest statement reported
Wang *et al.* 2010[110] (China) systematic and meta-analysis	The Cochrane Library, MEDLINE, EMBASE, CNKI, CBM, Chinese Science and Technology Periodical Database (VIP) from 1979 to 2009	Buvat *et al.* 2009,[113] Kaufman *et al.* 2008,[116] Pryor *et al.* 2006,[118] Safarinejad 2006,[85] Safarinejad 2008[119]	AMSTAR score, 2/11: • characteristics of included studies reported • study quality assessed

CBM, Chinese Biomedical Literature database; CNKI, China National Knowledge Infrastructure; NICE, National Institute for Health and Care Excellence.
a Acronym not defined in original study.
AMSTAR review quality criteria: a priori design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; and conflict of interest statement included.

has received approval for the treatment of PE in the UK,[24] these doses were used in the present review for analysis. One Phase II RCT evaluated doses of 20 mg and 40 mg and is not discussed further here.[115] Details of the RCTs extracted from these reviews are presented in *Table 18*. All RCTs in reviews were captured by the search strategy for this assessment report.

Randomised controlled trials not included in reviews The RCT by Lee *et al.*[120] was conducted in the Republic of Korea. Patients were randomised to dapoxetine 30 mg plus mirodenafil 50 mg per day ($n = 63$) or dapoxetine 30 mg plus placebo ($n = 57$). The trial was considered to be at overall low risk of bias. This trial is also evaluated in the section *Characteristics of included studies: selective serotonin reuptake inhibitors*.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews, and the overall study quality assessment (AMSTAR[33] for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 18*.

TABLE 18 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Buvat *et al.* 2009[113] (reviews[68,108–110])	Phase III, 24 weeks	Dapoxetine 30 mg ($n = 388$) on demand Dapoxetine 60 mg ($n = 389$) on demand Placebo ($n = 385$)	NR	NR	Method NR	CGI of change, CCCB (unclear); sexual satisfaction, control over ejaculation, distress, interpersonal difficulty
Hellstrom *et al.* 2004[114] (reviews[68,112])	Phase II, crossover, 72-hour washout, 2 weeks per treatment	Dapoxetine 60 mg on demand Dapoxetine 100 mg on demand Placebo (Total $n = 166$)	NR	NR	Method NR	NR
Hellstrom *et al.* 2005[115] (reviews[67,68,112])	Phase II, crossover, no washout, 4 weeks per treatment	Dapoxetine 20 mg on demand Dapoxetine 40 mg on demand Placebo (Total $n = 154$)	NR	NR	Method NR	NR
Kaufman *et al.* 2009[116] (reviews[68,108–110])	Phase II, 9 weeks	Dapoxetine 60 mg on demand Dapoxetine 60 mg daily Placebo (Total $n = 1238$)	NR	NR	IELT not assessed	Global impression of change (PGI), perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation
McMahon *et al.* 2010[168] (reviews[68,108,109])	Phase III, 12 weeks	Dapoxetine 30 mg ($n = 354$) on demand Dapoxetine 60 mg ($n = 356$) on demand Placebo ($n = 357$)	NR	NR	Method NR	Sexual satisfaction, control over ejaculation, distress (CGI)

continued

TABLE 18 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Pryor *et al.* 2006[118] (reviews[65,67,68,108–110])	Two RCTs (integrated analysis), Phase III, 12 weeks	Dapoxetine 30 mg ($n = 874$) on demand Dapoxetine 60 mg ($n = 870$) on demand Placebo ($n = 870$)	NR	NR	Method NR	Global impression of change (PGI), CCCB (unclear); sexual satisfaction, control over ejaculation
Safarinejad 2006[85] (reviews[65,110])	Phase III, 12 weeks	Dapoxetine 60 mg once daily ($n = 115$) Paroxetine 20 mg ($n = 113$) Placebo ($n = 112$)	NR	NR	Method NR	Sexual satisfaction
Safarinejad 2008[119] (reviews[109,110])	Phase III, 12 weeks	Dapoxetine 30 mg twice daily ($n = 106$) Placebo ($n = 106$)	NR	NR	Method NR	Sexual satisfaction
Further RCTs identified by searches (not captured in reviews)						
RCT (country), risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Lee *et al.* 2012[120] (Republic of Korea), low risk	12 weeks	Dapoxetine 30 mg + mirodenafil 50 mg, 1 to 3 hours precoitus ($n = 63$) Dapoxetine 30 mg + placebo 1 to 3 hours precoitus ($n = 57$) *Dapoxetine + mirodenafil 62/63 (98%)* *Dapoxetine + placebo, 56/57 (98%)*	DSM-IV diagnosis	Lifelong	Stopwatch	Time from foreplay to beginning intercourse, OSAT, PEP

CCCB, Composite Criteria for Clinical Benefit; CGI, Clinical Global Impression; NR, not reported; OSAT, overall sexual act time. PGI, patient-reported global impression.

Assessment of effectiveness: dapoxetine – intravaginal ejaculatory latency time outcomes

Intravaginal ejaculatory latency time data were reported for six RCTs[85,113–115,118,170] identified from existing reviews and the one further RCT[120] identified for inclusion in this review. The report by Pryor *et al.*[118] comprised an integrated analysis of two RCTs. Data from this study have been evaluated as a single trial in this assessment report. Three trials were not included in the IELT analysis in this assessment report: one Phase II RCT that evaluated doses of 20 mg and 40 mg dapoxetine,[115] one Phase II RCT for which no variance estimates or appropriate *p*-values were reported[114] and one Phase III RCT for which no IELT data were available.[116]

Intravaginal ejaculatory latency time: dapoxetine 30 mg or 60 mg compared with placebo

Meta-analysis of mean IELT (minutes) at 12 or 24 weeks' follow-up, based on three RCT[113,118,170] comparisons of dapoxetine 30 mg and placebo ($n = 3036$), displayed low heterogeneity (I^2=28%). The pooled MD in IELT was 1.16 minutes, significantly favouring dapoxetine 30 mg [MD (fixed effect); 95% CI 0.94 to 1.39 minutes; $p < 0.00001$]. Meta-analysis of mean IELT (minutes) at 12 or 24 -weeks' follow-up, based on five RCT[85,113,118,119,170] comparisons of dapoxetine 60 mg compared with placebo ($n = 3390$), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 1.66 minutes, significantly favouring dapoxetine 30 mg [MD (fixed effect); 95% CI 1.46 to 1.87 minutes; $p < 0.00001$]. The forest plot for this analysis is presented in *Figure 9*. Summary results for these and all other meta-analyses are presented in *Table 19*.

Intravaginal ejaculatory latency time: dapoxetine 30 mg compared with dapoxetine 60 mg

Meta-analysis of mean IELT (minutes) at 12 or 24 weeks' follow-up, based on three RCT[113,117,118] comparisons ($n = 3005$) displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT was 0.46 minutes, significantly favouring dapoxetine 60 mg [MD (fixed effect); 95% CI 0.19 to 0.74 minutes; $p = 0.0009$]. The forest plot for this analysis is presented in *Figure 10*.

Intravaginal ejaculatory latency time: dapoxetine 30 mg plus mirodenafil compared with dapoxetine 30 mg plus placebo

The between-group difference in mean IELT (minutes) at 4 weeks, based on one RCT[120] ($n = 118$), was 1.50 minutes (95% CI –0.55 to 3.55 minutes; p=0.15). The between-group difference in mean IELT (minutes) at 12 weeks, based on one RCT[120] ($n = 118$), was 2.20 minutes (95% CI –0.89 to 5.29 minutes; p=0.16). The forest plot for this analysis is presented in *Figure 11*.

Assessment of effectiveness: dapoxetine – outcomes other than intravaginal ejaculatory latency time

With the exception of the RCTs by Safarinejad[85] and Safarinejad,[119] all Phase III RCTs and the RCT by Lee *et al.*[120] reported outcomes other than IELT. These outcomes included control over ejaculation, sexual satisfaction, global impression of change and a composite criterion for clinical benefit. However, the reporting of these outcomes varied across the included RCTs and differed in how the outcome was assessed (either as mean scores or as numbers of participants achieving a threshold). Results for between-group comparisons undertaken using RevMan for this assessment report for all secondary outcomes are presented in *Table 19*. All RCTs reporting these outcomes evaluated dapoxetine over 9–24 weeks.

Control over ejaculation: dapoxetine 30 mg and 60 mg

Mean scores for this outcome were available for two Phase III RCTs.[116,118] High heterogeneity was observed for dapoxetine 60 mg compared with placebo (two RCTs,[116,118] $I^2 = 86\%$, meta-analysis not undertaken). Numbers of patients reporting a change in this outcome were available for two Phase III RCTs.[113,116] High heterogeneity was observed for dapoxetine 60 mg compared with placebo (two RCTs,[113,116] $I^2 = 76\%$, meta-analysis not undertaken). Between-group comparisons from individual RCTs estimated in RevMan for this assessment report (see *Table 19*) suggested that both dapoxetine 30 mg and dapoxetine 60 mg are significantly more effective then placebo on this outcome (MD, $p < 0.0001$ and $p < 0.0001$; RR, $p < 0.0001$ and $p < 0.0001$) and dapoxetine 60 mg is significantly more effective than dapoxetine 30 mg (MD, $p = 0.0002$; RR, $p = 0.0008$).

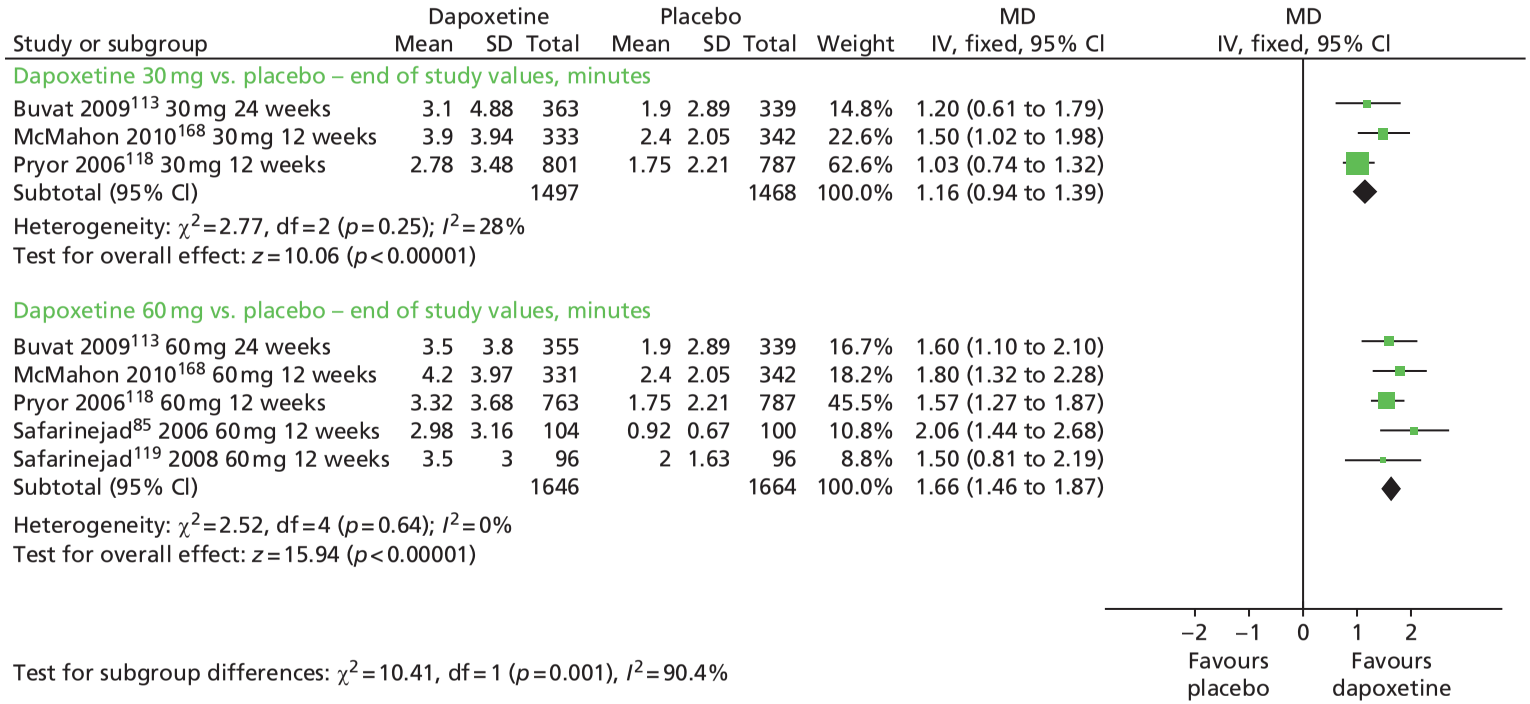

FIGURE 9 Dapoxetine 30 mg or 60 mg compared with placebo: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

TABLE 19 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): results summary

Comparison	Outcome	Study duration	No. of RCTs	No. of participants	I^2	Meta-analysis (model)	Effect estimate (95% CI)	Favours	*p*-value
IELT									
Dapoxetine 30 mg vs. placebo	IELT (minutes) – final values	12–24 weeks	3[113,117,118]	3036	28%	Yes (fixed)	MD 1.16 (0.94 to 1.39)	Dapoxetine 30 mg	< 0.00001
Dapoxetine 60 mg vs. placebo	IELT (minutes) – final values	12–24 weeks	5[85,113,117–119]	3390	0%	Yes (fixed)	MD 1.66 (1.46 to 1.87)	Dapoxetine 60 mg	< 0.00001
Dapoxetine 60 mg vs. dapoxetine 30 mg	IELT (minutes) – final values	12–24 weeks	3[113,117,118]	3005	0%	Yes (fixed)	MD 0.46 (0.19 to 0.74)	Dapoxetine 60 mg	0.0009
30 mg + mirodenafil vs. 30 mg + placebo	IELT (minutes) – final values	12 weeks	1[120]	120	N/A	N/A	MD 2.20 (–0.89 to 5.29)	NS	0.16
Control over ejaculation – mean scores									
Dapoxetine 30 mg vs. placebo	Control over ejaculation: mean scores	12 weeks	1[118]	1588	N/A	N/A	MD 0.60 (0.50 to 0.70)	Dapoxetine 30 mg	< 0.00001
Dapoxetine 60 mg vs. placebo	Control over ejaculation: mean scores	9–12 weeks	2[116,118]	2202	86%	Data not pooled	MD 0.77 (0.67 to 0.87) MD 0.50 (0.33 to 0.67)	Dapoxetine 60 mg	< 0.00001 < 0.00001
Dapoxetine 30 mg vs. dapoxetine 60 mg	Control over ejaculation mean scores	12 weeks	1[118]	1564	N/A	N/A	MD –0.17 (–0.28 to –0.06)	Dapoxetine 60 mg	0.0002
Control over ejaculation – patients reporting change									
Dapoxetine 30 mg vs. placebo	Control over ejaculation: patients reporting change	24 weeks	1[113]	723	N/A	N/A	RR 2.05 (1.48 to 2.84)	Dapoxetine 30 mg	< 0.00001
Dapoxetine 60 mg vs. placebo	Control over ejaculation: patients reporting change	9–24 weeks	2[113,116]	1369	76%	Data not pooled	RR 3.00 (2.21 to 4.07) RR 1.95 (1.46 to 2.59)	Dapoxetine 60 mg	< 0.00001 < 0.00001
Dapoxetine 30 mg vs. dapoxetine 60 mg	Control over ejaculation: patients reporting change	24 weeks	1[113]	712	N/A	N/A	RR 0.68 (0.55 to 0.85)	Dapoxetine 60 mg	0.0008

continued

TABLE 19 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): results summary (*continued*)

Comparison	Outcome	Study duration	No. of RCTs	No. of participants	I^2	Meta-analysis (model)	Effect estimate (95% CI)	Favours	*p*-value
Sexual satisfaction – mean scores									
Dapoxetine 30 mg vs. placebo	Sexual satisfaction: mean scores	12 weeks	1[118]	1588	N/A	N/A	MD 0.51 (0.41 to 0.61)	Dapoxetine 30 mg	< 0.00001
Dapoxetine 60 mg vs. placebo	Sexual satisfaction: mean scores	9–12 weeks	2[116,118]	2202	99%	Data not pooled	MD 0.61 (0.50 to 0.72)	Dapoxetine 60 mg	< 0.00001
							MD 0.50 (0.33 to 0.67)		< 0.00001
Dapoxetine 60 mg vs. dapoxetine 30 mg	Sexual satisfaction: mean scores	12 weeks	1[118]	1564	N/A	N/A	MD 0.10 (0.00 to 0.20)	NS	0.06
Sexual satisfaction – patients reporting change									
Dapoxetine 30 mg vs. placebo	Sexual satisfaction: patients reporting change	24 weeks	1[113]	298	N/A	N/A	RR 1.36 (1.14 to 1.62)	Dapoxetine 30 mg	0.0007
Dapoxetine 60 mg vs. placebo	Sexual satisfaction: patients reporting change	9–24 weeks	4[85,113,116,119]	1745	89%	Data not pooled	RR 1.56 (1.32 to 1.80)	Dapoxetine 60 mg	< 0.00001
							RR 1.61 (1.32 to 1.98)		< 0.00001
							RR 4.15 (2.59 to 6.63)		< 0.00001
							RR 4.19 (2.68 to 6.55)		< 0.00001
Dapoxetine 30 mg vs. dapoxetine 60 mg	Sexual satisfaction: patients reporting change	24 weeks	1[113]	712	N/A	N/A	RR 0.87 (0.75 to 1.00)	Dapoxetine 60 mg	0.05
Global impression of change – patients reporting change									
Dapoxetine 30 mg vs. placebo	Global impression of change: patients report change	12–24 weeks	3[113,117,118]	2950	48%	Yes (random)	RR 2.01 (1.69 to 2.38)	Dapoxetine 30 mg	< 0.00001
Dapoxetine 60 mg vs. placebo	Global impression of change: patients report change	9–24 weeks	4[113,116–118]	3566	57%	Yes (random)	RR 2.26 (1.91 to 2.67)	Dapoxetine 60 mg	< 0.00001
Dapoxetine 30 mg vs. dapoxetine 60 mg	Global impression of change: patients report change	12–24 weeks	3[113,117,118]	2950	0%	Yes (fixed)	RR 0.86 (0.80 to 0.90)	Dapoxetine 60 mg	< 0.0001

Comparison	Outcome	Study duration	No. of RCTs	No. of participants	I^2	Meta-analysis (model)	Effect estimate (95% CI)	Favours	*p*-value
Composite criteria for clinical benefit – patients reporting change									
Dapoxetine 30 mg vs. placebo	Composite criteria for clinical benefit: patients reporting change	12–24 weeks	2[113,117]	1376	0%	Yes (fixed)	RR 1.71 (1.40 to 2.08)	Dapoxetine 30 mg	< 0.00001
Dapoxetine 60 mg vs. placebo	Composite criteria for clinical benefit: patients reporting change	9–24 weeks	3[113,116,117]	2029	66%	Yes (random)	RR 2.15 (1.64 to 2.82)	Dapoxetine 60 mg	< 0.00001
Dapoxetine 30 mg vs. dapoxetine 60 mg	Composite criteria for clinical benefit: patients reporting change	12–24 weeks	2[113,117]	1375	76%	No	RR 0.68 (0.54 to 0.85)	Dapoxetine 60 mg	0.0008
							RR 0.93 (0.76 to 1.14)	NS	0.51

N/A, not applicable; NS, not significant.

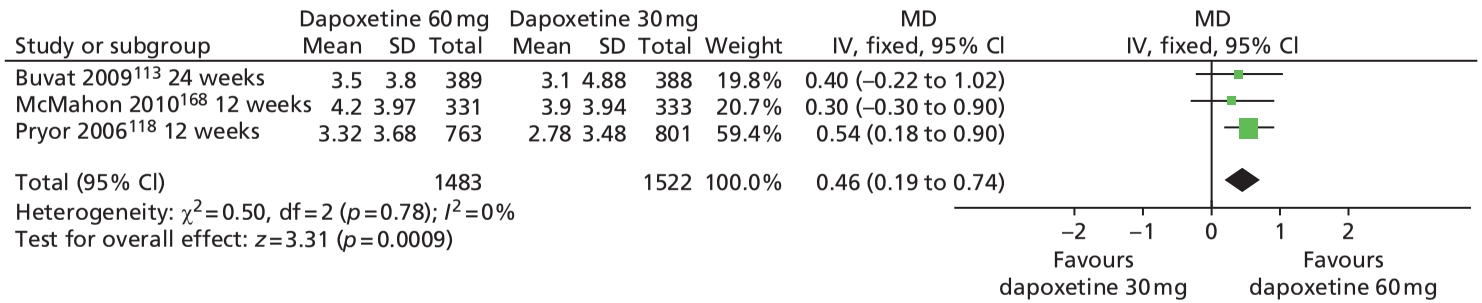

FIGURE 10 Dapoxetine 30 mg compared with 60 mg: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

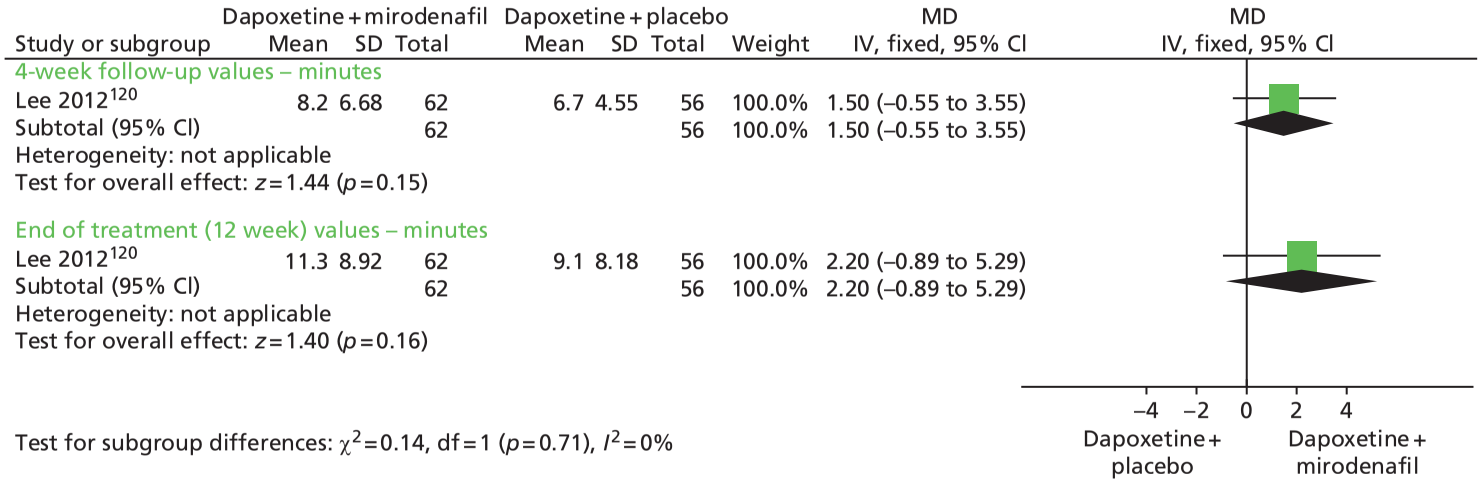

FIGURE 11 Dapoxetine + mirodenafil compared with dapoxetine + placebo: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Sexual satisfaction ejaculation: dapoxetine 30 mg and 60 mg Mean scores for this outcome were available for two Phase III RCTs.[116,118] A high level of heterogeneity was observed for dapoxetine 60 mg compared with placebo (two RCTs,[116,118] $I^2 = 99\%$, meta-analysis not undertaken). The number of patients reporting a change in this outcome was available for four Phase III RCTs.[85,113,116,119] High heterogeneity was observed for dapoxetine 60 mg compared with placebo (four RCTs,[85,113,116,119] $I^2 = 89\%$, meta-analysis not undertaken). Between-group comparisons from individual RCTs in RevMan for this assessment report (see *Table 19*) suggested that both dapoxetine 30 mg and dapoxetine 60 mg are significantly more effective than placebo on this outcome (MD, $p < 0.0001$ and $p < 0.0001$; RR, $p = 0.0007$ and $p < 0.0001$) and that dapoxetine 60 mg is significantly more effective than dapoxetine 30 mg on the number of patients reporting a change in this outcome (MD, $p = 0.06$; RR, $p = 0.05$) (see *Table 19*).

Global impression of change: dapoxetine 30 mg and 60 mg The numbers of patients reporting a change in this outcome were available for four Phase III RCTs.[113,116–118] Pooled effects across RCTs suggested that both dapoxetine 30 mg and dapoxetine 60 mg were significantly more effective than placebo (RR, $p < 0.0001$ and $p < 0.0001$) and that dapoxetine 60 mg is significantly more effective than dapoxetine 30 mg (RR, $p < 0.0001$) (see *Table 19*).

Composite criteria for clinical benefit: dapoxetine 30 mg and 60 mg The numbers of patients reporting a change in this outcome were available for three Phase III RCTs (Buvat *et al.*, 2009,[113] Kaufman *et al.*, 2009,[116] McMahon *et al.*, 2010[117]). Pooled effects across RCTs suggested that both dapoxetine 30 mg and dapoxetine 60 mg were significantly more effective than placebo (RR, $p < 0.0001$ and $p < 0.0001$) (see *Table 19*). High heterogeneity was observed for dapoxetine 30 mg compared with dapoxetine 60 mg (two RCTs, $I^2 = 76\%$, meta-analysis not undertaken). Between-group comparisons from individual RCTs estimated in RevMan for this assessment report for one RCT suggested that dapoxetine 30 mg was significantly more effective than dapoxetine 60 mg on this outcome (RR, $p = 0.0008$) (see *Table 19*).

Other outcomes: dapoxetine plus phosphodiesterase-5 inhibitor The RCT by Lee *et al.*[120] reported no statistically significant between-group difference in time from foreplay to beginning intercourse between dapoxetine plus mirodenafil and mirodenafil alone. Nor was any statistically significant between-group difference evident in overall sexual act time (OSAT) at week 4 or 12. The authors reported statistically significant between-group differences in favour of dapoxetine plus mirodenafil on the PEP domains of perceived control over ejaculation ($p = 0.019$), interpersonal difficulty related to ejaculation ($p = 0.013$) and the overall index score ($p = 0.046$).

Assessment of safety: dapoxetine – adverse events

Adverse event and withdrawal data for RCTs from reviews are summarised from the reports by McCarty and Dinsmore,[109] McMahon and Porst,[68] Hutchinson *et al.*[111] and Kendirci *et al.*[112] in *Table 20*.

These reviewers concluded that, among the Phase II studies, the most commonly reported AEs were nausea, diarrhoea, headache and dizziness, and that the incidence of most AEs appeared to be dose dependent. Amongst the Phase III studies, the most common treatment-related AEs included nausea, dizziness and headache.

Across the included RCTs, insufficient data for numbers of patients experiencing AEs were available for any meaningful pooling in a meta-analysis.

Assessment of effectiveness: dapoxetine – evidence summary

The current evidence base for dapoxetine at 30 mg and 60 mg on demand (approved doses for the treatment of PE in the UK[24]) in the treatment of PE comprises one Phase II RCT[114] and six Phase III RCT reports.[85,113,116,118,119,170] These RCTs are captured in six systematic reviews of effectiveness which are of low to moderate methodological quality.[65,67,108–110,169] One further RCT[120] evaluating the effects of dapoxetine combined with a PDE5 inhibitor (mirodenafil) is at overall low risk of bias. The pooled evidence across

TABLE 20 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): AEs and withdrawals

AEs (%)	Dapoxetine 30 mg	Dapoxetine 60 mg	Dapoxetine + mirodenafil	Placebo	References
Nausea	16.5	30.6		2.9	Buvat *et al.* 2009[113] (24 weeks)
		5.8		0.7	Hellstrom *et al.* 2004[114] (2 weeks)
		15.3		1.6	Kaufman *et al.* 2009[116] (9 weeks)
	10.5	26.4		2.0	McMahon 2010[117] (12 weeks)
	8.7	20.1		1.9	Pryor *et al.* 2006[118] (12 weeks)
		5.4		1.0	Safarinejad 2008[119] (12 weeks)
	10.7		8.1		Lee *et al.* 2012[120] (12 weeks)
Diarrhoea	3.9	11.3		1.6	Buvat *et al.* 2009[113] (24 weeks)
		5.0		0.7	Hellstrom *et al.* 2004[114] (2 weeks)
		6.1		2.0	Kaufman *et al.* 2009[116] (9 weeks)
	2.0	1.7		0.8	McMahon *et al.* 2010[168] (12 weeks)
	3.9	6.8		1.4	Pryor *et al.* 2006[118] (12 weeks)
		5.4		0.0	Safarinejad 2008[119] (12 weeks)
	3.6		4.8		Lee *et al.* 2012[120] (12 weeks)
Headache	6.4	13.6		8.3	Buvat *et al.* 2009[113] (24 weeks)
		4.3		0.0	Hellstrom *et al.* 2004[114] (2 weeks)
		8.1		6.1	Kaufman *et al.* 2009[116] (9 weeks)
	3.4	4.8		2.0	McMahon 2010[117] (12 weeks)
	5.9	6.8		4.0	Pryor *et al.* 2006[118] (12 weeks)
		4.3		1.0	Safarinejad 2008[119] (12 weeks)
	5.4		12.9		Lee *et al.* 2012[120] (12 weeks)
Dizziness	7.7	13.4		2.6	Buvat *et al.* 2009[113] (24 weeks)
		2.2		0.0	Hellstrom *et al.* 2004[114] (2 weeks)
		10.2		2.9	Kaufman *et al.* 2009[116] (9 weeks)
	10.5	18.8		3.9	McMahon *et al.* 2010[168] (12 weeks)
	3.0	6.2		0.8	Pryor *et al.* 2006[118] (12 weeks)
		3.2		0.0	Safarinejad 2008[119] (12 weeks)
	8.9		9.7		Lee *et al.* 2012[120] (12 weeks)
Somnolence	3.9	7.2		1.0	Buvat *et al.* 2009[113] (24 weeks)
		2.9		0.7	Hellstrom *et al.* 2004[114] (2 weeks)
		3.7		0.8	Kaufman *et al.* 2009[116] (9 weeks)
	3.4	6.2		0.6	McMahon *et al.* 2010[168] (12 weeks)
	3.2	3.7		0.2	Pryor *et al.* 2006[118] (12 weeks)
Vomiting	1.3	3.1		0.5	Buvat *et al.* 2009[113] (24 weeks)
	0.3	2.5		0.0	McMahon *et al.* 2010[168] (12 weeks)
Palpitation	1.8		6.5		Lee *et al.* 2012[120] (12 weeks)

TABLE 20 Selective serotonin reuptake inhibitors licensed for PE (dapoxetine): AEs and withdrawals (*continued*)

AEs (%)	Dapoxetine 30 mg	Dapoxetine 60 mg	Dapoxetine + mirodenafil	Placebo	References
Facial flushing	1.8		3.2		Lee *et al.* 2012[120] (12 weeks)
Any AE	32.1		45.2		Lee *et al.* 2012[120] (12 weeks)
Withdrawals (owing to AE)	3.9	8.2		1.3	Buvat *et al.* 2009[113] (24 weeks)
	1.7	5.1		0.3	McMahon *et al.* 2010[168] (12 weeks)
	4.0	10.0		0.9	Pryor *et al.* 2006[118] (12 weeks)
		3.5		0.0	Safarinejad 2006[85] (12 weeks)
		5.7		0.0	Safarinejad 2008[119] (12 weeks)
Withdrawals (overall)	42.8	46.8		50.9	Buvat *et al.* 2009[113] (24 weeks)
	28.5	31.2		17.4	McMahon *et al.* 2010[168] (12 weeks)
	22.7	29.7		22.8	Pryor *et al.* 2006[118] (12 weeks)
		8.7		8.9	Safarinejad 2006[85] (12 weeks)
		12.3		9.4	Safarinejad 2008[119] (12 weeks)
		0.0		0.7	Hellstrom *et al.* 2004[114] (2 weeks)

three RCTs[113,117,118] including 3036 participants and across five RCTs[85,113,117–119] comprising 3390 participants suggests that both dapoxetine 30 mg and dapoxetine 60 mg increase IELT in men with PE to a significantly greater extent than placebo (30 mg: MD 1.16 minutes, 95% CI 0.94 to 1.39 minutes; $p < 0.00001$; 60 mg: MD 1.66 minutes, 95% CI 1.46 to 1.87 minutes; $p < 0.00001$). The pooled evidence across three RCTs[113,117,118] including 3005 participants suggests that dapoxetine 60 mg is significantly more effective in increasing IELT in men with PE when compared with dapoxetine 30 mg (MD 0.46 minutes, 95% CI 0.19 to 0.74 minutes; $p = 0.0009$). Evidence from one RCT[120] (120 participants) showed no statistically significant difference in IELT between dapoxetine 30 mg combined with mirodenafil and dapoxetine 30 mg alone. Among the Phase III trials, treatment duration ranged from 9 to 24 weeks. The effects of longer-term treatment with dapoxetine for PE or the effects once treatment is withdrawn have not been evaluated in the current evidence base.

Evidence from individual Phase III RCTs suggests that both dapoxetine 30 mg and dapoxetine 60 mg are significantly more effective than placebo and that dapoxetine 60 mg is significantly more effective than dapoxetine 30 mg, on outcomes of ejaculatory control, sexual satisfaction, global impression of change and clinical benefit. However, the assessment and reporting of these outcomes is variable across trials. High levels of heterogeneity were observed when trials were pooled. These findings should be interpreted with caution given the observed levels of between-study heterogeneity.

The most commonly reported AEs with dapoxetine are nausea, diarrhoea, headache, dizziness and appear to be dose dependent. From the current evidence base there are no data regarding possible long-term AEs of dapoxetine in the treatment of PE.

The findings for dapoxetine are based on meta-analyses of RCT data extracted from existing reviews and meta-analyses. From a review presenting withdrawal data from Phase III trials, it is apparent that previous reviews have meta-analysed RCT data across per-protocol (patients completing) and intention-to-treat populations.[111] Thus, an attrition bias may be present. The results for dapoxetine in this assessment report should therefore be interpreted with caution.

Serotonin–noradrenaline reuptake inhibitors

Characteristics of included studies: serotonin–noradrenaline reuptake inhibitors

One RCT evaluating duloxetine was identified from one review.[68] The review was undertaken in Australia and was awarded an AMSTAR score of 2 out of 11 (see *Table 11* in the *Characteristics of included studies: selective serotonin reuptake inhibitors* section and *Appendix 4*). A further two RCTs were identified, both of which evaluated venlafaxine compared with placebo.[122,123]

Randomised controlled trials included in reviews Duloxetine 80 mg was compared with placebo in one trial.[121] The duration was 12 weeks and IELT was assessed using a stopwatch. This RCT was captured by the search strategy for this assessment report.

Randomised controlled trials not included in reviews The trial by Kilic *et al.*[122] was undertaken in Turkey and was a randomised crossover design trial recruiting 31 patients. Patients were randomised to venlafaxine extended-release 75 mg per day or placebo: 2 weeks treatment, 1 week washout, 2 weeks treatment. IELT was assessed using a stopwatch. The authors reported that 21 out of 31 (67.7%) patients completed the trial. This trial was considered at overall high risk of bias. The RCT by Safarinejad[123] was conducted in the Islamic Republic of Iran. Two hundred and twenty patients were randomised to either venlafaxine extended-release 75 mg per day or placebo. IELT was assessed using a stopwatch. Treatment duration was 12 weeks and the authors reported that 192 out of 222 (86%) patients completed the intervention. This trial was considered to be at overall unclear risk of bias.

Details of these trials are presented in *Table 21*.

Assessment of effectiveness: serotonin–noradrenaline reuptake inhibitors – intravaginal ejaculatory latency time outcomes

Intravaginal ejaculatory latency time: venlafaxine compared with placebo The crossover trial by Kilic *et al.*[122] reported that there was no statistically significant between-group difference in IELT post treatment ($p = 0.144$) while no variance estimates were reported for the RCT by Safarinejad.[123] The author reported that, during the study (fortnightly assessment points), there was no significant differences between venlafaxine and placebo ($p = 0.10$). After 12 weeks, IELT did not differ significantly between the two groups ($p = 0.10$ for geometric mean fold increase).

Intravaginal ejaculatory latency time: duloxetine compared with placebo The between-group difference in mean IELT for one RCT evaluating this comparison[121] was 1.52 minutes [MD (fixed effect), 95% CI 0.08 to 2.24 minutes; $p < 0.00001$] in favour of duloxetine at 12 weeks (estimated for this assessment report using RevMan; figure not presented and, therefore, there is no figure for this comparison in the report).

Assessment of effectiveness: serotonin–noradrenaline reuptake inhibitors – other outcomes

The RCT by Athanasios *et al.*[121] assessed score on the Clinical Global Impression – Improvement (CGI-I) scale. The trial by Kilic *et al.*[122] assessed sexual satisfaction, but did not report the instrument used. Safarinejad[123] assessed IIEF intercourse satisfaction and number of coitus episodes weekly.

Clinical global impression: duloxetine compared with placebo The proportion of patients reported as 'much improved' and 'very much improved' on a subjective measure of clinical improvement was greater with duloxetine than with placebo in one RCT.[121]

TABLE 21 Serotonin–noradrenaline reuptake inhibitor: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Athanasios *et al.* 2007[121] (review[68])	12 weeks	Duloxetine 40 mg twice daily ($n = 10$) Placebo twice daily ($n = 10$) (Following 1 week titration with duloxetine 20 mg or placebo twice daily)	Partially ISSM: IELT ≤ 4 minutes	NR	Stopwatch	CGI-I
Further RCTs identified by searches (not captured in reviews)						
RCT (country), risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Kilic *et al.* 2005[122] (Turkey), high	Crossover: 2 weeks treatment, 1 week washout, 2 weeks treatment	Venlafaxine extended-release 75 mg per day Placebo *21/31 (67.7%)*	IELT < 2 minutes on 50% occasions	All lifelong	Stopwatch	Sexual satisfaction of patient and partner – assessment method not reported
Safarinejad 2008[123] (the Islamic Republic of Iran), unclear	12 weeks	Venlafaxine extended-release 75 mg per day Placebo *Venlafaxine, 94/112 (84%)* *Placebo, 98/110 (89%)*	IELT < 2 minutes on 90% occasions	Lifelong, 83 Acquired, 119	Stopwatch	IIEF intercourse satisfaction Weekly coitus episodes

CGI-I, Clinical Global Impression – Improvement; NR, not reported.

Sexual satisfaction and weekly coitus: venlafaxine compared with placebo The trial by Kilic *et al.*[122] reported no statistically significant between-group difference in patient or partner sexual satisfaction between venlafaxine compared with placebo. Safarinejad[123] also reported no significant between-group difference in IIEF sexual satisfaction or number of episodes of coitus per week.

Details of these outcomes and AEs are presented in *Table 22*.

Assessment of safety: serotonin–noradrenaline reuptake inhibitors – adverse events

Dry mouth and nausea were reported in one RCT evaluating duloxetine;[121] however, it was unclear whether this was in the duloxetine or placebo group. The two trials that evaluated venlafaxine both reported proportions of patient experiencing specific AEs of treatment.[122,123] The trial by Kilic *et al.*[122] reported that only nausea was significantly higher with venlafaxine than with placebo. Safarinejad[123] reported that significantly more AEs were associated with venlafaxine.

Assessment of effectiveness: serotonin–noradrenaline reuptake inhibitors – evidence summary

The current evidence base for SNRIs in the treatment of PE comprises three RCTs,[121–123] one captured in a low methodological quality systematic review[121] and two further RCTs,[122,123] one[122] of which is at overall high risk of bias and the other at overall unclear risk of bias.[123]

There is evidence from one RCT[121] (20 participants) that duloxetine is significantly more effective than placebo in increasing IELT (MD 1.52 minutes, 95% CI 0.08 to 2.24 minutes; $p < 0.00001$). Measures of clinical improvement appear improved with duloxetine. Duloxetine-associated side effects are reported to be dry mouth and nausea. Evidence from two RCTs[122,123] suggests that venlafaxine is not effective at increasing IELT in men with PE when compared with placebo. Venlafaxine is associated with significantly more treatment-related side effects than placebo.

The long-term efficacy and side effects of these treatments along with patient acceptability are not assessed in the current evidence base.

Tricyclic antidepressants

Characteristics of included studies: tricyclic antidepressants

Two single-arm randomised crossover RCTs[39,76] were captured in several reviews (see *Characteristics of included studies: selective serotonin reuptake inhibitors*, *Table 11*). Both evaluated oral clomipramine. Eight further RCTs[124–131] that also evaluated oral clomipramine were identified from three reviews of low methodological quality.[52,68,69] Full details of the AMSTAR assessment for these and all other included reviews are presented in *Appendix 4*. A further three RCTs were identified from the literature search,[107,132,133] and the RCT by Tuncel *et al.*[107] evaluated clomipramine, sertraline, terazosin and placebo. The trials by Akilov *et al.*[132] and Leaker *et al.*[133] both evaluated nasally inhaled clomipramine. The trial by Tuncel *et al.*[107] is also evaluated in sections *Phosphodiesterase-5 inhibitors* and *Alpha-blockers*.

Randomised controlled trials included in reviews In total, 10 trials were identified from reviews.[39,76,124–131] Of the trials identified as having as crossover design, by Abdel-Hamid *et al.*,[39] evaluated clomipramine 25 mg, sildenafil 50 mg, paroxetine 20 mg, sertraline 50 mg and the squeeze technique over five separate 4-week treatment phases. IELT was assessed using a stopwatch. Kim and Seo[76] evaluated clomipramine 50 mg, fluoxetine 40 mg, sertraline 100 mg and placebo over 4-week treatment phases. The method of IELT assessment was not reported. Of the other trials, Althof *et al.*[124] evaluated clomipramine 25 mg, clomipramine 50 mg or placebo in 15 couples (unclear from existing reviews if crossover or pairwise comparison) over 2–7 weeks. Girgis *et al.*,[125] Goodman,[126] Haensel *et al.*,[127] Montorsi *et al.*,[128] Porto,[129] Segraves *et al.*[130] and Strassberg *et al.*[131] all evaluated clomipramine compared with placebo. The total number of participants per trial ranged from 16 to 33; however, numbers by treatment group were not reported and it was unclear from the reviews from which these trials were extracted which, if any, were

TABLE 22 Serotonin–noradrenaline reuptake inhibitors: other outcomes and AEs

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs: venlafaxine vs. placebo
Athanasios *et al.* 2007,[121] 12 weeks	Duloxetine 80 mg ($n = 10$) Placebo ($n = 10$)	CGI-I	Duloxetine 'much improved', 40%; (4/10); 'very much improved', 40% (4/10) Placebo 'much improved', 10% (1/10) *p*-value NR	Unclear	Nausea and dry mouth were reported in three subjects. Unclear which group
Kilic *et al.* 2005,[122] 2 weeks treatment, 1 week washout, 2 weeks treatment	Venlafaxine 75 mg Placebo (Total $n = 31$)	Sexual satisfaction of patient and partner – assessment method NR	No statistical difference was found in increases of sexual satisfaction scores of both patient and partner groups between venlafaxine and placebo ($p = 0.080$ for patients and $p = 0.067$ for partners)	No	Venlafaxine vs. placebo ($n = 21$ with data) Any AE, 48% vs. 29% Exhaustion, 10% vs. 5% Drowsiness, 24% vs. 10% Stagnation, 10% vs. 5% Sweating, 5% vs. 0% Gnashing of teeth, 5% vs. 5% Tension, 10% vs. 5% Dry mouth, 19% vs. 14% Reduced potency, 0% vs. 5% Increased potency, 5% vs. 0% Reduced libido, 5% vs. 5% Nausea, 19% vs. 0% Palpitation, 5% vs. 0% Sleeplessness, 5% vs. 5% Reduced attention, 5% vs. 0%

continued

TABLE 22 Serotonin–noradrenaline reuptake inhibitors: other outcomes and AEs (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs: venlafaxine vs. placebo
					Headache, 5% vs. 0%
					Only nausea was significantly higher in patients who took venlafaxine. No withdrawals due to side effects
Safarinejad 2008,[123] 12 weeks	Venlafaxine 75 mg ($n = 112$)	IIEF intercourse satisfaction	Mean IIEF intercourse satisfaction post treatment:	No	Venlafaxine ($n = 112$) vs. placebo ($n = 110$):
	Placebo ($n = 110$)	Weekly coitus episodes	• Venlafaxine, 13; placebo, 12		Any treatment-related AE, 29% vs. 7%
			Mean number of acts of coitus per week post treatment:	No	Nausea, 27% vs. 1%
			• Venlafaxine, post treatment, 2.1; placebo, 1.9		Dry mouth, 20% vs. 0%
			No variance estimates or *p*-value reported		Agitation, 11% vs. 1%
					Constipation, 10% vs. 0%
					Headache, 8% vs. 2%
					Dizziness, 3% vs. 2%
					Erectile dysfunction, 2% vs. 2%
					Loss of libido, 3% vs. 2%
					More AEs were associated with venlafaxine ($p = 0.02$)

NR, not reported.

crossover design trials. Duration across these trials ranged from 2 to 6 weeks. IELT was reported as being assessed using subject report or questionnaire. All RCTs in reviews were captured by the search strategy for this assessment report.

Details of these RCTs extracted from reviews are presented in *Table 23*.

Randomised controlled trials not included in reviews The RCT by Akilov *et al.*[132] was conducted in Uzbekistan and patients were randomised, 19 to a clomipramine 4 mg nasal spray and 15 to a placebo nasal spray. The authors reported that 33 out of 34 (97%) completed the 8-week follow-up. IELT was via patient self-report. The RCT by Leaker *et al.*[133] was conducted in the UK and inhaled clomipramine 1 mg or placebo (not described) before intercourse for a maximum of five occasions was compared with inhaled clomipramine 2 mg or placebo before intercourse for a maximum of five occasions in a randomised crossover design study. Thirty-nine patients were reported as included in an intention-to-treat analysis. IELT was assessed using a stopwatch and both RCTs were reported in abstract form only. The RCT by Tuncel *et al.*[107] was undertaken in Turkey and 90 patients were randomised to receive clomipramine 25 mg per day, sertraline 50 mg, terazosin 5 mg or placebo. Treatment was for 2 months and IELT was not assessed. The authors reported that 90 out of 90 (100%) patients completed the trial. Treatment was for 2 months and IELT was not assessed. All three RCTs were considered to be at overall unclear risk of bias.[107,132,133]

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews, and the overall study quality assessment (AMSTAR[33] for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 23*.

Assessment of effectiveness: tricyclic antidepressants – intravaginal ejaculatory latency time outcomes

Intravaginal ejaculatory latency time outcomes were reported by the two crossover RCTs[39,76] identified from existing reviews and the two further RCTs[132,133] evaluating nasal administration identified for inclusion in this review. IELT data with variance estimates or *p*-values were not available for the remaining RCTs identified from reviews; however, the review summaries of data for TCAs are reported in the next section, *Intravaginal ejaculatory latency time: clomipramine compared with placebo – summary data from existing reviews*.

Intravaginal ejaculatory latency time: clomipramine compared with placebo – summary data from existing reviews When IELT data post treatment were reported for the RCT by Althof *et al.*,[124] a latency increase of 3.37 minutes with clomipramine 25 mg and of 6.98 minutes with clomipramine 50 mg was reported. *p*-values or variance estimates were not reported. Placebo was reported as not significantly different from baseline; however, no data were reported. For the RCT by Haensel *et al.*,[127] an increase in latency from 2 to 8 minutes was reported (*p*-value not reported). For the RCT by Strassberg *et al.*,[131] post-treatment IELT was 3.82 minutes with clomipramine, compared with 0.87 minutes with placebo (*p*-value not reported).

When IELT was summarised across trials by reviews, Waldinger *et al.*[52] reported that, across RCTs, non-RCTs and single-arm studies, the mean percentage increase in delaying ejaculation was 512% (95% CI 234% to 1122%) with clomipramine. The reviewers reported a *p*-value compared with placebo of $p < 0.001$. Richardson *et al.*[69] estimated the mean increase in latency over baseline or placebo, combining data from different trials weighted by sample size. The latency increase was 3.66 minutes with clomipramine 25 mg and 5.31 minutes with clomipramine 50 mg. The reviewers reported a significant increase in latency for active treatment compared with baseline or placebo (*p*-values not reported).

TABLE 23 Tricyclic antidepressants: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Abdel-Hamid *et al.* 2001[39] (reviews[35,37,38,52,69,134,135,137,165])	Crossover (single-arm) 5 × 4 week phases each separated by a 2-week washout	Clomipramine 25 mg 3–5 hours precoitus Sildenafil 50 mg 1 hour precoitus Sertraline 50 mg 3–5 hours precoitus Paroxetine 20 mg 3–5 hours precoitus Squeeze technique Total $n = 31$	IELT ≤ 2 minutes	Lifelong	Stopwatch	Modified Erectile Dysfunction Inventory of Treatment Satisfaction, Arabic Anxiety Inventory (scale 0–30)
Althof *et al.* 1995[124] (reviews[68,69])	2–7 weeks	Clomipramine 25 mg/day Clomipramine 50 mg/day Placebo Total $n = 15$ couples	IELT < 2 minutes	NR	Stopwatch	Symptom Checklist-90-Revised, Dyadic Adjustment Scale, State-Trait Anxiety Inventory, Harder Self- Esteem Inventory
Kim and Seo 1998[76] (reviews[52,64–66,69])	Crossover (single-arm). Each agent for 4 weeks, with 1-week washout	Clomipramine 50 mg Fluoxetine 40 mg Sertraline 100 mg Placebo Total $n = 136$	DSM-III	NR	Method NR	A patient self-reported questionnaire was used to obtain information about patient and partner sexual satisfaction
Girgis *et al.* 1982[125] (reviews[52])	6 weeks	Clomipramine Placebo Total $n = 139$	NR	NR	Questionnaire	NR

RCTs extracted from reviews						
RCT	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Goodman 1980[126] (reviews[52])	4–16 weeks	Clomipramine Placebo Total $n = 116$	NR	NR	Questionnaire	NR
Haensel *et al.* 1996[127] (reviews[52,69])	6 weeks	Clomipramine 25 mg as needed (12–24 hours precoitus) Placebo Total $n = 14$	DSM-IV	8 men with primary PE	Subject report	Pelvic thrusts and time ejaculation, orgasm sooner than desired, within 1 to 2 minutes and after fewer than 10 pelvic thrusts

RCTs extracted from reviews						
RCT	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Montorsi *et al.* 1995,[128] (reviews[52])	8 weeks	Clomipramine Placebo Total $n = 33$	NR	NR	Questionnaire	NR
Porto 1981,[129] (reviews[52])	5 weeks	Clomipramine Placebo Total $n = 20$	NR	NR	Subject report	NR
Segraves *et al.* 1993,[130] (reviews[52])	3–5 weeks	Clomipramine 25–50 mg as needed (6 hours precoitus) Placebo Total $n = 20$	NR	NR	Subject report	NR
Strassberg *et al.* 1999,[131] (reviews[52])	2 weeks per treatment	Clomipramine 25 mg as needed (4–6 hours precoitus) Placebo Total $n = 23$	NR	NR	Subject report	NR

continued

TABLE 23 Tricyclic antidepressants: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Further RCTs identified by searches (not captured in reviews)						
RCT (country), risk of bias	**Duration**	**Treatments *Numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Akilov *et al.* 2011[132] (Uzbekistan), unclear	8 weeks	Clomipramine 4 mg nasal spray ($n = 19$) Placebo nasal spray ($n = 15$) *Total* n *33/34 (97%),* n *by group NR*	IELT < 2 minutes during least 6 last months	NR	Self-reported	CIPE IIEF-5
Leaker *et al.* 2008[133] (UK), unclear	Crossover: each treatment for five occasions	Inhaled clomipramine 1 mg or placebo (not described) Inhaled clomipramine 2 mg or placebo (not described) Before intercourse for a maximum of five occasions (*n* NR) *39 analysed in intention to treat*	IELT of 2 minutes during run-in	NR	Stopwatch	NR
Tuncel *et al.* 2008[107] (Turkey), unclear	Treatment 2 months, assessment 'after eight sexual attempts'	Clomipramine 25 mg/day ($n = 23$) Sertraline 50 mg/day ($n = 20$) Terazosin 5 mg/day ($n = 25$) Placebo ($n = 22$) *Clomipramine, 23/23 (100%)* *Sertraline, 20/20 (100%)* *Terazosin, 25/25 (100%)* *Placebo, 22/22 (100%)*	WHO ICD-10	NR	IELT not assessed	Clinical responses (assume control of ejaculation) self-assessed

DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*-Third Edition; IIEF-5, 5-item version of the International Index of Erectile Function; NR, not reported.

Intravaginal ejaculatory latency time: clomipramine compared with phosphodiesterase-5 inhibitors or selective serotonin reuptake inhibitors The between-group difference in mean IELT change (minutes) following a 4-week randomised crossover comparison[39] was 10.00 minutes in favour of sildenafil compared with clomipramine [MD (fixed effect); 95% CI 6.32 to 13.68 minutes; $p < 0.00001$]. Comparisons of clomipramine 25 mg with sertraline, paroxetine or the squeeze technique were not statistically significant (*Figure 12*). A paired analysis could not be undertaken for approximation purposes for this study. Data from this trial were not pooled with other RCTs in any meta-analysis in this assessment report. Summary results for these and all other meta-analyses are presented in *Table 24*.

Intravaginal ejaculatory latency time: clomipramine compared with selective serotonin reuptake inhibitors or placebo The crossover trial by Kim and Seo[76] reported that mean [standard deviation (SD)] post-treatment IELT (minutes) was 2.30 minutes (SD 2.08 minutes) with fluoxetine 40 mg, 4.27 minutes (SD 5.68 minutes) with sertraline 100 mg, 5.75 minutes (SD 6.68 minutes) with clomipramine 50 mg and 2.27 minutes (SD 3.78 minutes) with placebo, and that IELT was significantly increased in all treatment phases ($p < 0.001$). The between-group comparisons from this study estimated in RevMan for this assessment report are presented in *Figure 13*. The between-group difference in mean IELT (minutes) was 3.45 minutes in favour of clomipramine 100 mg compared with fluoxetine [MD (fixed effect); 95% CI 1.65 to 5.75 minutes; $p = 0.003$] and 3.48 minutes in favour of clomipramine 100 mg compared with placebo [MD (fixed effect); 95% CI 0.97 to 5.99 minutes; $p = 0.007$]. The comparison of clomipramine with sertraline was not statistically significant (*Figure 13*). A paired analysis could not be undertaken for approximation purposes for this study. Data from this trial were not pooled with other RCTs in any meta-analysis in this assessment report.

Intravaginal ejaculatory latency time: clomipramine nasal spray compared with placebo The between-group difference in mean IELT (minutes) post treatment, based on one RCT[132] ($n = 34$), was 1.68 minutes [MD (fixed effect) 95% CI 1.06 to 2.29 minutes; $p < 0.00001$] in favour of the clomipramine spray (figure not presented). The RCT by Leaker *et al.*[133] reported end of study IELT values without variance estimates. The authors reported a *p*-value of $p = 0.0108$ for the comparison of inhaled clomipramine 2 mg compared with placebo and that the comparison of inhaled clomipramine 1 mg with placebo was not statistically significant (*p*-value not reported).

Assessment of effectiveness: tricyclic antidepressants – other outcomes

With the exception of the RCTs that were reported only in the review by Waldinger *et al.*,[52] all of the included trials reported one or more outcomes in addition to IELT. However, these outcomes were diverse across the include trials and were often not reported in sufficient detail to permit any pooling across trials (*Table 25*).

Other outcomes: clomipramine compared with phosphodiesterase-5 inhibitors, selective serotonin reuptake inhibitors, alpha-blockers or placebo In the crossover study by Abdel-Hamid *et al.*,[39] Erectile Dysfunction Inventory of Treatment Satisfaction (EDIT) scores appeared lower with clomipramine than with sildenafil or paroxetine. Kim and Seo[76] reported that a sexual satisfaction rating was greater with clomipramine than other therapies; however, no data for clomipramine or *p*-value were reported. Tuncel *et al.*[107] reported that clomipramine, sertraline and terazosin were all significantly better than placebo on ejaculation control, but that there was no significant difference between the active treatments on this outcome.

Other outcomes: clomipramine nasal spray compared with placebo Akilov *et al.*[132] reported that CIPE scores improved significantly with nasal clomipramine; however, there was no significant change in the five-item version of the IIEF scores. Leaker *et al.*[133] assessed IELT sexual satisfaction but did not report any outcome data. The between-group difference in ejaculatory control between inhaled clomipramine and placebo was statistically significant in favour of clomipramine 2 mg spray, but not 1 mg spray.

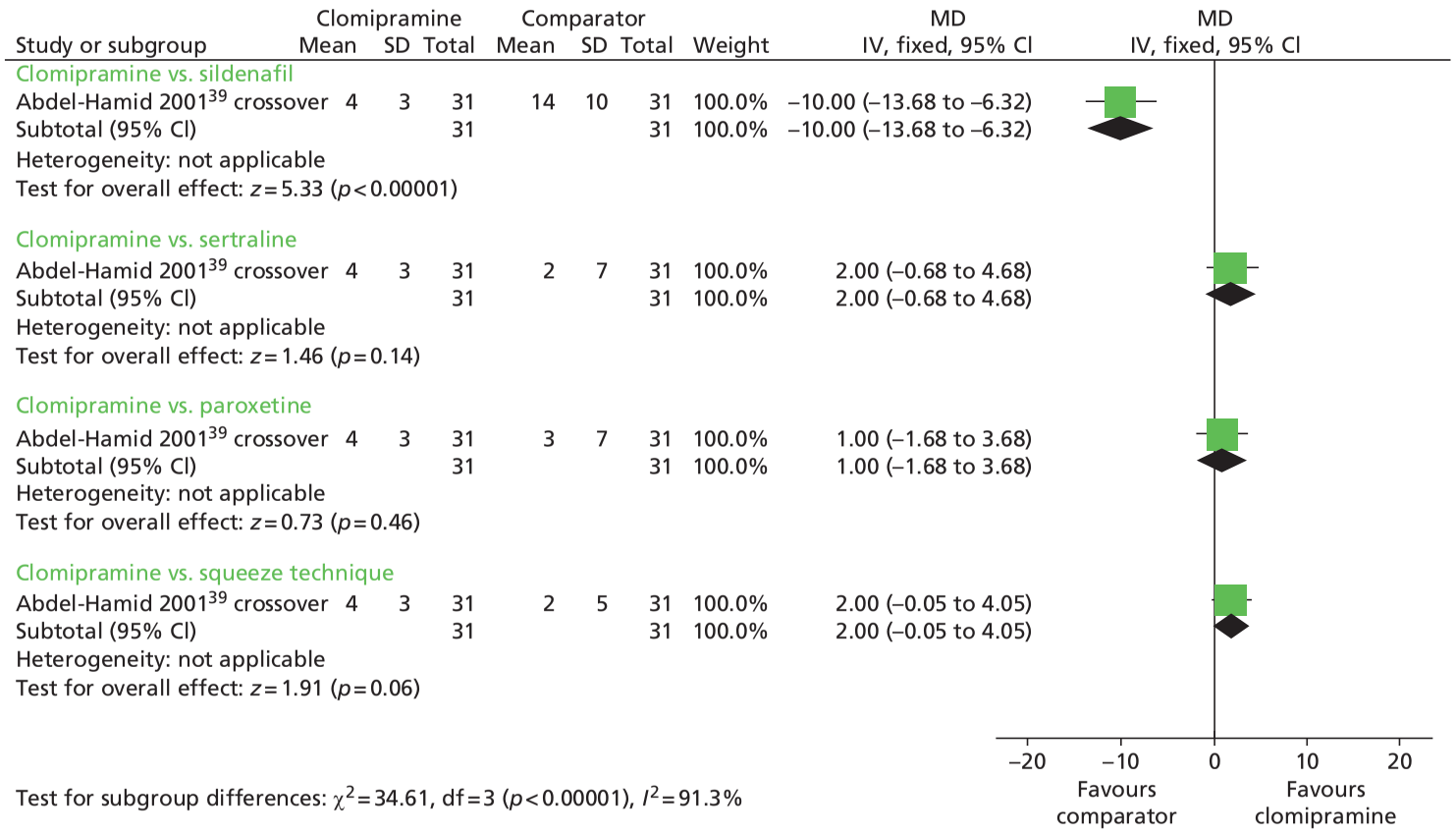

FIGURE 12 Tricyclic antidepressants, clomipramine compared with PDE5 inhibitors: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

TABLE 24 Tricyclic antidepressants: results summary

Comparison							
IELT	**Outcome**	**Study duration**	**No. of RCTs**	**No. of participants**	**Effect estimate (MD) (95% CI)**	**Favours**	***p*-value**
Clomipramine vs. sildenafil	IELT (minutes) – end of study values	Crossover 4-week phases	1[39]	31 per treatment	–10.00 (–13.68 to – 6.32)	Sildenafil	< 0.00001
Clomipramine vs. sertraline	IELT (minutes) – end of study values	Crossover 4-week phases	1[39]	31 per treatment	2.00 (–0.68 to 4.68)	NS	0.14
Clomipramine vs. paroxetine	IELT (minutes) – end of study values	Crossover 4-week phases	1[39]	31 per treatment	1.00 (–1.68 to 3.68)	NS	0.46
Clomipramine vs. squeeze technique	IELT (minutes) – end of study values	Crossover 4-week phases	1[39]	31 per treatment	2.00 (–0.05 to 4.05)	NS	0.06
Clomipramine vs. fluoxetine	IELT (minutes) – end of study values	Crossover 4-week phases	1[76]	36 per treatment	3.45 (1.16 to 5.74)	Clomipramine	0.003
Clomipramine vs. sertraline	IELT (minutes) – end of study values	Crossover 4-week phases	1[76]	36 per treatment	1.48 (–1.38 to 4.34)	NS	0.31
Clomipramine vs. placebo	IELT (minutes) – end of study values	Crossover 4-week phases	1[76]	36 per treatment	3.48 (0.97 to 5.99)	Clomipramine	0.007
Clomipramine vs. placebo	IELT various subjective and objective assessment measures	Varies	Varies – review summaries	Varies	Review summaries (including non-RCTs): % increase in delay in ejaculation: 512% (234–1122%)[52] Latency increase over baseline or placebo: clomipramine 25 mg, 3.66 minutes; 50 mg, 5.31 minutes	Clomipramine	NR
Inhaled 4mg clomipramine vs. placebo	IELT (minutes) – end of study values	8 weeks	1[132]	34	1.68 (1.06 to 2.29)	Clomipramine 4 mg	< 0.00001
Inhaled clomipramine 1 or 2 mg vs. placebo	IELT (minutes) – end of study values	Crossover each five occasions	1[133]	39	Not assessed	NS (1 mg), clomipramine 2 mg	NR, 0.0108

continued

TABLE 24 Tricyclic antidepressants: results summary (*continued*)

Comparison							
IELT	**Outcome**	**Study duration**	**No. of RCTs**	**No. of participants**	**Effect estimate (MD) (95% CI)**	**Favours**	***p*-value**
Other outcomes							
Clomipramine vs. PDE5 inhibitors, SSRIs or placebo	Other effectiveness outcomes (various)	Crossover 4-week phases	2[39,76]	31 and 36 per treatment	Evidence from one crossover trial suggests treatment satisfaction scores was lower with clomipramine than sildenafil or paroxetine.[39] Evidence from one crossover trial suggests that sexual satisfaction rating was greater with clomipramine than other therapies[76]		
		2 months	1[107]	90	Evidence from one RCT suggests no difference between clomipramine, sertraline and terazosin in ejaculatory control		
Inhaled clomipramine vs. placebo	Other effectiveness outcomes (various)	8 weeks or five occasions	2[132,133]	34 and 39	Evidence from one RCT suggested nasal clomipramine improved CIPE scores but not IIEF-5 scores.[132] Evidence from one RCT suggested ejaculatory control was statistically improved for clomipramine 2 mg spray, but not 1 mg spray, over placebo[133]		
Clomipramine (oral) vs. placebo	AEs	2–7 weeks	2[76,124]	15 couples	Evidence from one RCT suggests a greater proportion of reporting of dry mouth, feeling 'different', and constipation with 50 mg compared with 25 mg.[76] Evidence from one crossover trial suggests a greater proportion of patients receiving clomipramine experienced AEs than when receiving fluoxetine, sertraline or placebo[124]		
Inhaled clomipramine vs. placebo	AEs	RCT 8 weeks	1[132]	34	Clomipramine 4 mg, nasal irritation, dry mouth and headache		
		Crossover five occasions	1[133]	39	Clomipramine 1 and 2 mg – dose-related: local irritation (cough, throat irritation, respiratory tract irritation)		
		2 months	1[107]	90	Evidence from one RCT suggests no difference between clomipramine, sertraline and terazosin in AEs		

IIEF-5, 5-item version of the International Index of Erectile Function; NR, not reported; NS, not significant.

FIGURE 13 Tricyclic antidepressants, clomipramine compared with SSRIs or placebo: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

TABLE 25 Tricyclic antidepressants: outcomes other than IELT and AEs

RCT, duration	Treatment	Outcome measure	Results of sexual satisfaction score	Between-group difference reported as significant	AEs
Abdel-Hamid *et al.* 2001,[39] 4 weeks	Clomipramine 25 mg	Sexual satisfaction score	Sildenafil, 3; clomipramine, 1.1; sertraline, 1; paroxetine, 1.2; squeeze technique, 0.6	Unclear	Headache, flushing, and nasal congestion: sildenafil, 18%
	Sertraline 50 mg	EDITS (scale 0–5)	Clomipramine, 11; sertraline, 11; sildenafil, 30; paroxetine, 9; squeeze technique, 6	Unclear	The incidence of side effects was similar among groups. Numbers NR
	Sildenafil 50 mg	Arabic Anxiety Inventory (scale 0–30)	Unclear if reported values are means or medians. No variance estimates or *p*-values reported		
	Paroxetine 20 mg				
	Squeeze technique				
	Total $n = 31$				
Akilov *et al.* 2011,[132] 8 weeks	Clomipramine 4 mg nasal spray ($n = 19$)	CIPE	CIPE change from baseline: nasal clomipramine – $p < 0.05$; placebo – NR	Unclear	Nasal irritation: Cl spray, $n = 3$; placebo, $n = 1$
	Placebo nasal spray ($n = 15$)	IIEF-5	IIEF-5 change from baseline: nasal clomipramine – $p > 0.01$; placebo – $p > 0.01$	Unclear	Dry mouth and headache: Cl spray: $n = 2$ (caused discontinuation in $n = 1$)
Althof *et al.* 1995,[124] 2 to 7 weeks	Clomipramine 25 mg	Symptom Checklist- 90-Revised, Dyadic Adjustment Scale, State-Trait Anxiety Inventory, Harder Self-Esteem Inventory	NR	NR	Clomipramine 25 mg/day: dry mouth (7%), feeling 'different' (8%), constipation (1%)
	Clomipramine 50 mg				Clomipramine 50 mg/day: dry mouth (33%), feeling 'different' (21%), constipation (18%)
	Placebo				
	Total $n = 15$ couples				

RCT, duration	Treatment	Outcome measure	Results of sexual satisfaction score	Between-group difference reported as significant	AEs
Haensel *et al.* 1966,[127] 6 weeks	Clomipramine 25 mg Placebo Total $n = 24$	Pelvic thrusts and time ejaculation, orgasm sooner than desired, within 1–2 minutes and after fewer than 10 pelvic thrusts	NR	NR	NR
Montorsi *et al.* 1995,[128]	Clomipramine Placebo	NR	NR	NR	NR
Porto 1981[129]	Clomipramine Placebo	NR	NR	NR	NR
Segraves *et al.* 1993[130]	Clomipramine Placebo	NR	NR	NR	NR
Strassberg *et al.* 1999[131]	Clomipramine Placebo	NR	NR	NR	NR
Kim and Seo 1998,[76] each agent for 4 weeks, with 1-week washout	Clomipramine 50 mg Fluoxetine 40 mg Sertraline 100 mg Placebo Total $n = 36$	Patient self-reported questionnaire on patient and partner sexual satisfaction	Sexual satisfaction, *n*/N 'yes': satisfaction rating greater with clomipramine (*n* NR). *p*-value for between-group difference NR	Results of sexual satisfaction ratings were reported as statistically significant	Percentage experiencing AEs: clomipramine 50 mg, 23%; fluoxetine 40 mg, 13%; sertraline 100 mg, 12%. Placebo, NR. *p*-value for clomipramine vs. sertraline and fluoxetine $p < 0.05$
Leaker *et al.* 2008,[133] each treatment for five occasions	Inhaled clomipramine 1 mg or placebo Inhaled clomipramine 2 mg or placebo 39 analysed	IVELT sexual satisfaction score Ejaculatory control (no details of instrument)	IVELT – no data or *p*-value Ejaculatory control: inhaled clomipramine 1 mg vs. placebo – *p*-value NR; inhaled clomipramine 2 mg vs. placebo – $p = 0.0082$	Unclear Yes for clomipramine 2 mg spray	Dose-related incidence of AEs characterised by local irritation for the 2 mg group – cough, 70%; throat irritation, 70%; and respiratory tract irritation 35%

continued

TABLE 25 Tricyclic antidepressants: outcomes other than IELT and AEs (*continued*)

RCT, duration	Treatment	Outcome measure	Results of sexual satisfaction score	Between-group difference reported as significant	AEs
Tuncel *et al.* 2008,[107] treatment was for 2 months	Clomipramine 25 mg/day ($n = 20$)	Clinical responses (assume control of ejaculation), self-assessed	Ejaculation control: *n*/*N* (%) reporting 'no change', 'improvement', 'under control'	Yes compared with placebo	% AEs: Clomipramine – headache, 34.8%; hypotension, 4%; drowsiness, 8.6%; ejaculation disorder, 0%
	Sertraline 50 mg/day ($n = 23$)		All three treatments were 'superior to placebo' – $p = 0.0017$		Sertraline – headache, 25%; hypotension, 0%; drowsiness, 15%; ejaculation disorder, 0%
	Terazosin 5 mg/day ($n = 25$)		No significant difference in efficacy between 'medical treatments' – $p = 0.53$		Terazosin – headache, 20%; hypotension, 12%; drowsiness, 0%; ejaculation disorder, 8%
	Placebo ($n = 22$)				Placebo – headache, 9.1%; hypotension, 0%; drowsiness, 0%; ejaculation disorder, 0%
					No significant differences between 'medical treatment groups' – $p = 0.204$

IIEF-5, 5-item version of the International Index of Erectile Function; NR, not reported.

Assessment of safety: tricyclic antidepressants – adverse events

Adverse events: clomipramine compared with placebo Althof *et al.*[124] reported the proportion of patients receiving clomipramine 25 mg or 50 mg who experienced dry mouth, feeling 'different' and constipation (number not reported). The proportions were noticeably higher in the 50 mg group than in the 25 mg group (see *Table 25*). Proportions for the placebo group were not reported. Tuncel *et al.*[107] reported that there were no significant differences between clomipramine, sertraline and terazosin in the number of patients reporting AEs of headache, hypotension, drowsiness and ejaculation disorder.

Adverse events: clomipramine compared with phosphodieterase-5 inhibitors or selective serotonin reuptake inhibitor Abdel-Hamid *et al.*[39] reported that the incidence of side effects was similar among groups, but the types of side effects associated with clomipramine were not reported. A greater proportion of patients receiving clomipramine experienced AEs than when receiving fluoxetine, sertraline or placebo in the crossover trial by Kim and Seo.[76] The authors reported that the between-group difference compared with placebo was significant. No other statistical comparison between groups was reported.

Adverse events: clomipramine nasal spray compared with placebo Akilov *et al.*[132] reported that the most common side effect with nasal clomipramine was nasal irritation. Leaker *et al.*[133] reported that the incidence of AEs of local irritation cough, sore throat and respiratory tract infection was dose related (1 mg or 2 mg).

Assessment of effectiveness: tricyclic antidepressants – evidence summary

The current evidence base for clomipramine in the treatment of PE comprises 13 RCTs, 10 captured in low to moderate methodological quality systematic reviews[39,76,107,124–133] and three further RCTs which are at overall unclear risk of bias.[39,76,124–131] Both oral and nasal administration of clomipramine is evaluated in the evidence base. The quality of reporting in some reviews does not facilitate data extrapolation of IELT and other data from RCTs therein.

Evidence from one crossover trial suggests that oral sildenafil is more effective than oral clomipramine in increasing IELT in men with PE.[39] Evidence from another crossover trial suggests that oral clomipramine is more effective than fluoxetine at increasing IELT.[76] There is evidence from one RCT (39 participants)[132] that clomipramine administered nasally (spray) at 4 mg is significantly effective when compared with placebo at increasing IELT [1.68 minutes (95% CI 1.06 to 2.29 minutes); $p < 0.00001$)]. Evidence from a further crossover trial (39 participants) suggests that inhaled clomipramine at 2 mg is also significantly effective compared with placebo.[133] No significant effects are evident at 1 mg. Summary evidence from one review[52] that estimated a weighted mean increase in IELT across included studies and one review that estimated a mean percentage increase in IELT across RCTs, non-RCTs, and from single-arm studies, suggests that oral clomipramine may be more effective than placebo on this outcome.[69]

Various assessment methods in terms of treatment satisfaction, sexual satisfaction and ejaculation control have been used across RCTs to measure the effectiveness of clomipramine. Evidence from one crossover trial suggests that treatment satisfaction is greater with oral sildenafil and paroxetine than with oral clomipramine.[39] Evidence from one crossover trial suggests that sexual satisfaction is greater with oral clomipramine than with SSRIs (fluoxetine and sertraline).[39] Evidence from one RCT suggests that there is no difference between oral clomipramine, sertraline and terazosin in effect on ejaculatory control.[107] Evidence from one RCT suggests that ejaculatory control is better with inhaled clomipramine at 2 mg than 1 mg.[133] Evidence from one crossover trial suggests that clomipramine is associated with a greater incidence of AEs than fluoxetine or sertraline; however, the nature of the AEs is unknown.[76] Evidence from one RCT suggests that there is no significant difference between oral clomipramine, sertraline and terazosin in the number of patients reporting AEs of headache, hypotension, drowsiness and ejaculation disorder.[107]

Nasal clomipramine is associated with nasal, throat and respiratory tract irritation, with greater incidence at 2 mg than 1 mg application.[133]

Clomipramine appears to be more effective than fluoxetine or paroxetine but not as effective as sildenafil in the treatment of PE. However, these findings should be interpreted with caution given that they are extrapolated from poorly reported crossover observations with low patient numbers. Inhaled clomipramine appears effective at increasing IELT but efficacy appears to be dose dependent, as do treatment-related side effects of application-associated irritation. The current evidence base for oral administration in the treatment of PE in terms of both efficacy and safety of clomipramine along with patient acceptability is limited.

Phosphodiesterase-5 inhibitors

Characteristics of included studies: phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors were evaluated by five systematic reviews,[37,134–137] one of which pooled data in a meta-analysis.[134] Two further RCTs evaluating PDE5 inhibitors were identified.[101,120]

Reviews Two of the systematic reviews were conducted in Italy,[134,135] one review was conducted in Australia,[136] one in Israel[137] and one in the USA.[37] Details of the review type, the databases searched and dates, included RCTs and the AMSTAR quality assessment for these reviews of effectiveness are presented in *Table 26*. The overall AMSTAR quality score was 2 out of 11 in three of the reviews,[134,136,137] 3 out of 11 in one review[135] and 4 out of 11 in one review.[37] However, the review by Asimakopoulos *et al.*[134] was the most comprehensive in terms of included studies. Full details of the AMSTAR assessment for these and all other included reviews are presented in *Appendix 4*. The search methodology and inclusion criteria for studies were varied across these reviews. In the review by Asimakopoulos *et al.*,[134] which included a meta-analysis, the authors pooled IELT effect estimates across studies using a standardised MD. These authors also pooled data across different study types (observation studies and RCTs) in the same meta-analysis.

Randomised controlled trials included in reviews The reviews above varied in terms of which RCTs they included. In total, 10 RCTs[39,55,138–145] (total 795 participants) were included in the review by Asimakopoulos *et al.*[134] The other reviews included different subsets of these RCTS. Seven RCTs assessed sildenafil.[39,55,139,142–145] Among these trials the dose was 50 mg or greater, administered a few hours preintercourse. Sildenafil was combined with fluoxetine in one trial[139] and with behavioural therapy in another,[143] i.e. there was no sildenafil-only arm in these two trials. One RCT assessed tadalafil 20mg one to 36 hours preintercourse[141] and two RCTs assessed vardenafil.[138,140] The vardenafil doses for these RCTs were not available from any reviews.

Intravaginal ejaculatory latency time was reported as being measured using a stopwatch in all but one RCT.[55] When reported, duration of the RCTs included in the reviews ranged from 4 weeks to 4 months. Comparators to PDE5 inhibitors within these RCTs were SSRIs (various), clomipramine, behavioural therapy (squeeze technique), CBT, topical anaesthetics (EMLA cream) and placebo. Details of the RCTs extracted from these reviews are presented in *Table 27*. All RCTs in reviews were captured by the search strategy for this assessment report.

Randomised controlled trials not included in reviews The RCT by Culba *et al.*[101] was undertaken in Turkey and patients were randomised to fluoxetine 20 mg per day plus tadalafil 20 mg twice weekly, fluoxetine 20 mg per day alone, or placebo. The authors reported that 158 out of 180 (88%) completed the 10-week follow-up. This study was reported in abstract form only and outcome data were not presented by the treatments evaluated. This trial was considered to be at overall unclear risk of bias. The RCT by Lee *et al.*[120] was undertaken in the Republic of Korea and patients were randomised to dapoxetine 30 mg plus mirodenafil 50 mg or dapoxetine 30 mg plus placebo. All agents were taken 1–3 hours preintercourse. IELT was assessed using a stopwatch. In each group, 98% of patients were analysed. This trial was considered to be at overall low risk of bias and is also evaluated in the section *Selective serotonin reuptake inhibitors licensed for premature ejaculation (dapoxetine)*.

TABLE 26 Phosphodiesterase-5 inhibitors: details of reviews and AMSTAR quality score

Author (country), review type	Databases searched and dates	Included RCTs relevant to this section	AMSTAR review quality assessment
Asimakopoulos *et al.* 2012[134] (Italy), systematic review and meta-analysis	PubMed January 1990 and June 2011	Abdel-Hamid *et al.* 2001,[39] Atan *et al.* 2006,[55] Aversa *et al.* 2009,[138] Hosseini and Yarmohammadi 2007,[139] Mathers *et al.* 2009,[140] Mattos *et al.* 2008,[141] McMahon *et al.* 2005[142] Tang *et al.* 2004,[143] Wang *et al.* 2007,[144] Zhang *et al.* 2005[145]	AMSTAR score, 2/11: • characteristics of included studies reported • conflict of interest statement reported
Aversa *et al.* 2011[135] (Italy), systematic review	MEDLINE up to a May 2010. No start date	Abdel-Hamid *et al.* 2001,[39] Aversa *et al.* 2009,[138] Hosseini *et al.* 2007,[139] Mathers *et al.* 2009,[140] Mattos *et al.* 2008,[141] McMahon *et al.* 2005,[142] Wang *et al.* 2007[144]	AMSTAR score, 3/11: • duplicate study selection extraction • characteristics of included studies reported • conflict of interest statement reported
Burton and Liday 2011[136] (Australia), systematic review	MEDLINE (January 1980–April 2011) and International Pharmaceutical Abstracts (January 1970–April 2011)	Hosseini and Yarmohammadi 2007,[139] Mattos *et al.* 2008,[141]	AMSTAR score, 2/11: • characteristics of included studies reported • conflict of interest statement reported
Chen *et al.* 2007[137] (Israel), systematic review	MEDLINE 1 January 1990 to 28 February 2007	Abdel-Hamid *et al.* 2001,[39] Atan *et al.* 2006,[55] McMahon *et al.* 2005[142]	AMSTAR score, 2/11: • characteristics of included studies reported • conflict of interest statement reported
McMahon *et al.* 2006[37] (USA), systematic review	MEDLINE, Web of Science, PICA[a] and EMBASE between 1998 and 2005	Abdel-Hamid *et al.* 2001,[39] Atan *et al.* 2006,[55] McMahon *et al.* 2005,[142] Tang *et al.* 2004,[143] Zhang *et al.* 2005[145]	AMSTAR score, 4/11: • comprehensive literature search • studies included regardless of publication type • characteristics of included studies reported • conflict of interest statement reported

a Acronym not defined in original study.
AMSTAR review quality criteria: a priori design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; and conflict of interest statement included.

TABLE 27 Phosphodiesterase-5 inhibitors: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/ acquired**	**IELT assessment**	**Other outcomes**
Abdel-Hamid *et al.* 2001[39] (reviews[37,134,135,137])	RCT crossover 4 weeks each 2-week washout	Sildenafil 50 mg 1 hour precoitus Clomipramine 25 mg 3–5 hours precoitus Sertraline 50 mg 3–5 hours precoitus Paroxetine 20 mg 3–5 hours precoitus Squeeze technique (total $n = 31$)	IELT ≤ 2 minutes	Lifelong	Stopwatch	Modified Erectile Dysfunction Inventory of Treatment Satisfaction, Arabic Anxiety Inventory (scale 0–30)
Atan *et al.* 2006[55] (reviews[37,134,137])	8 weeks	Sildenafil 50 mg 45 minutes precoitus ($n = 20$) Sildenafil 50 mg 45 minutes precoitus + topical EMLA 15 minutes precoitus ($n = 15$) Topical EMLA 15 minutes precoitus ($n = 22$) Placebo ($n = 20$)	DSM-IV	Lifelong and acquired	IELT not assessed	Self-reported improvement: 'no change', 'improvement', 'cure'
Aversa *et al.* 2009[138] (reviews[134,135])	NR	Vardenafil ($n = 31$) Placebo ($n = 11$)	NR	Lifelong	Stopwatch	IPE
Hosseini *et al.* 2007[139] (reviews[134–136])	4 months	Sildenafil 50 mg 1 hour precoitus + fluoxetine 20 mg 2–3 hours precoitus ($n = 43$) Fluoxetine 10 mg twice daily for 4 weeks then 20 mg 3 hours precoitus ($n = 48$)	NR	Lifelong	Stopwatch	Intercourse satisfaction (instrument not reported)
Mathers *et al.* 2009[140] (reviews[134,135])	NR	Behavioural therapy (not described) followed by vardenafil ($n = 36$) Behavioural therapy followed by sertraline ($n = 36$)	NR	Lifelong	Stopwatch	PE grade

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/ acquired**	**IELT assessment**	**Other outcomes**
Mattos *et al.* 2008[141] (reviews[134–136])	12 weeks	Tadalafil 20 mg 1–36 hours precoitus ($n = 15$) Fluoxetine 90 mg weekly ($n = 15$) Tadalafil + fluoxetine ($n = 15$) Placebo ($n = 15$)	NR	Lifelong	Stopwatch	NR
McMahon *et al.* 2005[142] (reviews[37,134,135,137])	8 weeks	Sildenafil 50–100 mg 1 hour precoitus ($n = 78$) Placebo ($n = 79$)	DSM-IV, IELT ≤ 2 minutes	Lifelong	Stopwatch	IPE
Tang *et al.* 2004[143] (reviews[37,134])	6 weeks	Sildenafil 50mg + behavioural therapy ($n = 30$) Behavioural therapy ($n = 30$)	NR	NR	Stopwatch	Patient/partner sexual satisfaction (0–5-point Likert scale)
Wang *et al.* 2007[144] (reviews[134,135])	NR	Sildenafil as needed ($n = 60$) Paroxetine ($n = 60$) Squeeze technique ($n = 60$)	NR	Lifelong	Stopwatch	PE grade, intercourse satisfactory score, frequency of intercourse
Zhang *et al.* 2005[141] (reviews[37,134])	12 weeks	Sildenafil 50 mg + sertraline 50 mg 4–6 hours precoitus Sertraline 50 mg 4–6 hours precoitus (Total $n = 72$)	NR	Lifelong and acquired	Stopwatch	IIEF

continued

TABLE 27 Phosphodiesterase-5 inhibitors: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Further RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/ acquired**	**IELT assessment**	**Other outcomes**
Culba *et al.* 2008[101] (Turkey), unclear	10 weeks	Tadalafil 20 mg twice weekly + fluoxetine 20 mg per day	NR	NR	Visual scale of ELTQ	IIEF
		Fluoxetine 20 mg per day				IIEC
		Placebo				PE question of CMASH questionnaire
		(Total $n = 180$)				
		Total 158/180 (88%)				
Lee *et al.* 2012[120] (Republic of Korea), low	12 weeks	Mirodenafil 50 mg + dapoxetine 30 mg, 1–3 hours precoitus ($n = 63$)	DSM-IV	Lifelong	Stopwatch	Time from foreplay to beginning intercourse
		Dapoxetine 30 mg + placebo, 1–3 hours precoitus ($n = 57$)				OSAT
		Mirodenafil + dapox, 62/63 (98%)				PEP
		Dapoxetine + placebo, 56/57 (98%)				

CMASH, Center for Marital and Sexual Health; ELTQ, ejaculatory latency time questionnaire; IIEC, International Index of Ejaculatory Control; NR, not reported.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews, and the overall study quality assessment (AMSTAR[33] for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 27*.

Assessment of effectiveness: phosphodiesterase-5 inhibitors – intravaginal ejaculatory latency time outcomes

For three RCTs, IELT data suitable for meta-analysis were not available. One RCT[55] that evaluated sildenafil and EMLA cream did not assess IELT. Post-treatment IELT data were available for one RCT assessing sildenafil and fluoxetine;[139] however, no variance estimates or *p*-values were reported. In one RCT assessing tadalafil and fluoxetine,[101] no IELT data were reported. These trials were therefore not included in any IELT meta-analysis in this assessment report.

Evidence synthesis intravaginal ejaculatory latency time

Phosphodiesterase-5 inhibitors compared with placebo The between-group difference in mean increase in IELT (minutes) was 2.59 minutes in favour of tadalafil compared with placebo at 8 weeks [MD (fixed effect); 95% CI 1.28 to 3.90 minutes; $p = 0.0001$]. However, the between-group difference at 12 weeks between sildenafil and placebo was not significant [MD (fixed effect) 1.03 minutes; 95% CI –0.39 to 2.45 minutes; $p = 0.16$]. The pooled effect estimate across these RCTs ($I^2 = 59.9\%$, random effects) was 1.84 minutes (95% CI 0.31 to 3.36 minutes; $p = 0.02$). The between-group difference in geometric mean increase in IELT from one RCT[138] was 3.80 minutes in favour of vardenafil compared with placebo [MD (fixed effect); 95% CI 3.30 to 4.30 minutes; $p < 0.00001$]. The forest plot for this analysis is presented in *Figure 14*. Results for this and all other meta-analyses are presented in *Table 28*.

Intravaginal ejaculatory latency time: phosphodiesterase-5 inhibitors compared with selective serotonin reuptake inhibitors or tricyclic antidepressants The between-group difference in mean IELT change (minutes) following a 4-week randomised crossover comparison[39] was 12.00 minutes in favour of sildenafil compared with sertraline [MD (fixed effect); 95% CI 7.70 to 16.30 minutes; $p < 0.00001$], 11.00 minutes in favour of sildenafil compared with paroxetine [MD (fixed effect); 95% CI 6.70 to 15.30 minutes; $p < 0.00001$] and 10.00 minutes in favour of sildenafil compared with clomipramine [MD (fixed effect) 95% CI 6.32 to 13.68 minutes; $p < 0.00001$]. A paired analysis could not be undertaken for approximation purposes for this study. Data from this trial were not pooled with other RCTs in any meta-analysis in this assessment report. This trial is also evaluated in the *Behavioural interventions, Selective serotonin reuptake inhibitors not currently licensed for premature ejaculation, Selective serotonin reuptake inhibitors licensed for premature ejaculation* and *Tricyclic antidepressants* sections.

The between-group difference in mean increase in IELT was 1.26 minutes in favour of sildenafil compared with paroxetine (duration unclear) [MD (fixed effect); 95% CI 0.81 to 1.71 minutes; $p < 0.00001$]. The between-group difference in mean increase in IELT (minutes) between tadalafil and fluoxetine at 12 weeks was –0.06 minutes [MD (fixed effect); 95% CI –1.56 to 1.44 minutes; $p = 0.94$].

The between-group difference in mean increase in IELT was 1.89 minutes in favour of behavioural therapy followed by vardenafil compared with behavioural therapy followed by sertraline (duration unclear) [MD (fixed effect); 95% CI, 0.54 to 3.24 minutes; $p = 0.006$]. A moderate level of heterogeneity was observed across the non-crossover RCTs comparing PDE5 inhibitors with SSRIs ($I^2 = 47\%$). The between-group difference in mean increase in IELT across these RCTs (random effects) was 1.14 minutes [95% CI 0.31 to 1.96 minutes; $p = 0.007$].

The forest plot for these comparisons is presented in *Figure 15*.

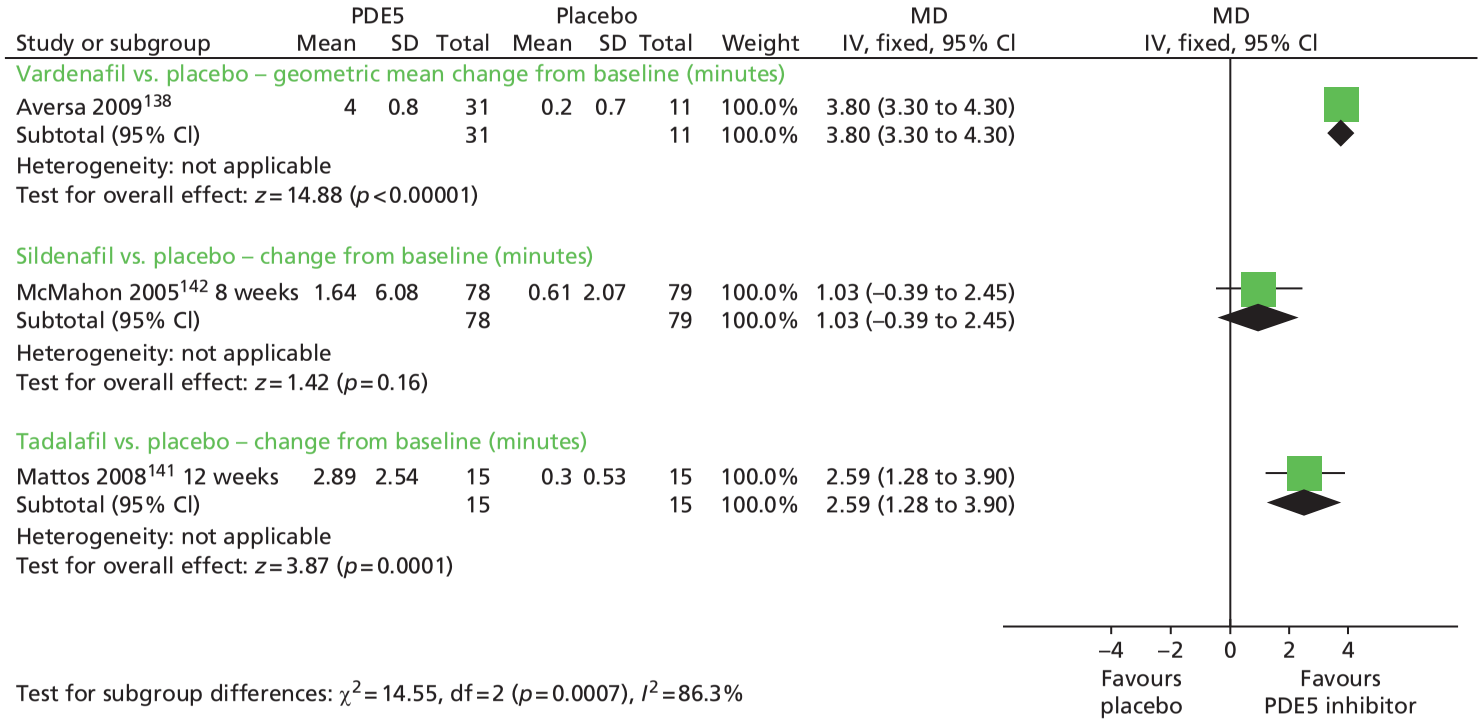

FIGURE 14 Phosphodiesterase-5 inhibitors compared with placebo: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

TABLE 28 Phosphodiesterase-5 inhibitors: results summary

Comparison	Outcome	*n* RCTs[a]	Participants	Model	MD effect estimate (95% CI)	Favours	*p*-value
Vardenafil vs. placebo	IELT (minutes) – geometric mean change from baseline	1[138]	42	N/A	3.80 (3.30 to 4.30)	Vardenafil	< 0.00001
Sildenafil vs. placebo	IELT (minutes) – end of study values	1[142]	157	N/A	1.03 (–0.39 to 2.45)	NS	0.16
Tadalafil vs. placebo	IELT (minutes) – change from baseline	1[141]	30	N/A	2.59 (1.28 to 3.90)	Tadalafil	0.0001
Sildenafil vs. sertraline	IELT (minutes) – single-arm, randomised crossover	1[39] crossover	31	N/A	12.00 (7.70 to 16.30)	Sildenafil	< 0.00001
Sildenafil vs. paroxetine	IELT (minutes) – single-arm, randomised crossover	1[39] crossover	31	N/A	11.00 (6.70 to 15.30)	Sildenafil	< 0.00001
Sildenafil vs. paroxetine	IELT (minutes) – change from baseline	1[144]	120	N/A	1.26 (0.81 to 1.71)	Sildenafil	< 0.00001
Tadalafil vs. fluoxetine	IELT (minutes) – change from baseline	1[145]	30	N/A	–0.06 (–1.56 to 1.44)	NS	0.94
BT then vardenafil vs. BT then sertraline	IELT (minutes) – change from baseline	1[140]	72	N/A	1.89 (0.54 to 3.24)	Vardenafil	0.006
Sildenafil vs. clomipramine	IELT (minutes) – single-arm, randomised crossover	1[39] crossover	31	N/A	10.00 (6.32 to 13.68)	Sildenafil	< 0.00001
PDE5 inhibitors + SSRIs vs. SSRIs	IELT (minutes)	3[120,141,145]	222	Fixed effect $I^2 = 0\%$	1.70 (1.64 to 1.76)	PDE5 + SSRI	< 0.00001
Sildenafil vs. squeeze technique	IELT (minutes) – single-arm, randomised crossover	1[39] crossover	31	N/A	12.00 (8.06 to 15.94)	Sildenafil	< 0.00001
Sildenafil vs. squeeze technique	IELT (minutes) – change from baseline	1[144]	120	N/A	3.56 (3.16 to 3.96)	Sildenafil	< 0.00001
Sildenafil + BT vs. BT	IELT (minutes) – end of study values	1[143]	60	N/A	1.81 (1.53 to 2.09)	Sildenafil	< 0.00001

BT, behavioural therapy; N/A, not applicable; NS, not significant.
a Crossover indicates that the estimate is from a crossover RCT.

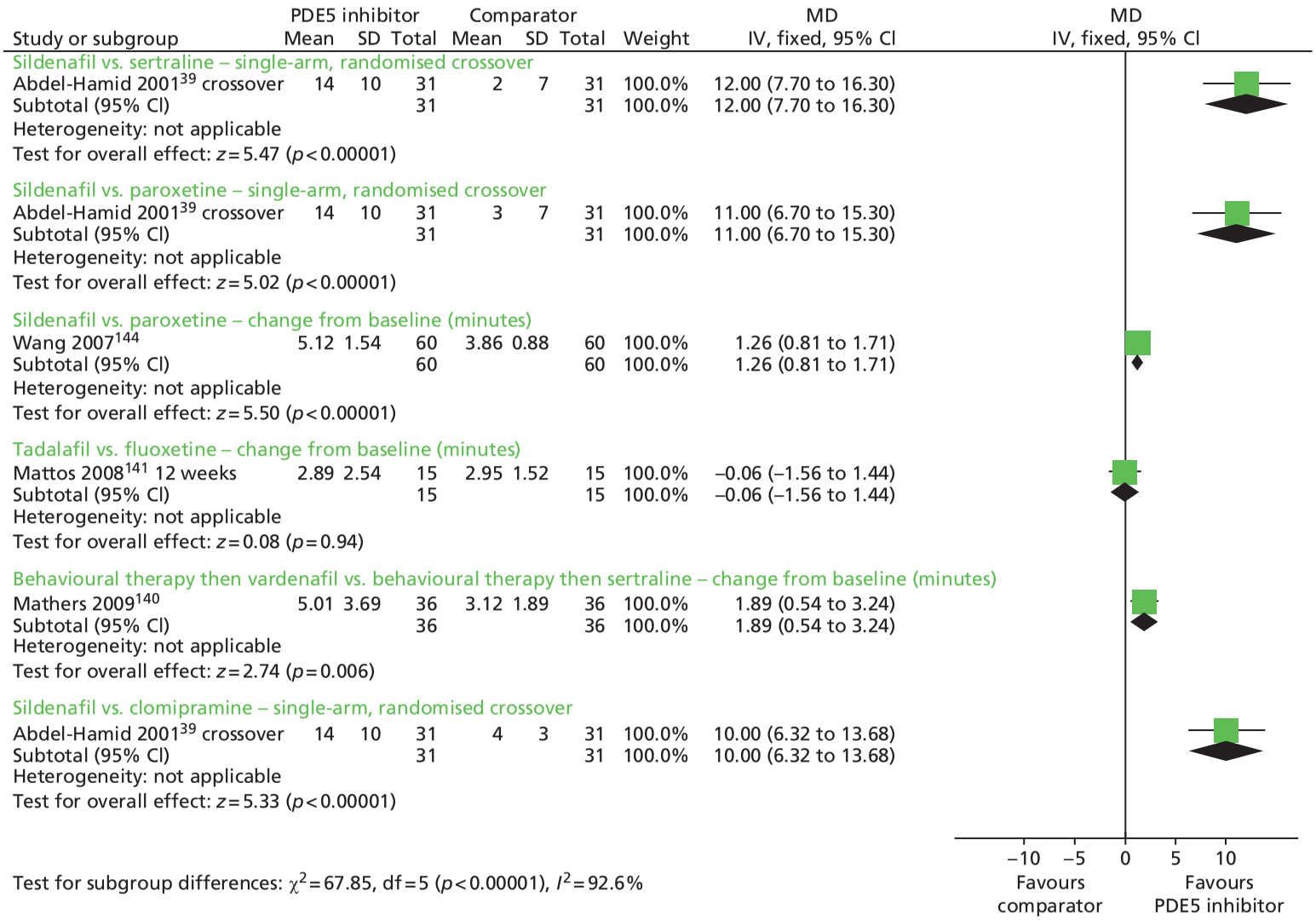

FIGURE 15 Phosphodiesterase-5 inhibitors compared with SSRIs or TCAs: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

Intravaginal ejaculatory latency time: phosphodiesterase-5 inhibitors plus selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors Meta-analysis of mean IELT (minutes) at 12 weeks, based on three RCT comparisons[120,141,145] (222 participants), displayed low heterogeneity ($I^2 = 0\%$). The pooled MD in IELT in favour of PDE5 inhibitors plus SSRIs compared with PDE5 inhibitors alone was 1.70 minutes [MD (fixed effect); 95% CI 1.64 to 1.76 minutes; $p < 0.00001$]. Of note, the trial evaluating sildenafil plus sertraline by Zhang *et al.*,[145] which was highly significant, was awarded 99.9% of the weight in the analysis. The forest plot for this analysis is presented in *Figure 16*.

Intravaginal ejaculatory latency time: phosphodiesterase-5 inhibitors compared with behavioural interventions The between-group difference in mean IELT change (minutes) following a 4-week randomised crossover comparison[39] was 12.00 minutes in favour of sertraline compared with the squeeze technique [MD (fixed effect); 95% CI 8.06 to 15.94 minutes; $p < 0.00001$]. A paired analysis could not be undertaken for approximation purposes. Data from this trial were not pooled with other RCTs.

The between-group difference in mean IELT (minutes) post treatment (duration unclear) was 3.56 minutes in favour of sildenafil compared with the squeeze technique [MD (fixed effect); 95% CI 3.16 to 3.96 minutes; $p < 0.00001$]. The between-group difference in mean IELT change (minutes) post treatment was 1.81 minutes in favour of sildenafil plus behavioural therapy compared with behavioural therapy (duration 4 weeks) [MD (fixed effect); 95% CI 1.53 to 2.09 minutes; $p < 0.00001$]. A high level of heterogeneity was observed across the non-crossover RCTs comparing PDE5 inhibitors with behavioural interventions ($I^2 = 97\%$, meta-analysis not undertaken). The forest plot for this analysis is presented in *Figure 17*.

Assessment of effectiveness: phosphodiesterase-5 inhibitors – other outcomes

Outcomes other than IELT were reported across the RCTs that were captured in reviews using a diversity of instruments (sometimes not reported which) and outcome data. In some instances it was unclear if the metric was an end of study or change from baseline value, or if the value was a mean or median. In a large proportion of the RCTs, a variance estimate for the outcome was not reported. Either *p*-values were not available for the majority of the RCTs or, when they had been reported, it was unclear if this was for a between- or across-group comparison (*Table 29*).

Where between-group differences were estimatable, sildenafil plus behavioural therapy appeared to be more effective than behavioural therapy alone in the number of patients answering 'satisfied' on a patient/partner sexual satisfaction Likert scale ($p = 0.04$). Sildenafil plus sertraline also appeared to be more effective than sertraline alone on the IIEF sexual satisfaction and intercourse frequency domains ($p < 0.001$).

Across the RCTs, *p*-values for outcomes other than IELT either were not reported or, if they were, it was unclear whether the comparison was between groups or from baseline. The available data suggest that, in terms of secondary outcomes to IELT, PDE5 inhibitors are better than placebo and that PDE5 inhibitors combined with another therapy (SSRI or behavioural therapy) are better than the other therapy alone.

Assessment of safety: phosphodiesterase-5 inhibitors – adverse events

Of all the included RCTs, AE data were available for only a subset of trials evaluating sildenafil,[39,55,145] for which it was reported that sildenafil was associated with a greater incidence of flushing and headache. However, data from these trials were insufficient for any meaningful pooling to be undertaken.

Assessment of effectiveness: phosphodiesterase-5 inhibitors – evidence summary

The current evidence base for PDE5 inhibitors in the treatment of PE comprises 10 RCTs[39,55,138–145] captured in five systematic reviews[37,134–137] of low to moderate methodological quality reviews and two further RCTs,[101,120] one of which is at overall low risk of bias and the other at overall unclear risk.

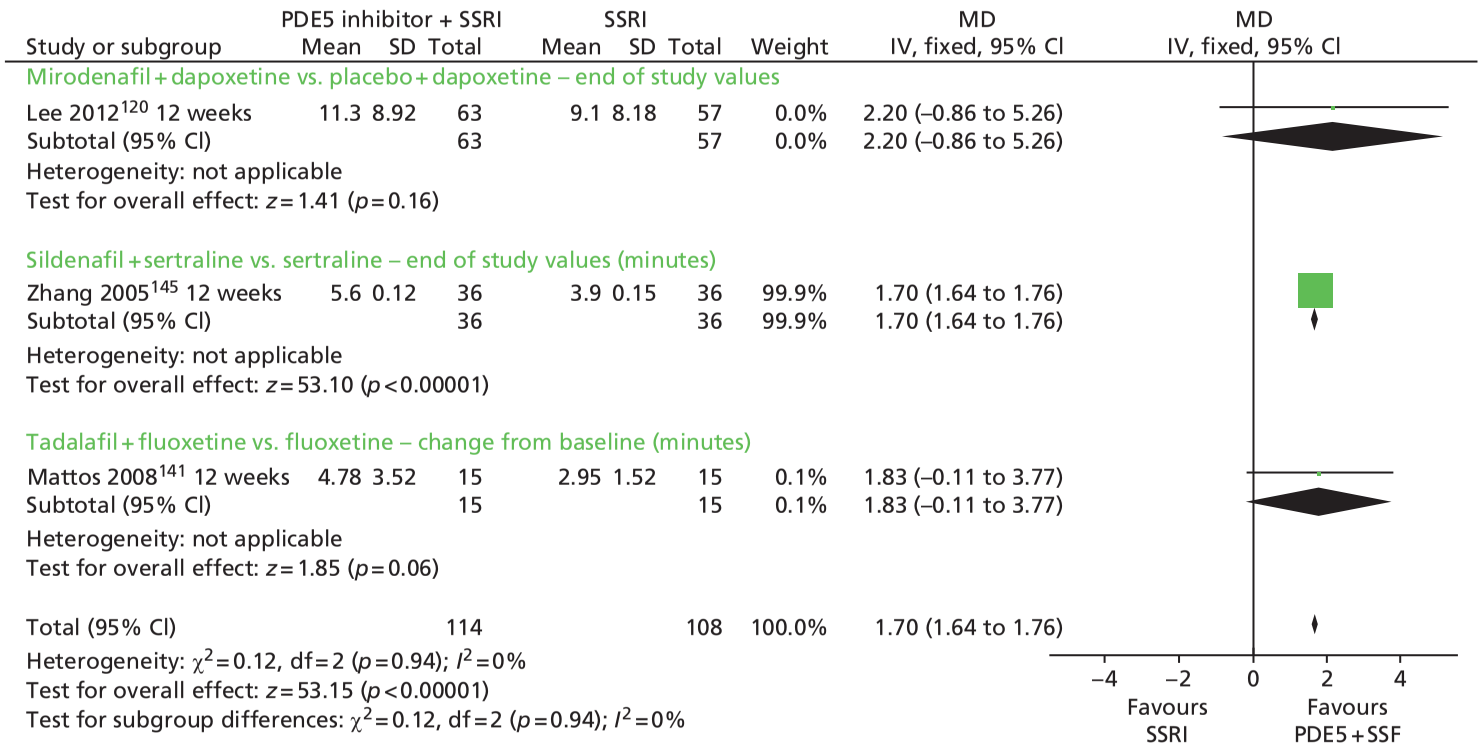

FIGURE 16 Phosphodiesterase-5 inhibitors plus SSRIs compared with SSRIs: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

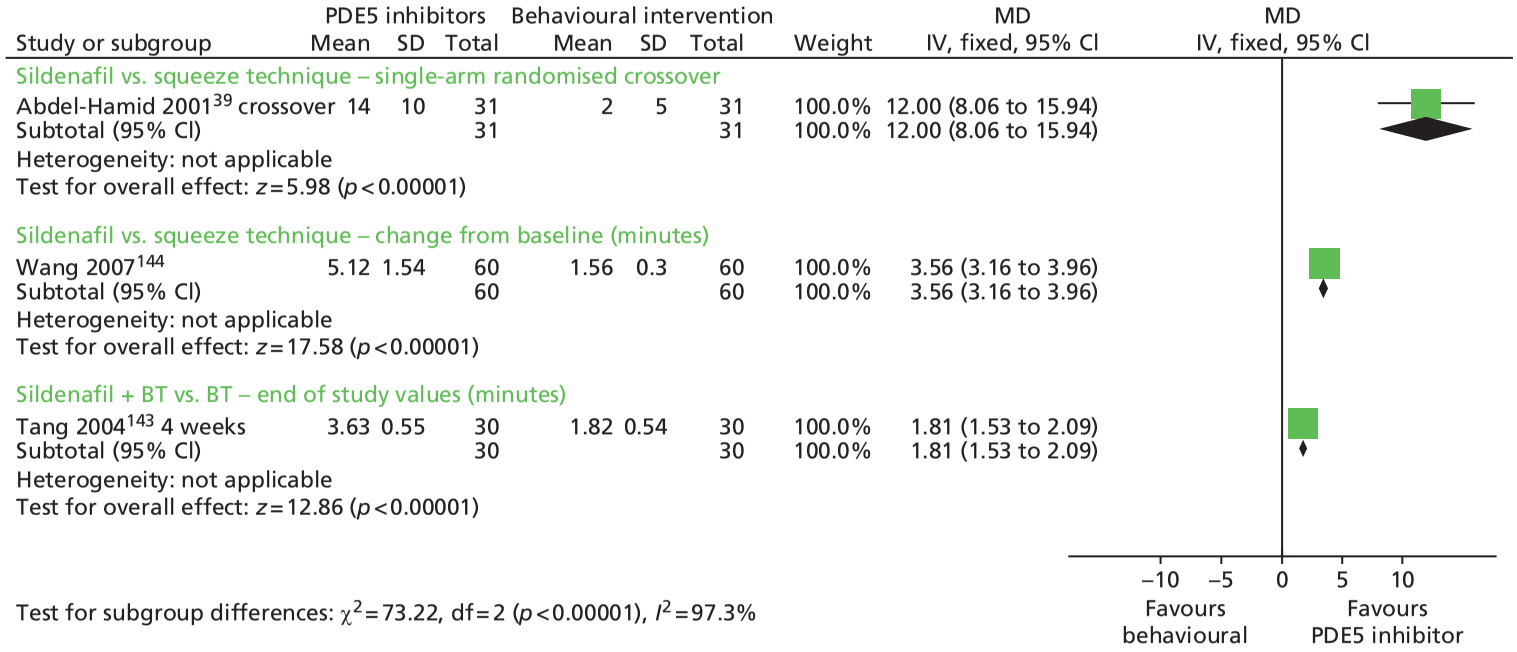

FIGURE 17 Phosphodiesterase-5 inhibitors compared with behavioural interventions: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

TABLE 29 Phosphodiesterase-5 inhibitors: outcomes other than IELT and AEs

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Abdel-Hamid *et al.* 2001,[39] 4 weeks	Sildenafil 50 mg	EDITS (scale 0–5): sexual satisfaction score	Clomipramine, 11; sertraline, 11; sildenafil, 30; paroxetine, 9; squeeze technique, 6	NR	Headache, flushing, and nasal congestion: sildenafil, 18%
	Clomipramine 25 mg	Arabic Anxiety Inventory (scale 0–30)	Clomipramine, 11; sertraline, 10; sildenafil, 15; paroxetine, 12; squeeze technique, 3	NR	The incidence of side effects was similar among groups (numbers NR)
	Sertraline 50 mg		(Unclear if means or medians; no SD or *p*-values reported)		
	Paroxetine 20 mg				
	Squeeze technique				
	(Total $n = 31$)				
Atan *et al.* 2006,[55] 8 weeks	Sildenafil 50 mg ($n = 20$)	Self-reported improvement: 'no change', 'improvement', 'cure'	'Improvement' or 'cure': Sildenafil, 55% ($p > 0.05$)	Unclear	Headache: sildenafil, 26%; flushing: sildenafil, 26%. Only patients receiving sildenafil experienced side effects
	Sildenafil 50 mg + EMLA ($n = 15$)		Sildenafil + EMLA, 86%		
	EMLA ($n = 22$)		EMLA, 77%		
	Placebo ($n = 20$)		Placebo, 40% (NR if *p*-value across or between-groups)		
Aversa *et al.* 2009,[138] duration NR	Vardenafil ($n = 31$)	IPE: sexual satisfaction	% increase (fold increase): vardenafil, 114% (twofold)	Unclear	NR
	Placebo ($n = 11$)		Placebo, % NR, (0-fold) (*p*-value NR)		

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Culba *et al.* 2008,[101] 10 weeks	Tadalafil 20 mg + fluoxetine 20 mg	IELT via visual scale ELTQ and IIEF	Patients who were treated with fluoxetine + tadalafil had better scores than placebo with all questionnaires	Yes	Minor side effects owing to tadalafil and fluoxetine were temporary. No data reported
	Fluoxetine 20 mg	IIEC	Difference was not significant compared with fluoxetine group. No data reported		
	Placebo	PE question of CMASH questionnaire			
	(Total $n = 180$)				
Hosseini *et al.* 2007,[139] 4 months	Sildenafil 50 mg + fluoxetine 20 mg ($n = 43$)	Sexual satisfaction, instrument NR	% increase (fold increase): sildenafil + fluoxetine, 55% (3.3-fold)	Unclear	NR
	Fluoxetine 20 mg		Fluoxetine, 20% (1.2-fold) (p-value NR)		
Lee *et al.* 2012,[120] 12 weeks	Mirodenafil 50 mg + dapoxetine 30 mg ($n = 63$)	Time from foreplay to beginning intercourse	Significant between-group difference in:	Yes, but only some OSAT and PEP outcomes	See dapoxetine section in this assessment report
	Dapoxetine 30 mg + placebo ($n = 57$)	OSAT	OSAT week 4, $p = 0.049$; week 8, $p = 0.026$; week 4 to 8, $p = 0.040$		
		PEP	PEP week 12: perceived control over ejaculation, $p = 0.019$; interpersonal difficulty related to ejaculation, $p = 0.013$; index score, $p = 0.046$		

continued

TABLE 29 Phosphodiesterase-5 inhibitors: outcomes other than IELT and AEs (*continued*)

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Mathers *et al.* 2009,[140] duration NR	BT then vardenafil ($n = 36$)	NR	NR	N/A	Tadalafil: headache (3 patients), facial redness (2 patients), palpitation (2 patients)
	BT then sertraline ($n = 36$)				Fluoxetine: yawning and somnolence (3 patients), asthenia (3 patients), nausea (1 patient)
					Fluoxetine + tadalafil: yawning and somnolence (3 patients), nausea (2 patients), palpitation (1 patient), muscle soreness (1 patient)
Mattos *et al.* 2008,[141] 12 weeks	Tadalafil 20 mg ($n = 15$)	NR	NR	N/A	NR
	Tadalafil 20 mg + fluoxetine 90 mg ($n = 15$)				
	Fluoxetine 90 mg ($n = 15$)				
	Placebo ($n = 15$)				
McMahon *et al.* 2005,[142] 8 weeks	Sildenafil 50–100 mg ($n = 78$)	IPE: sexual satisfaction	Sildenafil, 3.1; placebo, 2.2	Unclear	NR
	Placebo ($n = 79$)	IPE: ejaculatory control	Sildenafil, 1.8; placebo, 1.2	Unclear	NR
		IPE: ejaculatory confidence	Sildenafil, 2.2; placebo, 1.3	Unclear	NR
		Global efficacy	Sildenafil, 48%; placebo, 16%	Unclear	NR
Tang *et al.* 2004,[143] 6 weeks	Sildenafil 50mg + BT ($n = 30$)	Patient/partner composite sexual satisfaction (0–5-point Likert scale)	Sildenafil + BT, 26/30 'satisfied'	Yes	NR
	BT ($n = 30$)		BT, 19/30 'satisfied'		
			Estimated *p*-value 0.04		

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Wang *et al.* 2007,[144] duration NR	Sildenafil ($n = 60$)	Change in intercourse satisfactory score (instrument NR)	% increase (fold increase): sildenafil, 164% (threefold)	Unclear	NR
	Paroxetine ($n = 60$)		Paroxetine, 115% (2.2-fold)		
	Squeeze technique ($n = 60$)		Squeeze technique, 53% (1.8-fold)		
			p-values NR		
Zhang *et al.* 2005,[145] 12 weeks	Sildenafil 50 mg + sertraline 50 mg	IIEF: sexual satisfaction	Sildenafil + sertraline, 13.8	Yes	Sildenafil + sertraline had more AEs (headache, flushing). Numbers NR
	Sertraline 50 mg		Sertraline, 10.8 ($p < 0.001$ between groups)	Yes	
	(Total $n = 72$)	Intercourse frequency (per week)	Sertraline + sildenafil, 2.7		
			Sertraline, 1.9 ($p < 0.005$ between groups)		

BT, behavioural therapy; CMASH, Center for Marital and Sexual Health; ELTQ, ejaculatory latency time questionnaire; IIEC, International Index of Ejaculatory Control; N/A, not applicable; NR, not reported.

Evidence from two RCTs[138,141] suggests that vardenafil (42 participants) and tadalafil (30 participants) are both significantly effective in increasing IELT in men with PE [MD 3.80 minutes (95% CI 3.30 to 4.30 minutes; $p = 0.0001$) and 2.59 minutes (95% CI 1.28 to 3.90 minutes; $p < 0.00001$), respectively] when compared with placebo. Evidence from one RCT (157 participants) suggests that there is no statistically significant difference between sildenafil and placebo.[142]

In comparison with SSRIs, sildenafil appears significantly more effective than paroxetine (one RCT,[144] 120 participants) [MD 1.26 minutes (95% CI 0.81 to 1.71 minutes)] and vardenafil (preceded by behavioural therapy) appears significantly more effective than sertraline preceded by behavioural therapy (one RCT,[140] 72 participants) [MD 1.89 minutes (95% CI 0.54 to 3.24 minutes); $p < 0.00001$ and $p = 0.006$, respectively]. No significant difference was evident between tadalafil and fluoxetine. A crossover RCT of 31 participants also suggests that sildenafil is more effective than paroxetine, sertraline or clomipramine.[39] No significant difference was evident between tadalafil and fluoxetine from one RCT.[145] Pooled effects across three RCTs[120,141,145] (222 participants) suggests that PDE5 inhibitors in combination with a SSRI are significantly more effective than a SSRI alone with sildenafil plus sertraline demonstrating the greatest significant effect [MD 1.70 minutes (95% CI 1.64 to 1.76 minutes); $p < 0.0001$].

In comparison with behavioural interventions, sildenafil appears to be significantly more effective than the squeeze technique (one RCT[144] with 120 participants and one crossover RCT[39] with 31 participants) [(data not pooled) and one RCT[144] with 120 participants (MD 3.56 minutes, 95% CI 3.16 to 3.96 minutes)], and sildenafil combined with behavioural therapy is significantly more effective than behavioural therapy alone (one RCT,[143] 60 participants) [MD 1.81 minutes (95% CI 1.53 to 2.09 minutes)].

Various assessment methods have been used across RCTs to measure effectiveness in terms of patient/partner sexual satisfaction, and other outcomes, although the between-group significance is often unclear or not reported. Outcomes appear to favour PDE5 inhibitors in comparison with placebo and PDE5 inhibitors combined with another therapy (SSRI or behavioural therapy) compared with another therapy (SSRI or behavioural therapy) alone. However, in the current evidence base, data are poorly reported and do not permit any meaningful interpretation of the efficacy of PDE5 inhibiters on efficacy outcomes other than IELT.

There is some evidence suggesting that both sildenafil and tadalafil are associated with a greater incidence of flushing and headache, and that tadalafil is also associated with palpitations. However, these data are difficult to extrapolate in order to estimate any between-group comparisons with other treatments. In addition, AE data are limited across the current evidence base for other PDE5 inhibitors.

Certain PDE5 inhibitors have been evaluated against placebo, while others are evaluated against SSRIs or behavioural therapy, or, in combination with a SSRI or behavioural therapy, have been evaluated against SSRI monotherapy or behavioural monotherapy. This variability of treatment comparisons in RCTs assessing PDE5 inhibitors limits definitive conclusions regarding an appropriate choice in terms of efficacy and safety for the treatment of men with PE. In addition, the long-term effects of PDE5 inhibitors in the treatment of PE are not evaluated in the current evidence base.

Alpha-blockers

Characteristics of included studies: alpha-blockers

Two RCTs were identified that evaluated alpha-blockers[107,146] and both were captured by the search strategy for this assessment report. The RCT by Cavallini[146] was evaluated by two systematic reviews evaluating pharmacotherapies.[52,69] The overall AMSTAR quality score was 1 out of 11 for both of these reviews (see *Table 11*). Full details of the AMSTAR assessment for these and all other included reviews are presented in *Appendix 4*. The RCT by Tuncel *et al.*[107] was identified by the literature search.

Cavallini[146] included men with primary PE with an IELT ≤ 1 minute on more than 50% of occasions. Ninety-one patients were allocated to alfuzosin 6 mg, terazosin 5 mg or vitamin C 1 mg in a crossover design trial, 2 months per treatment phase. Ejaculatory control was assessed by patient self-report. The RCT by Tuncel *et al.*[107] was undertaken in Turkey and 90 patients were randomised to receive clomipramine 25 mg per day, sertraline 50 mg, terazosin 5 mg or placebo. Treatment duration was 2 months, but IELT was not assessed. The authors reported that 90 out of 90 (100%) patients completed the trial. This trial considered to be at overall unclear risk of bias. This trial is also evaluated in the *SSRIs inhibitors* and *PDE5 inhibitors* sections of this report.

Details of these trials are presented in *Table 30*.

Assessment of effectiveness: alpha-blockers – intravaginal ejaculatory latency time outcomes

An objective assessment of IELT was not reported by either of the two RCTs evaluating alpha-blockers identified for inclusion in this assessment report.

Assessment of effectiveness – alpha-blockers: other outcomes

Details of outcome results other than IELT and AEs are presented in *Table 31*.

Other outcomes: terazosin compared with tricyclic antidepressants, selective serotonin reuptake inhibitors or placebo Tuncel *et al.*[107] reported that terazosin, clomipramine and sertraline were all significantly better than placebo on ejaculation control, but that there was no significant difference between the active treatments on this outcome.

Other outcomes: alfuzosin or terazosin compared with vitamin C A significant ejaculatory latency increase was reported for the RCT by Cavallini.[146] The proportion of patients by treatment group with a 'positive' result for this outcome was reported as 46.2% with alfuzosin, 53.7% with terazosin and 24.2% with vitamin C. However, no *p*-values were reported and it was unclear whether the reported 'significant increase' was across or between groups.

Assessment of safety: alpha-blockers – adverse events

Adverse events: clomipramine compared with placebo Tuncel *et al.*[107] reported that there were no significant differences between clomipramine, sertraline and terazosin in the number of patients reporting AEs of headache, hypotension, drowsiness and ejaculation disorder.

Adverse events: alfuzosin or terazosin compared with vitamin C Adverse events were not reported for the RCT by Cavallini.[146]

Assessment of effectiveness: alpha-blockers – evidence summary

The current evidence base for alpha-blockers in the treatment of PE comprises two RCTs,[39,107] one captured in low methodological quality systematic reviews[39] and one further RCT which is at overall unclear risk of bias.[107] An assessment of IELT is not reported for either these trials.

Ejaculation control is reported by both RCTs assessing alpha-blockers. Evidence from one of these trials suggests that terazosin, clomipramine and sertraline were all significantly better than placebo on the outcome of ejaculation control,[107] but that there is no significant difference between the active treatments on this outcome. Other RCT evidence for this outcome is unclear.[39]

One RCT suggests that there is no significant difference between terazosin, clomipramine and sertraline and in the number of patients reporting AEs of headache,[107] hypotension, drowsiness and ejaculation disorder. However, this observation should be interpreted with caution given the unclear methodological

TABLE 30 Alpha-blockers: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/ acquired**	**IELT assessment**	**Other outcomes**
[a]Cavallini 1995[146] (reviews[52,69])	2 months per treatment	Alfuzosin 6 mg Terazosin 5 mg Vitamin C 1 mg Total $n = 91$	IELT ≤1 minute	Lifelong	Method NR	Ejaculatory control
Further RCTs identified by searches (not captured in reviews)						
RCT (country), risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/ acquired**	**IELT assessment**	**Other outcomes**
Tuncel *et al.* 2008[107] (Turkey), unclear	2 months, assessment 'after eight sexual attempts'	Terazosin 5 mg/day ($n = 25$) Clomipramine 25 mg/day ($n = 23$) Sertraline 50 mg/day ($n = 20$) Placebo ($n = 22$) *Terazosin, 25/25 (100%)* *Clomipramine, 23/23 (100%)* *Sertraline, 20/20 (100%)* *Placebo, 22/22 (100%)*	WHO ICD-10	NR	IELT not assessed	Clinical responses (assume control of ejaculation) self-assessed

NR, not reported.
a Crossover study.

TABLE 31 Alpha-blockers: outcomes other than IELT and AEs

RCT duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
[a]Cavallini 1995,[146] 2 months per treatment	Alfuzosin 6 mg Terazosin 5 mg Vitamin C 1 mg Total $n = 91$	Ejaculatory control	Percentage of 'positive' results: alfuzosin, 46.2%; terazosin, 53.7%; vitamin C, 24.2%	Unclear	NR
Tuncel *et al.* 2008,[107] treatment was for 2 months	Sertraline 50 mg/day ($n = 23$)	Ejaculation control, self-assessed	Ejaculation control: *n/N* (%) reporting 'no change', 'improvement', 'under control'	Yes compared with placebo	% AEs:
	Clomipramine 25 mg/day ($n = 20$)		All three treatments were 'superior to placebo' – $p = 0.001$		Clomipramine – headache, 34.8%; hypotension, 4%; drowsiness, 8.6%; ejaculation disorder, 0%
			No significant difference in efficacy between 'medical treatments' – $p = 0.537$		Sertraline – headache, 25%; hypotension, 0%; drowsiness, 15%; ejaculation disorder, 0%
	Terazosin 5 mg/day ($n = 25$)				Terazosin – headache, 20%; hypotension, 12%; drowsiness, 0%; ejaculation disorder, 8%
	Placebo ($n = 22$)				Placebo – headache, 9.1%; hypotension, 0%; drowsiness, 0%; ejaculation disorder, 0%
					No significant differences between 'medical treatment groups' – $p = 0.204$

NR, not reported.
a Crossover study.

quality of the trial. The current evidence base for alpha-blockers in the treatment of PE in terms IELT and other secondary outcomes is limited.

Opioid analgesics

Characteristics of included studies: opioid analgesics

Tramadol was evaluated by three systematic reviews,[147–149] two of which pooled data in a meta-analysis.[148,149] A further two RCTs were identified, one of which evaluated tramadol at 25 mg, 50 mg and 100 mg per day doses (no other comparator or placebo arm),[154] while the other evaluated 25 mg per day against placebo.[155]

Reviews The three systematic reviews were all conducted in China.[147–149] The overall AMSTAR quality score was 1 out of 11 in one of the reviews,[147] 2 out of 11 in another[148] and 6 out of 11 in the last.[149] Details of the review type, the databases searched and dates, relevant included RCTs and the AMSTAR points awarded to these reviews, are presented in *Table 32*. Full details of the AMSTAR assessment for these and all other include reviews are presented in *Appendix 4*. The search methodology and inclusion criteria varied across these reviews. Of the two reviews including a meta-analysis, the review by Wu *et al.*[148] pooled data across different study types

TABLE 32 Opioid analgesics, tramadol: details of reviews and AMSTAR quality score

Author (country) review type	Databases searched and dates	Included RCTs relevant to this section	AMSTAR review quality assessment
Wong and Malde 2013147 (China) systematic review	PubMed 2006 to March 2012	Alghobary *et al.* 2010,[150] Bar-Or *et al.* 2012,[151] Kaynar *et al.* 2012,[152] Safarinejad and Hosseini 2006[153]	AMSTAR score, 1/11: • characteristics of included studies reported
Wu *et al.* 2012[148] (China) systematic review and meta-analysis	The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded Until the end of February 2012, with no lower date limit	Alghobary *et al.* 2010,[150] Bar-Or *et al.* 2012,[151] Kaynar *et al.* 2012,[152] Safarinejad and Hosseini 2006,[153] Xiong *et al.* 2011[46]	AMSTAR score, 2/11: • characteristics of included studies reported • study quality assessed
Yang *et al.* 2013[149] (China) systematic review and meta-analysis	PubMed, EMBASE, CCRT and the Cochrane Database of Systematic Reviews 1980 to April 2012 all databases	Bar-Or *et al.* 2012,[151] Kaynar *et al.* 2012,[152] Safarinejad and Hosseini 2006,[153] Xiong *et al.* 2011[46]	AMSTAR score, 6/11: • duplicate study selection and extraction • comprehensive literature search • characteristics of included studies reported • study quality assessed • appropriate methods used to pool data • conflict of interest statement reported

AMSTAR review quality criteria: a priori design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; and conflict of interest statement included.

(observational studies and RCTs) using a MD. The authors also included different dosing arms from studies separately in the meta-analysis, but included the comparator arm (placebo) against each dosing arm in effect counting participants twice in the analysis. Likewise, the authors also pooled together data from the same arm at different time points (i.e. the same study group was counted twice in the analysis). In the review by Yang *et al.*,[149] the authors pooled IELT effect estimates across studies using a standardised MD.

Randomised controlled trials included in reviews The reviews above varied in terms of which RCTs they included. In total, five RCTs[46,150–153] (total $n = 863$) were included in at least one review. IELT was reported as being assessed using a stopwatch in all five RCTs. Duration of the RCTs included in these reviews ranged from 6 to 12 weeks and comparators to tramadol within the RCTs included in these review were behavioural therapy, paroxetine, or placebo. Tramadol doses varied from 25 mg to 89 mg, taken as needed, usually 2–3 hours preintercourse. Details of the RCTs extracted from these reviews are presented in *Table 33*. All RCTs in reviews were captured by the search strategy for this assessment report.

Randomised controlled trials not included in reviews The RCT by Eassa and El-Shazly[154] was conducted in Egypt and patients were randomised 100 per group to tramadol at 25 mg, 50 mg and 100 mg 2 to 3 hours preintercourse. The authors reported that all patients completed the 24 week follow-up and IELT was stopwatch assessed. Of note, the authors reported a mean baseline IELT of 2.82, 2.79 and 2.99 minutes for each of the treatment groups, respectively. This was noticeably higher than any other RCT, for any treatment, identified for inclusion in this assessment report. The RCT by Generali and Cada[155] was conducted in the USA. Patients were randomised to tramadol 50 mg 2 hours before intercourse or placebo. Fifty-seven patients

TABLE 33 Opioid analgesics, tramadol: characteristics of RCTs included reviews and additional RCTs not captured in reviews

RCTs extracted from reviews						
RCT (source)	**Duration**	**Treatments**	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Alghobary *et al.* 2010[150] (reviews[147,148])	Crossover weeks per treatment (2-week washout)	Tramadol 50 mg ($n = 35$) Paroxetine 20 mg ($n = 35$) 2–3 hours preintercourse	NR	Lifelong	Stopwatch	AIPE
Bar-Or *et al.* 2012[151] (reviews[147–149])	12 weeks	Tramadol 62 mg ($n = 206$) Tramadol 89 mg ($n = 198$) Placebo ($n = 200$) 2–8 hours preintercourse	Ejaculation ≤ 1 minute	Lifelong	Stopwatch	PEP
Kaynar *et al.* 2012[152] (reviews[147–149])	8 weeks	Tramadol 25 mg ($n = 30$) Placebo ($n = 30$) 2 hours preintercourse	IELT ≤ 2 minutes during 90% intercourse episodes	Lifelong	Stopwatch	AEC Sexual satisfaction scores
Safarinejad 2006[153] (reviews[147–149])	8 weeks	Tramadol 50 mg ($n = 29$) Placebo ($n = 28$) 2 hours preintercourse	IELT ≤ 2 minutes during 90% coitus	Lifelong	Stopwatch	IIEF
Xiong *et al.* 2011[46] (reviews[148,149])	12 weeks	Tramadol 50 mg 2 hours preintercourse with behavioural therapy (NR which) ($n = 36$) Behavioural therapy alone ($n = 36$)	IELT ≤ 2 minutes	Lifelong	Stopwatch	IIEF

TABLE 33 Opioid analgesics, tramadol: characteristics of RCTs included reviews and additional RCTs not captured in reviews (*continued*)

Further RCTs identified by searches (not captured in reviews)						
RCT (country risk of bias)	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Eassa and El-Shazly 2013,[154] (Egypt) unclear	24 weeks	Tramadol 25 mg ($n = 100$) Tramadol 50 mg ($n = 100$) Tramadol 100 mg ($n = 100$) 2–3 hours preintercourse *Tramadol 25 mg, 100/100 (100%)* *Tramadol 50 mg, 100/100 (100%)* *Tramadol 100 mg, 100/100 (100%)*	NR	Lifelong	Stopwatch	None
Generali and Cada 2006[155] (USA) unclear	8 weeks	Tramadol 50 mg Placebo 2 hours preintercourse (Total $n = 64$) *Total* n *57/64 (89%),* n *per group NR*	NR	NR	Method NR	IIEF number of acts of coitus per week IIEF intercourse satisfaction

AEC, ability of ejaculation control; NR, not reported.

completed the 8-week study and the IELT assessment method was not reported. Variance estimates for the outcome data were not reported by the authors and were imputed for this assessment report using the reported *p*-values employing methods detailed in the Cochrane Reviewer's Handbook.[31] Both of these trials were considered to be at overall unclear risk of bias.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews, and the overall study quality assessment (AMSTAR[33] for reviews and Cochrane risk of bias assessment[34] for the RCTs not included by reviews) are presented in *Table 33*.

Assessment of effectiveness: opioid analgesics – intravaginal ejaculatory latency time outcomes

Intravaginal ejaculatory latency time outcomes were reported for all of the RCTs identified from existing reviews and the two further RCTs identified for inclusion in this review.

Intravaginal ejaculatory latency time: tramadol compared with placebo Meta-analysis of mean IELT change (minutes) at 8- or 12-week follow-up, based on five RCT study group comparisons from four RCTs ($n = 776$),[151–153,155] displayed moderate heterogeneity ($I^2 = 70\%$). The pooled MD in IELT was 1.35 minutes, significantly favouring tramadol [MD (random effects) 95% CI 0.63 to 2.07 minutes; $p = 0.0002$]. The forest plot for this analysis is presented in *Figure 18*. Summary results for these, and all other meta-analyses, are presented in *Table 33*.

Intravaginal ejaculatory latency time: tramadol compared with paroxetine The between-group difference in mean IELT change (minutes) at 6 weeks, based on one RCT[150] ($n = 70$) was –0.83 minutes (95% CI –1.80 to 0.14 minutes; $p = 0.09$). The forest plot for this analysis is presented in *Figure 18*.

Intravaginal ejaculatory latency time: tramadol with behavioural therapy compared with behavioural therapy alone The between-group difference in mean IELT (minutes) at 12 weeks, based on one RCT[46] ($n = 72$) was 1.65 minutes, significantly favouring tramadol with behavioural therapy (95% CI 0.30 to 3.00 minutes; $p = 0.02$). The forest plot for this analysis is presented in *Figure 18*.

Intravaginal ejaculatory latency time: tramadol 25 mg, 50 mg or 100 mg One RCT[154] ($n = 300$) evaluated three different doses of tramadol. The between-group differences in mean IELT (minutes) at 24 weeks were 10.65 minutes in favour of tramadol 50 mg compared with 25 mg (95% CI 9.76 to 10.76 minutes; $p < 0.00001$); 23.32 minutes in favour of tramadol 100 mg compared with 25 mg (95% CI 22.59 to 24.05 minutes; $p < 0.00001$); and 13.06 minutes in favour of tramadol 100 mg compared with 50 mg (95% CI 12.33 to 13.79 minutes; $p < 0.00001$). The forest plot for this analysis is presented in *Figure 19*.

Assessment of effectiveness: opioid analgesics – other outcomes

With the exception of the RCT by Eassa and El-Shazly[154] that did not report any outcomes other than IELT, all of the included trials reported one or more other outcomes. However, these were diverse across the include trials and were often not reported in sufficient detail to permit any pooling across trials (*Table 34*).

Other outcomes: tramadol compared with placebo Bar-Or *et al.*[151] reported an improvement in 62-mg and 89-mg tramadol dose groups compared with placebo on measures of the PEP ($p < 0.05$ for all). Generali and Cada[155] reported a change from baseline in the IIEF mean number of acts of coitus per week and mean intercourse satisfaction associated with tramadol ($p < 0.05$). However, *p*-values were not reported for the placebo group (data by group not reported). Kaynar *et al.*[152] reported improvements on ability of ejaculation control (AEC) (AEC score: placebo increased from 0.93 to 1.50; tramadol increased from 0.83 to 2.83) and sexual satisfaction scores (placebo increased from 0.80 to 1.33) for tramadol over placebo ($p < 0.001$ for both), although the instrument was not described. Safarinejad and Hosseini[153] reported a between-group difference of $p < 0.05$ on the IIEF intercourse satisfaction score (tramadol mean change 4, placebo –1).

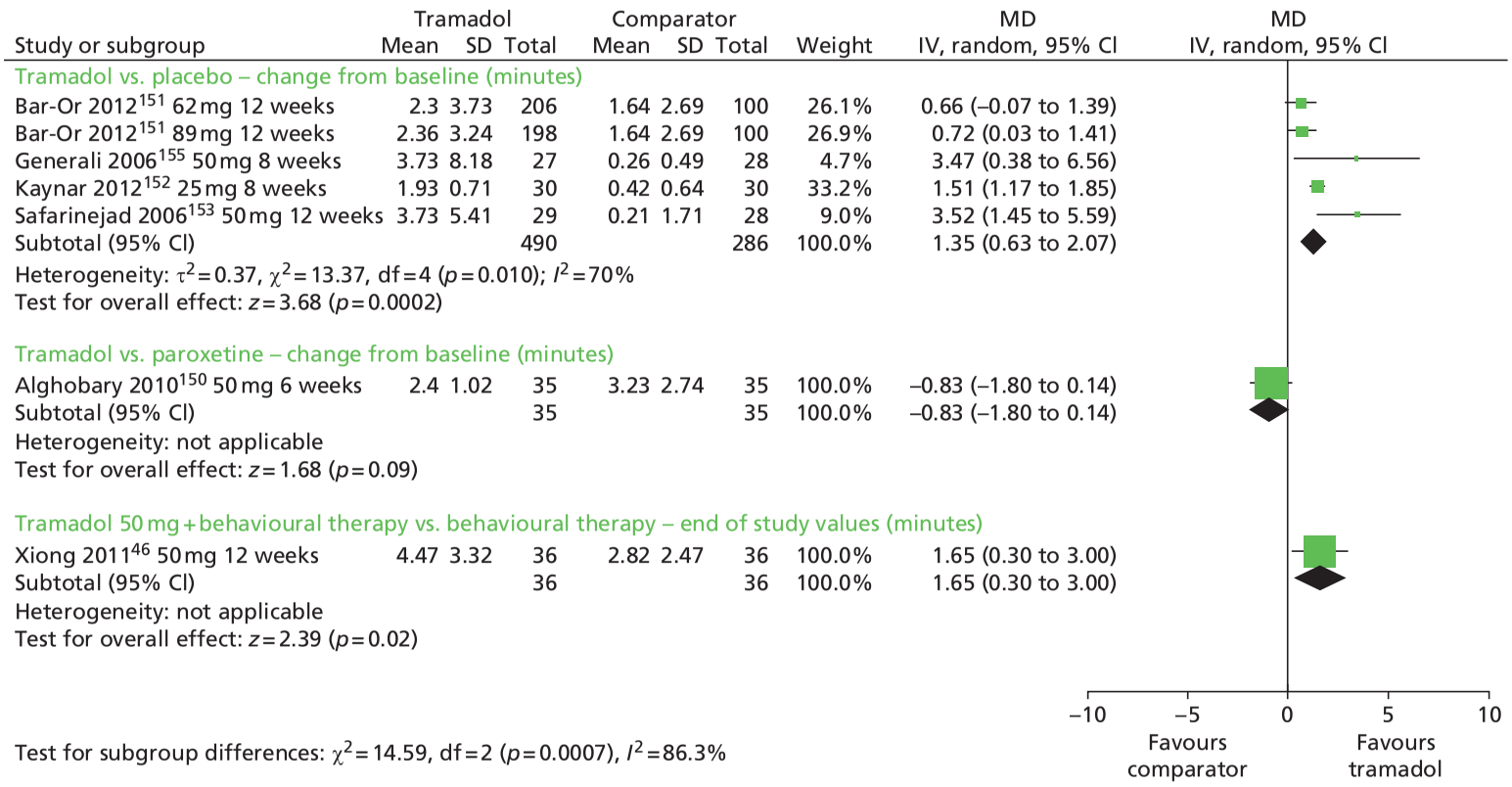

FIGURE 18 Opioid analgesics, tramadol compared with comparator: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

Study or subgroup	Tramadol higher dose Mean	SD	Total	Tramadol lower dose Mean	SD	Total	Weight	MD IV, fixed, 95% CI
Tramadol 50 mg vs. 25 mg – final values (minutes)								
Eassa 2013[154] 24 weeks	23.43	1.78	100	13.17	1.83	100	100.0%	10.26 (9.76 to 10.76)
Subtotal (95% CI)			100			100	100.0%	10.26 (9.76 to 10.76)
Heterogeneity: not applicable								
Test for overall effect: $z = 40.19$ ($p < 0.00001$)								
Tramadol 100 mg vs. 25 mg – final values (minutes)								
Eassa 2013[154] 24 weeks	36.49	3.25	100	13.17	1.83	100	100.0%	23.32 (22.59 to 24.05)
Subtotal (95% CI)			100			100	100.0%	23.32 (22.59 to 24.05)
Heterogeneity: not applicable								
Test for overall effect: $z = 62.52$ ($p < 0.00001$)								
Tramadol 100 mg vs. 50 mg – final values (minutes)								
Eassa 2013[154] 24 weeks	36.49	3.25	100	23.43	21.78	100	100.0%	13.06 (12.33 to 13.79)
Subtotal (95% CI)			100			100	100.0%	13.06 (12.33 to 13.79)
Heterogeneity: not applicable								
Test for overall effect: $z = 35.24$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 845.20$, df = 2 ($p < 0.00001$), $I^2 = 99.8\%$								

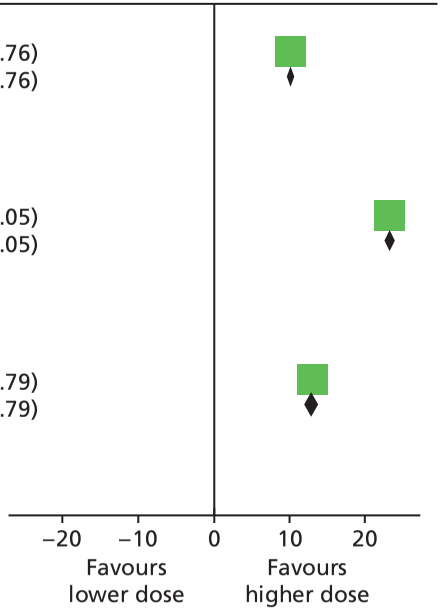

FIGURE 19 Opioid analgesics, tramadol different doses: forest plot of IELT outcomes. df, degrees of freedom; IV, inverse variance.

TABLE 34 Opioid analgesics, tramadol: outcomes other than IELT and AEs

RCT duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Bar-Or *et al.* 2012,[151] 12 weeks	Tramadol 62 mg ($n = 206$)	PEP: 4 measures (intercourse satisfaction, control over ejaculation, ejaculation-related distress, ejaculation-related interpersonal difficulty)	Mean change for all 4 measures significantly higher in both tramadol groups than placebo ($p < 0.05$ for all)	Yes	Any AE, tramadol 62 mg: 12%
	Tramadol 89 mg ($n = 198$)	Female partner PEP scores	Significantly more had improvement (≥ 1 category) for tramadol than placebo on all four measures	Yes	Tramadol 89 mg: 16%
	Placebo ($n = 200$)				Placebo: 7%
Generali *et al.* 2006,[155] 8 weeks	Tramadol 50 mg	IIEF: number of acts of coitus per week	Tramadol: mean change 1.23; placebo: mean change 0.2	Unclear	Any AE: tramadol: 28%; placebo: 16%, $p < 0.05$
	Placebo	IIEF: intercourse satisfaction	Tramadol: mean change 4; placebo: mean change –1	Unclear	Nausea: tramadol: 16%; placebo: 3%, $p < 0.05$. No differences between groups for vomiting (6.2% each), dizziness (3.1% vs. 6.2%), or constipation (2.6% vs. 0.0%)
Kaynar *et al.* 2012,[152] 8 weeks	Tramadol 25 mg ($n = 30$)	AEC score	Tramadol: mean increase 2.00; placebo: mean increase 0.57. Tramadol better than placebo ($p < 0.001$)	Yes	Any AE: tramadol: 27%; placebo: 0%
	Placebo ($n = 30$)	Sexual satisfaction scores	Tramadol: mean increase 1.80 (SD 0.98); placebo: mean increase 0.53 (SD 0.92). Tramadol better than placebo ($p < 0.001$)	Yes	Mild nausea/headache: tramadol: 20%
					Mild somnolence: tramadol: (6.5%)
Safarinejad 2006,[153] 8 weeks	Tramadol 50 mg ($n = 29$)	IIEF: intercourse satisfaction	Tramadol: mean change 4	Yes	Any AE: tramadol: 28%
	Placebo ($n = 28$)		Placebo: mean change –1		Placebo: 16% (mainly nausea)
			Between-groups $p < 0.05$		

RCT duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Alghobary *et al.* 2010,[150] 6 weeks per treatment	Tramadol 50 mg ($n = 35$)	AIPE	Tramadol: improved at 6 weeks but not at 12 weeks	Unclear	No AEs reported
	Paroxetine 20 mg ($n = 35$)	Libido	Paroxetine: improved at 6 weeks ($p < 0.05$) and 12 weeks ($p < 0.05$)	No	
			Difference between groups not significant. Tramadol group had less rigid erections than paroxetine group ($p < 0.05$)		
Xiong *et al.* 2011,[46] 12 weeks	Tramadol 50 mg + BT (behaviour modification) ($n = 36$)	IIEF	Tramadol + BT: mean change 4	Yes	Any AE: tramadol: 28%; placebo: 0%
	Behaviour modification ($n = 36$)		BT alone: mean change 2		Tramadol: nausea (11.1%), vomiting (2.8%), dry mouth (5.6%), dizziness (8.3%)
			Between-groups $p < 0.05$		
Eassa and El-Shazly 2013,[154] 24 weeks	Tramadol 25, 50 and 100 mg ($n = 100$ per group)	No other outcomes reported	N/A	N/A	Tramadol 25 mg – somnolence (100%); pruritus (100%)
					Tramadol 50 mg – somnolence (100%); pruritus (100%); dizziness (18%); headache (16%); dry mouth (13%)
					Tramadol 100 mg – somnolence (100%); pruritus (100%); dizziness (38%); headache (30%); dry mouth (20%); nausea (20%); vomiting (17%)

AEC, ability of ejaculation control; BT, behavioural therapy; N/A, not applicable.

Other outcomes: tramadol plus behavioural therapy compared with behavioural therapy

Xiong *et al.*[46] reported a significant between-group difference in IIEF intercourse satisfaction ($p < 0.05$) in favour of tramadol plus behavioural therapy.

Other outcomes: tramadol compared with paroxetine

Alghobary *et al.*[150] was the only RCT to employ the AIPE. The reviewers reported that paroxetine improved AIPE at 6 weeks ($p < 0.05$) and 12 weeks ($p < 0.05$), whereas tramadol improved AIPE at 6 weeks but not at 12 weeks.

Other outcomes: tramadol with behavioural therapy compared with behavioural therapy alone

Xiong *et al.*[46] reported a between-group difference at 8 weeks of $p < 0.05$ on the IIEF favouring the tramadol group. This trial is also evaluated in the *Behavioural therapies* section.

Assessment of safety: opioid analgesics – adverse events

No AEs were reported for the RCT by Alghobary *et al.*[150] When reported, AEs associated with tramadol included erectile dysfunction, constipation, nausea, headache, somnolence, dry mouth, dizziness, pruritus (itching) and vomiting. Numbers of patients by treatment groups experiencing AEs were reported by all RCTs. The trial by Eassa and El-Shazly,[154] which compared tramadol at different doses, reported that all patients in the trial experienced one or more AEs (all experienced somnolence and pruritus).

Adverse events: tramadol compared with placebo

Meta-analysis of numbers experiencing AEs at 8- or 12-week follow-up displayed low heterogeneity ($I^2 = 0\%$). The pooled RR across trials was 2.14 experiencing AEs [RR (fixed effect) 95% CI 1.36 to 3.38; $p = 0.001$] in favour of placebo (lower risk). The forest plot for this analysis is presented in *Figure 20*. Results for these, and all other meta-analyses, are presented in *Table 35*.

Adverse events: tramadol with behavioural therapy compared with behavioural therapy alone

The between-group difference in RR at 12 weeks was 21.00 [RR (random effects) 95% CI 1.28 to 345.410; $p = 0.03$] in favour of behavioural therapy alone (lower risk). The forest plot for this analysis is presented in *Figure 20*. An assessment of between study heterogeneity could not be undertaken for this comparison as only one trial was included.

Assessment of effectiveness: opioid analgesics – evidence summary

The current evidence base for tramadol in the treatment of PE comprises seven RCTs,[46,150–155] five[46,150–153] captured in three low to moderate methodological quality systematic reviews and two further RCTs[154,155] which are at overall unclear risk of bias. The pooled evidence across five RCT study groups[151–153,155] (776 participants) suggests that tramadol is effective in increasing IELT in men with PE when compared with placebo [MD 1.35 minutes (95% CI 0.63 to 2.07 minutes); $p = 0.0002$]. Evidence from one RCT[46] (72 participants) suggests that tramadol combined with behavioural therapy is significantly more effective than behavioural therapy alone in increasing IELT [MD 1.65 minutes (95% CI 0.30 to 3.00 minutes); $p = 0.02$]. The evidence from one RCT[150] (70 participants) suggests that there is no statistically significant difference in IELT between tramadol and paroxetine.

Various assessment methods in terms of ejaculation control, patient/partners sexual satisfaction, anxiety and other patient-reported outcomes have been used across RCTs to measure the effectiveness of tramadol. Four[46,151–153] out of five RCTs[46,151–153,155] reported that tramadol was significantly more effective than placebo for various patient-reported outcomes, while one RCT[155] did not report any significant between-group differences. Pooled evidence across trials[151–153,155] (587 participants) suggests that tramadol is associated with significantly more AEs including erectile dysfunction, constipation, nausea, headache, somnolence, dry mouth, dizziness, pruritus (itching) and vomiting, than placebo or behavioural therapy over 8–12 weeks of treatment. Addiction to tramadol by patients treated with this agent for PE is not assessed in the current evidence base. Likewise, patient acceptability of treatment is not reported.

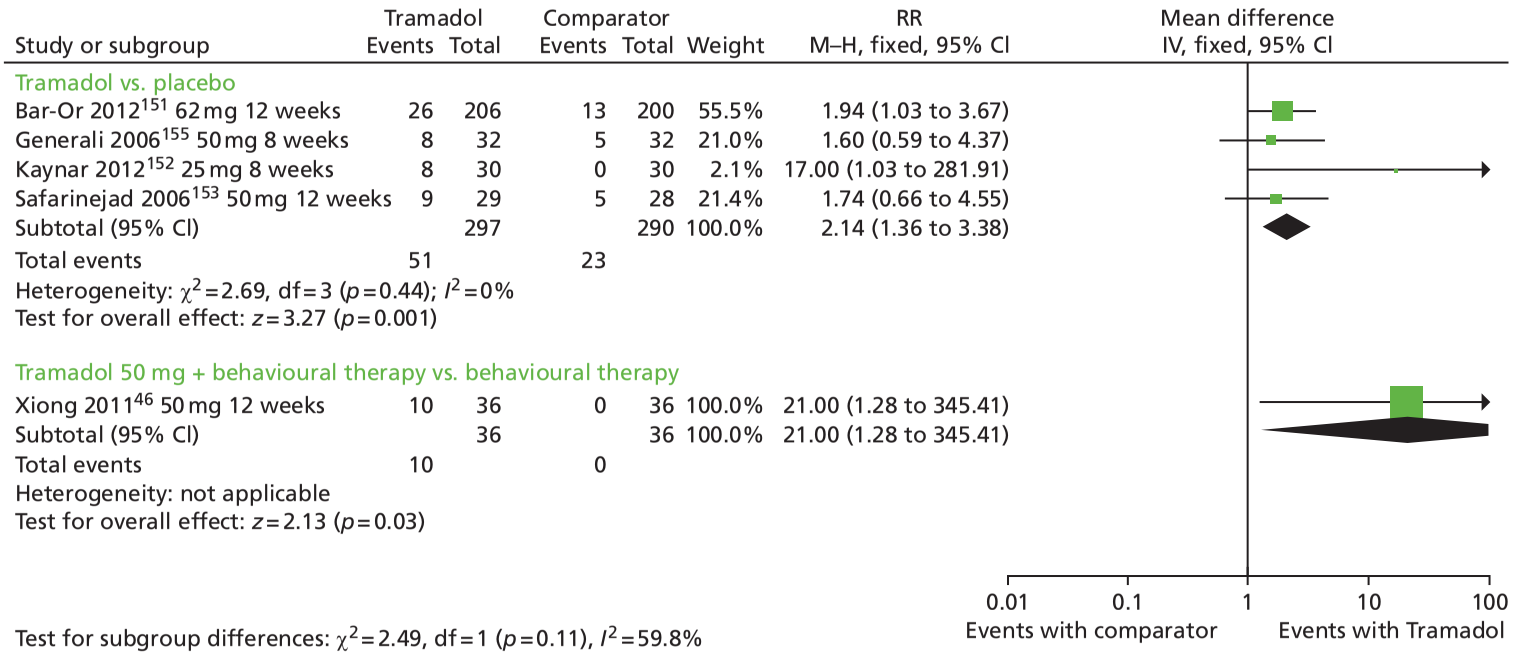

FIGURE 20 Opioid analgesics, tramadol compared with comparator: forest plot for AEs. df, degrees of freedom; IV, inverse variance; M–H, Mantel–Haenzel.

TABLE 35 Opioid analgesics, tramadol: results summary

Comparison	Outcome	*n* RCTs	Participants	I^2	Model	Effect estimate (95% CI)	Favours	*p*-value
IELT								
Tramadol vs. placebo	IELT (minutes) – change from baseline	5[151–153,155]	776	70%	Random-effects	MD 1.35 (0.63 to 2.07)	Tramadol	0.0002
Tramadol vs. paroxetine	IELT (minutes) – change from baseline	1[150]	70	N/A	N/A	MD –0.83 (–1.80 to 0.14)	Between-group difference NS	0.09
Tramadol 50 mg + BT vs. BT	IELT (minutes) – end of study values	1[46]	72	N/A	N/A	MD 1.65 (0.30 to 3.00)	Tramadol	0.02
Tramadol 50 mg vs. 25 mg	IELT (minutes) – final values, minutes	1[154]	200	N/A	N/A	MD 10.26 (9.76 to 10.76)	Tramadol	< 0.0001
Tramadol 100 mg vs. 25 mg	IELT (minutes) – final values, minutes	1[154]	200	N/A	N/A	MD 23.32 (22.59 to 24.05)	Tramadol	< 0.0001
Tramadol 100 mg vs. 50 mg	IELT (minutes) – final values, minutes	1[154]	200	N/A	N/A	MD 13.06 (12.33 to 13.79)	Tramadol	< 0.0001
Other outcomes								
Tramadol vs. placebo	AEs	4[151–153,155]	587	0%	Fixed effect	RR 2.14 (1.36 to 3.38)	Placebo (fewer AEs)	0.001
Tramadol 50 mg + BT vs. BT	AEs	1[46]	72	N/A	N/A	RR 21.00 (1.28 to 345.41)	Placebo (fewer AEs)	0.03

Comparison	Outcome	*n* RCTs	Participants	I^2	Model	Favours
Other outcomes						
Tramadol vs. placebo	Other effectiveness outcomes (various)	5[46,151–153,155]	Varies	N/A	N/A	Tramadol significantly more effective than placebo on: PEP,[151] AEC score[152] IIEF-IS,[153] IIEF,[46]; unclear on IIEF-NC and IS[155]
Tramadol vs. paroxetine	Other effectiveness outcomes (various)	1[150]	70	N/A	N/A	Between-group difference not significant/unclear in one study AIPE[150]
Tramadol 50 mg + BT vs. BT	Other effectiveness outcomes (various)	1[46]	72	N/A	N/A	Tramadol + BT significantly more effective than BT alone in one study[46] IIEF

BT, behavioural therapy; IS, intercourse satisfaction; N/A, not applicable; NC, number of acts of coitus; NS, not significant.

Tramadol appears more effective than placebo or behavioural therapy in the treatment of PE. However, these findings should be interpreted with caution given the observed levels of between-study heterogeneity and the methodological quality of the available evidence. In addition, the variability across placebo-controlled trials in terms of the tramadol dose evaluated and the treatment duration does not permit any assessment of a safe and effective minimum daily dose. Furthermore, the long-term effects and side effects of the treatment for men with PE have not been evaluated in the current evidence base.

Other therapies: acupuncture

Characteristics of included studies: acupuncture

No RCTs evaluating acupuncture were included in any of the systematic reviews identified for inclusion in this assessment report. Two RCTs were identified through the literature searches, one of which evaluated acupuncture compared with citalopram,[156] while the other evaluated acupuncture compared with sham acupuncture or paroxetine.[157]

Randomised controlled trials not included in reviews The RCT by Chen[156] was conducted in China. A total of 111 patients were randomised to daily acupuncture or citalopram (described as Sailete tablets) 20 mg per day. The trial was reported in Chinese with an English-language abstract. Treatment duration was 4 weeks and the authors reported that 111 out of 111 (100%) patients completed the trial, but the assessment method of IELT was not reported. The RCT by Sunay *et al.*[157] was conducted in Turkey and 90 patients were recruited to the trial and were randomised to either acupuncture twice a week, sham acupuncture twice a week or paroxetine 20 mg per day. The authors reported that 90 out of 90 (100%) patients completed the intervention. Both of these trials were considered to be at overall unclear risk of bias.

Details of the treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration, along with the study country for the further RCTs not in reviews and the overall study quality assessment (Cochrane risk of bias assessment[34]) are presented in *Table 36*.

Assessment of effectiveness: acupuncture – intravaginal ejaculatory latency time outcomes

The RCT by Chen[156] employed the CIPE. The CIPE has 10 questions focusing on libido, erectile function, ejaculatory latency, sexual satisfaction and difficulty in delaying ejaculation, self-confidence and depression. However, the authors only reported an overall score (see *Assessment of effectiveness: acupuncture – other outcomes*). Sunay *et al.*[157] reported IELT outcomes as median and mean rank values post treatment and change from baseline. The mean rank increase with paroxetine, acupuncture and sham acupuncture were 1.38 minutes, 1.10 minutes and 0.55 minutes, respectively. The authors reported that statistically significant between-group differences were determined for mean rank IELTs for paroxetine compared with sham acupuncture in favour of paroxetine ($p = 0.001$), acupuncture compared with sham acupuncture in favour of acupuncture ($p = 0.001$) and paroxetine compared with acupuncture in favour of paroxetine ($p = 0.001$) after treatment.

Assessment of effectiveness: acupuncture – other outcomes

Chen[156] reported that the change from baseline in cumulative CIPE scores were statistically significant with both acupuncture and with citalopram and that the between-group difference post treatment was statistically significant in favour of acupuncture (*Table 37*). The RCT by Sunay *et al.*[157] reported that median PEDT scores were significantly improved from baseline in both the acupuncture and paroxetine groups, but not in the sham acupuncture group. The authors also reported that both acupuncture and paroxetine were significantly better than sham acupuncture on this outcome; however, that there was no statistically significant between-group difference between acupuncture and paroxetine. Similarly, that no significant differences were found between PEDT subscores (ejaculation control, frequency, minimal stimulation, distress, interpersonal difficulty) for the paroxetine and acupuncture groups before and after treatment, but significant differences were determined between the paroxetine and placebo groups and between the acupuncture and placebo groups after treatment.

TABLE 36 Acupuncture: characteristics of RCTs not captured in reviews

RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Chen 2009[156] (China) unclear risk	4 weeks	Acupuncture daily ($n = 56$) Citalopram 20 mg per day ($n = 55$) *Acupuncture daily 56/56 (100%)* *Citalopram 55/55 (100%)*	NR	NR	No objective assessment	Chinese index of sexual function for PE (CIPE)
Sunay *et al.* 2011,[157] (Turkey) unclear risk	4 weeks	Acupuncture two times weekly ($n = 30$) Sham acupuncture two times weekly ($n = 30$) Paroxetine 20 mg per day ($n = 30$) *Acupuncture 30/30 (100%)* *Sham acupuncture 30/30 (100%)* *Paroxetine 30/30 (100%)*	IELTs of 2 minutes in > 70% of attempts	Lifelong 66%, acquired 34%	Stopwatch	PEDT

NR, not reported.

TABLE 37 Acupuncture: outcomes other than IELT and AEs

RCT, duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Chen 2009,[156] 4 weeks	Acupuncture daily ($n = 56$)	CIPE	Change from baseline: acupuncture, $p < 0.01$; citalopram, $p < 0.05$	Yes	NR
	Citalopram 20 mg per day ($n = 55$)		Between group difference in post-treatment scores, $p < 0.05$ (favouring acupuncture)		
Sunay *et al.* 2011,[157] 4 weeks	Acupuncture 2 × weekly ($n = 30$)	PEDT	Change from baseline: paroxetine, $p = 0.001$; acupuncture, $p = 0.001$	Yes for acupuncture and paroxetine from baseline and vs. sham acupuncture	No AEs were reported by patients
	Sham acupuncture 2 × week ($n = 30$)		Sham acupuncture, $p = 0.314$		
	Paroxetine 20 mg per day ($n = 30$)		Between-group differences: paroxetine vs. acupuncture, $p =$ NS; paroxetine vs. sham $p = 0.001$; acupuncture vs. sham, $p = 0.001$	No between acupuncture and paroxetine	

NR, not reported; NS, not significant.

Assessment of safety: acupuncture – adverse events

Adverse event data were not reported for the RCT by Chen.[156] Sunay *et al.*[157] reported that no questionnaire was used to evaluate the side effects; however, no side effects were observed in any of the patients.

Assessment of effectiveness: acupuncture – evidence summary

The current evidence base for acupuncture in the treatment of PE comprises two RCTs[156,157] that compare acupuncture with SSRIs (citalopram and paroxetine) that are at overall unclear risk of bias. Evidence from one of these RCTs[157] suggests that both acupuncture and paroxetine are both effective in increasing IELT in men with PE when compared with sham acupuncture. However, that paroxetine is more effective than acupuncture in increasing IELT.

Evidence from one RCT[156] suggests that subjective measures of libido, erectile function, ejaculatory latency, sexual satisfaction and difficulty in delaying ejaculation, self-confidence and depression are significantly improved with both acupuncture and citalopram and that the difference is greater with acupuncture. Conversely, evidence from one RCT[157] suggests that there is no statistically significant difference in subjective measures of ejaculation control, frequency, minimal stimulation, distress and interpersonal difficulty, between acupuncture and paroxetine. Treatment-related AEs for acupuncture in the treatment of PE are not well reported in the current literature.

Acupuncture appears more effective than citalopram but not paroxetine in the treatment of PE. The AEs associated with acupuncture in the treatment of PE are unclear. However, these finding should be interpreted with caution given the limited available evidence for this treatment.

Other therapies: Chinese medicine

Characteristics of included studies: Chinese medicine

No RCTs evaluating Chinese medicine were included in any of the systematic reviews identified for inclusion in this assessment report, but five RCTs[158–162] were identified through the literature searches. One compared Chinese medicine combined with sertraline and counselling with sertraline alone,[158] one compared Chinese medicine with treatment as usual,[159] one compared Chinese medicine with fluoxetine,[160] one compared Chinese medicine alone with Chinese medicine combined with trazodone [a serotonin antagonist and reuptake inhibitor (SARI) antidepressant][161] and one compared Chinese medicine adjuvant to behavioural therapy with behavioural therapy alone.[162]

Randomised controlled trials not included in reviews All five RCTs[158–162] were undertaken in China and three were reported in Chinese with an English-language abstract.[158,160,161] Pei and Shi[158] randomised 110 patients to *Wu Bei Zi* (*Galla Chinensis*) and *Xi Xin* (*Asari Herba*) combined with sertraline and counselling or sertraline alone; no further treatment details were reported. The assessment method of IELT was not reported. Treatment duration was 4 weeks and the authors reported that 110 out of 110 (100%) patients completed the trial. In the trial by Song *et al.*,[159] 68 patients were randomised to *Uighur medicine* (ingredients: *Radix anacycli pyrethri, Mastiche, Fructus Cardamomi, Rhizoma Cyperi, Stigma Croci, Semen Myristicae, Radix Curcumae, Folium Syringae oblatae, Radix et Rhizoma Nardostachyos, Fructus Tsaoko* and *Flos Rosae rugosae*), four tablets twice a day or treatment as usual (no tablets). IELT was assessed by a questionnaire designed for the study and all patients were reported as completing the 15-day trial. Sun *et al.*[160] evaluated *Yimusake* (*Arabian Olibanum, Moschus, Stigma Croci, Testis Et penis Bovis seu Bubali, Ambra Grisea, Semen Myristicae, Rhizoma Alpiniae Officinarum, Flos Caryophylli, Salep, Semen Strychni, Pericarpium Papaveris*) 1.5 g per day, fluoxetine 20 mg per day, and *Yimusake* 1.5 g combined with fluoxetine 20 mg per day. Thirty-eight patients were randomised to each of the three treatment groups and all were reported as completing. The IELT assessment method was not reported, but duration was 4 weeks. The RCT by Xu *et al.*[161] compared *Yimusake* 50 mg per day with *Yimusake* 50 mg per day combined with trazodone 50 mg per day. The IELT assessment method was not reported, but duration was 4 weeks. The authors reported that 68 out of 68 (100%) patients completed the trial. The RCT by Zhang *et al.*[162] randomised 28 patients to *Xuanju* compound (*Formica fusca, Herba epimedii, Fructus cnidii and Fructus lycii*) with sensate focus and 24 patients to sensate focus alone. The IELT assessment method was not reported, but treatment was for 4 weeks and all patients (100%) were reported as completing. All five trials were at overall unclear risk of bias.

Details of treatments evaluated, definition of PE, IELT assessment method, other outcomes assessed, study duration and country for the further RCTs not in reviews, and the overall study quality assessment (Cochrane risk of bias assessment[34]) are presented in *Table 38*.

Assessment of effectiveness: Chinese medicine – intravaginal ejaculatory latency time outcomes

With the exception of the RCTs by Pei and Shi[158] and Zhang *et al.*,[162] IELT outcomes were reported for all of the included trials.

Intravaginal ejaculatory latency time: Chinese medicine (*Uighur medicine*) compared with treatment as usual The between-group difference in mean IELT change (minutes) at 4 weeks, based on one RCT ($n = 68$) was 1.57 minutes (95% CI 1.11 to 2.03 minutes; $p < 0.00001$) in favour of Chinese medicine.[159]

Intravaginal ejaculatory latency time: Chinese medicine (*Yimusake*) compared with fluoxetine The between-group difference in mean IELT change (minutes) after 15 days, based on one RCT ($n = 76$) was 0.60 minutes (95% CI 0.19 to 1.01 minutes; $p = 0.004$) in favour of fluoxetine.[160]

TABLE 38 Chinese medicine: characteristics of RCTs not captured in reviews

RCTs identified by searches (not captured in reviews)						
RCT (country) risk of bias	**Duration**	**Treatments, *numbers analysed/randomised (%)***	**PE definition**	**Lifelong/acquired**	**IELT assessment**	**Other outcomes**
Pei and Shi 2008[158] (China) unclear	4 weeks	Chinese medicine (*Wu Bei Zi* and *Xi Xin*) + sertraline + sexual counselling ($n = 60$) Sertraline ($n = 50$) *Chinese medicine + sertraline + sexual counselling, 60/60 (100%)* *Sertraline, 50/50 (100%)*	NR	NR	IELT not assessed	Total effectiveness rates
Song *et al.* 2007[159] (China) unclear	15 days	Chinese medicine (*Uighur*) ($n = 35$) Treatment as usual ($n = 33$) *Chinese medicine, 35/35 (100%)* *Treatment as usual, 33/33 (100%)*	American Urological Association and DSM-IV diagnosed; IELT ≤ 2 minutes	Acquired and lifelong (*n* NR)	Questionnaire designed for the study	CIPE5 and CIPE10 Sexual partner's satisfaction rate and 'wish fulfilment' (assume ejaculation control)
Sun *et al.* 2010[160] (China) unclear	4 weeks	Chinese medicine (*Yimusake* 1.5 g/day) ($n = 38$) Fluoxetine 20 mg per day ($n = 38$) Chinese medicine + fluoxetine ($n = 38$) *Chinese medicine, 38/38 (100%)* *Fluoxetine, 38/38 (100%)* *Chinese medicine + fluoxetine, 38/38 (100%)*	NR	NR	Method NR	Patient and partners intercourse satisfaction
Xu *et al.* 2012[161] (China) unclear	4 weeks	Chinese medicine (*Yimusake* 50 mg/day) ($n = 32$) Chinese medicine + trazodone 50 mg/day ($n = 36$) *Chinese medicine, 32/32 (100%)* *Chinese medicine + trazodone, 36/36 (100%)*	NR	Lifelong	Method NR	Patients 'cured', 'improved', 'unimproved', total 'efficacious'
Zhang *et al.* 2006[162] (China) unclear	4 weeks	Chinese medicine (*Xuanju*) + sensate focus ($n = 28$) Placebo + sensate focus ($n = 24$) *Chinese medicine + sensate focus, 28/28 (100%)* *Sensate focus, 24/24 (100%)*	NR	NR	IELT not assessed	Sexual satisfaction

CIPE10, Chinese Index of Premature Ejaculation 10 premature ejaculation-related items; NR, not reported.

Intravaginal ejaculatory latency time: Chinese medicine (*Yimusake*) compared with Chinese medicine combined with fluoxetine The between-group difference in mean IELT change (minutes) after 15 days, based on one RCT ($n = 76$) was 2.50 minutes (95% CI 2.08 to 2.92 minutes; $p < 0.00001$) in favour of Chinese medicine combined with fluoxetine.[160]

Intravaginal ejaculatory latency time: Chinese medicine (*Yimusake*) combined with fluoxetine compared with fluoxetine The between-group difference in mean IELT change (minutes) after 15 days, based on one RCT ($n = 76$) was 1.90 minutes (95% CI 1.47 to 2.33 minutes; $p < 0.00001$) in favour of Chinese medicine combined with fluoxetine.[160]

Intravaginal ejaculatory latency time: Chinese medicine (*Yimusake*) compared with Chinese medicine combined with trazodone The between-group difference in mean IELT change (minutes) at 4 weeks, based on one RCT ($n = 68$) was not significant (MD 0.08 minutes 95% CI –0.19 to 0.35 minutes; $p = 0.56$).[161]

The forest plot for these analyses is presented in *Figure 21*.

Assessment of effectiveness: Chinese medicine – other outcomes

A greater proportion of patients receiving Chinese medicine combined with sertraline and sexual counselling than those receiving sertraline alone reported an effectiveness rating of 'effective' or 'improved' in the RCT by Pei and Shi.[158] The between-group difference in the number of patients reporting 'effective' or 'improved' estimated using RevMan for this assessment reported was 1.21 in favour of Chinese medicine combined with sertraline and sexual counselling compared with sertraline alone [RR (fixed effect), 95% CI 1.01 to 1.43; $p = 0.03$] (figure not presented).

Song *et al.*[159] reported a statistically significant between-group difference in Chinese medicine compared with care as usual in favour of Chinese medicine on sexual satisfaction and ejaculation control measures of the Chinese index of sexual function for PE scale for PE-related items. Sun *et al.*[160] reported that Chinese medicine combined with fluoxetine was significantly better than fluoxetine alone or Chinese medicine alone, on a measure of patient and partner intercourse satisfaction. Xu *et al.*[161] reported the number of patients as 'total efficacious' (assume 'improved' or 'cured'). The between-group difference was not significant ($p = 0.27$). In the RCT by Zhang *et al.*,[162] a greater proportion of patients in the Chinese medicine combined with behavioural therapy than those in the behavioural therapy alone group reported a 'cure rate' of 'cured' or 'improved' on an overall 'Cure rate and rate of sexual satisfaction improvement' rating. The between-group difference in the number of patients reporting 'cured' or 'improved' estimated using RevMan for this assessment reported was 1.92 in favour of Chinese medicine combined with behavioural therapy [RR (fixed effect), 95% CI 1.27 to 2.92; $p < 0.00001$] (figure not presented).

Details of outcomes other than IELT and AEs are presented in *Table 39*.

Assessment of safety: Chinese medicine – adverse events

Reporting of AEs was only available for one of the included RCTs[160] for which it was reported that the AEs observed with Chinese medicine combined with fluoxetine were not significantly different to those observed with Chinese medicine alone or fluoxetine alone. However, no details of the AEs assessed or a *p*-value for between-group differences were reported.

Assessment of effectiveness: Chinese medicine – evidence summary

The current evidence base for Chinese medicine in the treatment of PE comprises five RCTs all at unclear risk of bias. One comparing *Wu Bei Zi* and *Xi Xin* combined with sertraline and counselling with sertraline alone, one comparing *Uighur medicine* with treatment as usual, one comparing *Yimusake* with fluoxetine or *Yimusake* combined with fluoxetine, one comparing *Yimusake* with *Yimusake* combined with trazodone, and one comparing *Xuanju* compound plus sensate focus with sensate focus alone. No placebo-controlled trials of any Chinese medicine have been identified from the current literature. Evidence from one RCT[159]

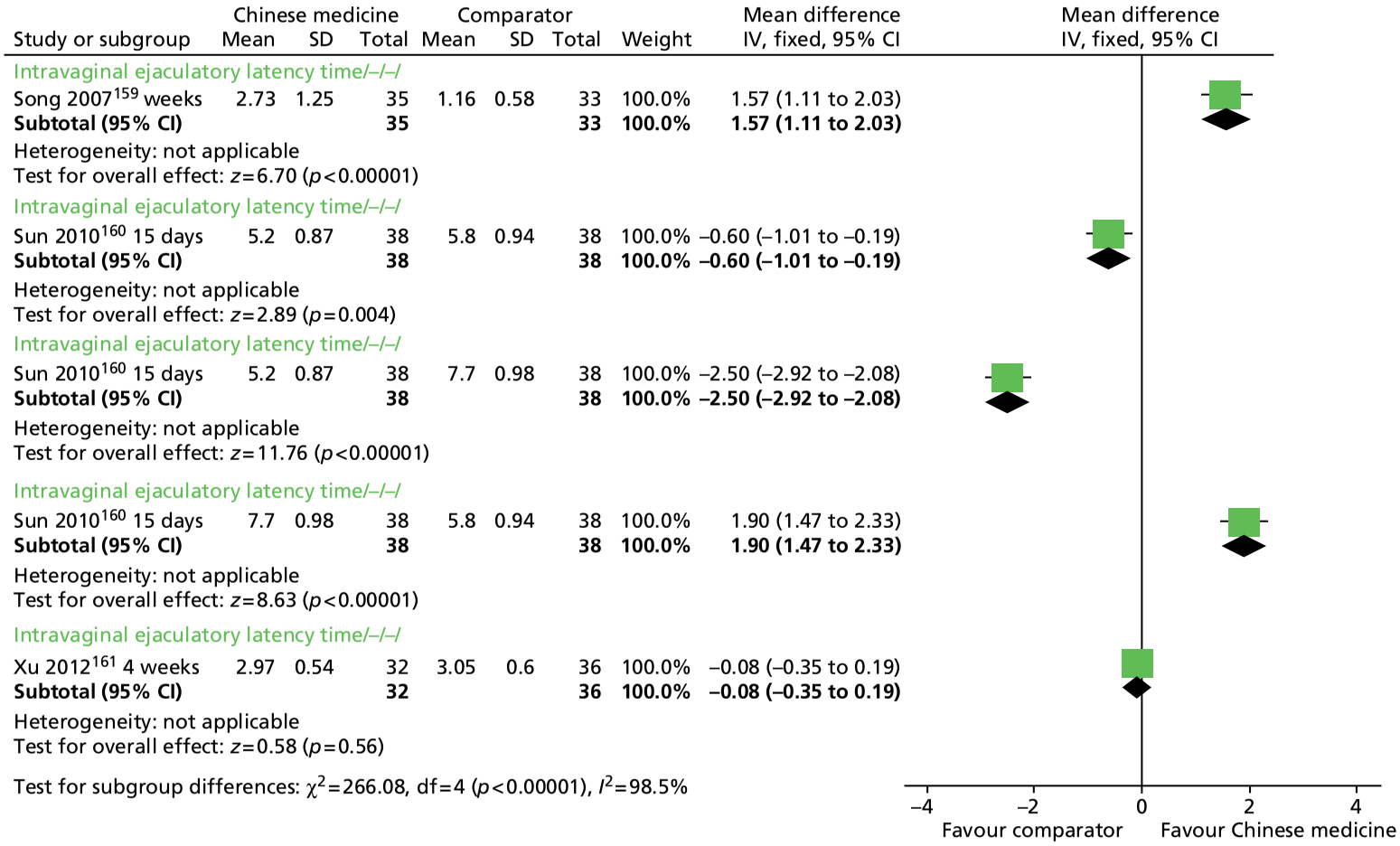

FIGURE 21 Chinese medicine compared with comparator: forest plot of IELT outcomes. IV, inverse variance.

TABLE 39 Chinese medicine: outcomes other outcomes than IELT and AEs

RCT Duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Pei and Shi 2008,[158] 4 weeks	Chinese medicine (*Wu Bei Zi* and *Xi Xin*) + sertraline + sexual counselling ($n = 60$)	Total effectiveness rates	Chinese medicine + sertraline + counselling: 'effective', 53.3%; 'improved', 38.3%; 'ineffective', 8.4%; 'total', 91.6%	Unclear	NR
	Sertraline ($n = 50$)		Sertraline: 'effective', 40.0%; 'improved', 36.0%; 'ineffective', 24.0%; 'total', 76.0%		
Song *et al.* 2007,[159] 15 days	Chinese medicine (*Uighur*) ($n = 35$)	Chinese index of sexual function for PE	CIPE5, CIPE10, satisfaction and control were improved following treatment at $p < 0.01$ and were different from the control group at $p < 0.01$	Yes	NR
	Treatment as usual ($n = 33$)	CIPE10 and the scale for five PE-related items			
		CIPE5			
Sun *et al.* 2010,[160] 4 weeks	Chinese medicine (*Yimusake*) ($n = 38$)	Patient and partners intercourse satisfaction	Patients intercourse satisfaction change from baseline (same for partner satisfaction): Chinese medicine, $p < 0.05$; fluoxetine, $p < 0.05$; Chinese medicine + fluoxetine, $p < 0.01$	Yes	AEs with Chinese medicine + fluoxetine were not significantly different to Chinese medicine or fluoxetine alone. No data or *p*-value
	Fluoxetine ($n = 38$)		Between-group (same for partner satisfaction): Chinese medicine + fluoxetine vs. Chinese medicine, $p < 0.05$		
	Chinese medicine + fluoxetine ($n = 38$)		Chinese medicine + fluoxetine vs. fluoxetine, $p < 0.05$		

RCT Duration	Treatment	Outcome measure	Results	Between-group difference reported as significant	AEs
Xu *et al.* 2012,[161] 4 weeks	Chinese medicine (*Yimusake*) ($n = 32$)	Patients 'cured', 'improved', 'unimproved', total 'efficacious'	Total 'efficacious': Chinese medicine: 18/32 (56.25%)	No	NR
	Chinese medicine + trazodone ($n = 36$)		Chinese medicine + trazodone: 25/36 (69.44%)		
			Between-group difference, $p = 0.27$		
Zhang *et al.* 2006,[162] 4 weeks	Chinese medicine (*Xuanju*) + sensate focus ($n = 28$)	'Cure rate' and rate of sexual satisfaction improvement	Between-group difference in number improved $p < 0.05$	Yes	NR
	Sensate focus ($n = 24$)		Between-group difference in n cured $p < 0.01$ (both favouring Chinese medicine + sensate)		

CIPE10, Chinese Index of Premature Ejaculation 10 premature ejaculation-related items; NR, not reported.

suggests Chinese medicine is significantly more effective than treatment as usual (no tablet) in increasing IELT in men with PE (1.57 minutes, 95% CI 1.11 to 2.03; $p < 0.00001$). One RCT[160] suggests that fluoxetine is better than Chinese medicine and that Chinese medicine combined with fluoxetine is significantly better than Chinese medicine alone or fluoxetine alone in increasing IELT [(0.60 minutes, 95% CI 0.19 to 1.01; 2.50 minutes, 95% CI 2.08 to 2.92; and 1.90 minutes, 95% CI 1.47 to 2.33 minutes), $p = 0.004$, $p < 0.00001$ and $p < 0.00001$, respectively]. One RCT[159] suggests no significant difference in IELT between Chinese medicine combined with trazodone and Chinese medicine alone.

Evidence from one RCT each suggests that CIPE-assessed sexual satisfaction and ejaculation control are better with Chinese medicine than treatment as usual and that a subjective measure of intercourse satisfaction is better with Chinese medicine combined with a SSRI than Chinese medicine or SSRI alone. Treatment-related AEs for Chinese medicine in the treatment of PE are not well reported in the current literature.

Limited evidence suggests that Chinese medicine may be effective in the treatment of PE and that greater efficacy is evident when Chinese medicine is combined with a SSRI. However, AEs associated with Chinese medicine, with or without these secondary agents, in the treatment of PE are unclear. The long-term effects of Chinese medicine in the treatment of PE and patient acceptability of the treatment are not evaluated in the current evidence base.

Other therapies: delay devices

Characteristics of included studies: delay devices

No studies evaluating delay devices were included in any of the systematic reviews identified for inclusion in this assessment report. One RCT was identified through the literature searches which evaluated a novel desensitising band.[163]

The study was undertaken in the UK and PE was defined by DSM-IV diagnosis.[163] The numbers of lifelong/acquired PE was not reported. The device evaluated was a desensitising ring comprising a stretchable latex ring with stimulating ridged plate which was used three times per week combined with the stop–start technique which was compared with CBT (six sessions with a trained therapist) combined with the stop–start technique. Twenty-six patients were randomised to each treatment group. The trial was reported in conference poster format and treatment duration was unclear (possibly eight weeks). Assessment was at the end of therapy and three months post treatment. The authors assessed PE and other subscales of the GRISS questionnaire. The authors reported that 52 out of 52 (100%) patients completed the study. This trial was considered at overall unclear risk of bias.

Assessment of effectiveness: delay devices – intravaginal ejaculatory latency time outcomes

Wise *et al.*[163] reported that the mean latency for coitus at completion was 8.8 minutes in the desensitising band group and 2.6 minutes in the CBT group and that the between-group difference favouring the desensitising band was significant ($p < 0.002$). However, it was unclear how this outcome was assessed as the authors reported that stopwatches were not used.

Wise *et al.*[163] reported that 16 out of 26 (62%) patients in the desensitising band group reported an improvement in latency, compared with 11 out of 26 (42%) in the CBT group. The between-group difference estimated using RevMan for this assessment report was 1.60 [RR (fixed effect), 95% CI 0.90 to 2.84; $p = 0.11$] (figure not presented).

Assessment of effectiveness: delay devices – other outcomes

Wise *et al.*[163] reported that the GRISS subscales showed no statistically significant differences between groups except in the PE subscale. The GRISS mean rank score was reported as being significantly lower (better) in the desensitising band group compared with the CBT group at 8 weeks ($p \leq 0.05$) and 3 months ($p < 0.05$).

Assessment of safety: delay devices – adverse events

Adverse events were not reported in the RCT by Wise *et al.*[163] A case study (six patients) report from the same research group[171] reported that the only side effect associated with the desensitising band was slight soreness with over-use which was resolved when used as instructed.

Assessment of effectiveness: delay devices – evidence summary

The current RCT evidence base for delay devices in the treatment of PE comprises one study that compares a desensitising band combined with the stop–start technique compared with behavioural therapy combined with the stop–start technique.[163] The RCT is considered to be at overall unclear risk of bias. Evidence from this study suggests that a desensitising band combined with the stop–start technique is more effective than behavioural therapy combined with the stop–start technique in increasing IELT in men with PE.

Evidence from the same RCT suggests that GRISS questionnaire assessed IELT appears improved with the desensitising band and is continued with use over 3 months. Evidence from one case series study suggests that soreness is reported with over-use but appears resolved when the device is used as instructed.[171]

Evidence from one RCT,[163] that is considered to be at unclear risk of bias, suggests that desensitising bands combined with the stop–start technique appear effective in increasing IELT in men with PE. The effects of desensitising bands alone on PE are not evaluated in the current evidence base. AEs appear minimal when these devices are used as directed.

Other therapies: yoga

Characteristics of included studies: yoga

No RCTs evaluating yoga were included in any of the systematic reviews identified for inclusion in this assessment report. One observational study (non-RCT) was identified through the literature searches which evaluated yoga compared with fluoxetine.[164] In the absence of any RCT evidence for the effects of yoga in the treatment of PE, this study was included in this assessment report.

The study was undertaken in India and PE was defined by DSM-IV diagnosis.[164] The number of patients with lifelong/acquired PE was not reported. Yoga (14 active and passive postures for 1 hour each day) was compared with fluoxetine, 20–60 mg per day (single dose). Patients self-selected to treatment groups and study duration was 12 weeks. IELT was assessed using a stopwatch and partner satisfaction ('good', 'fair', 'poor' responses) was also assessed. The authors reported that 68 out of 68 (100%) patients completed the study. This trial was considered at overall high-risk of bias.

Assessment of effectiveness: yoga – intravaginal ejaculatory latency time outcomes

The observational study by Dhikav *et al.*[164] reported that the mean post-treatment IELT at the 8-week follow-up was 1.07 minutes (SD 0.49 minutes) in the yoga group compared with 1.88 minutes (SD 0.59 minutes) in the fluoxetine groups. The authors reported that the change from baseline was significant in both groups ($p < 0.0001$). The between-group difference estimated using RevMan for this assessment report was 0.81 minutes in favour of fluoxetine [MD (fixed effect), 95% CI 0.55 to 1.08 minutes; $p < 0.0001$] (figure not presented).

Assessment of effectiveness: yoga – other outcomes

Dhikav *et al.*[164] reported that in the yoga group, partner satisfaction was rated as 'good' by 25 out of 38 (65.6%) patients, 'fair' by 13 out of 38 (34.2%) patients and 'poor' by 0 out of 38 (0.0%) patients. No data were reported for the fluoxetine group.

Assessment of safety: yoga – adverse events

Dhikav *et al.*[164] reported that there were no significant side effects or dropouts during course of treatment with yoga; however, no data were reported. The authors reported numbers of patients experiencing AEs in the fluoxetine group of: nausea 14 out of 30 (46.7%); vomiting, 4 out of 30 (13.3%); anxiety, 4 out of 30 (13.3%); and insomnia, 8/30 (26.7%).

Assessment of effectiveness: yoga – evidence summary

The current evidence base for yoga in the treatment of PE comprises one observational study that compares yoga with fluoxetine. The study is considered to be at overall high risk of bias base on participants self-selecting to treatment groups (selection bias).[164] In this study, both yoga and fluoxetine were reported as significantly effective at increasing IELT following treatment. However, the between-group estimate post treatment for this study suggests that fluoxetine is more effective than yoga in increasing IELT in men with PE. However, these results should be interpreted with caution given the possibility of selection bias in this study.

Evidence from the same study suggests that a high proportion of partners report a satisfaction rating of yoga of 'good'. No data for fluoxetine are reported for this outcome. AEs associated with fluoxetine include nausea, vomiting, anxiety and insomnia, and AEs associated with yoga are not reported.

Based on one observational study that is considered to be at high risk of selection bias, fluoxetine appears more effective than yoga in the treatment of PE, but is associated with AEs. The long-term effects of yoga in treating men with PE and patient acceptability compared with fluoxetine are not adequately assessed in the current evidence base.

Chapter 4 Discussion

The purpose of this report was to systematically review the evidence for interventions in the treatment of PE in men and to summarise this in the form of a short report. The treatments evaluated were those relevant to the UK setting. RCTs in adult men with PE that evaluated a treatment of interest compared with other interventions, waiting list control, placebo or no treatment were eligible for inclusion. When RCT evidence was not available, other study types were considered. RCTs were identified from existing systematic reviews and through literature searching. Data for RCT publications reported in existing systematic reviews were extrapolated from the review article (not from the original RCT publications). Methodological quality of included reviews and additional RCTs was assessed. The primary outcome was IELT; other outcomes included sexual satisfaction, control over ejaculation, relationship satisfaction, self-esteem, quality of life, treatment acceptability and AEs. When possible, data were pooled across trials in a meta-analysis.

Statement of principal findings

Behavioural interventions

The evidence for behavioural therapy was reported in 12 RCTs:[39–50] nine[39–47] captured in two low-quality reviews and one moderate quality Cochrane review, plus three further RCTs[48–50] of unclear methodological quality. The quality of reporting and diversity of outcome data did not permit pooling of effect estimates. Individual trial results suggest that behavioural therapies improved both IELT and sexual satisfaction compared with waiting list control. Behavioural therapies combined with pharmacological therapies (PDE5 inhibitors, SSRIs, chlorpromazine, tramadol) were better than behavioural therapy alone or pharmacological agents alone in improving IELT, sexual satisfaction, sexual anxiety and ejaculation control. No AEs specific to behavioural therapies were reported.

Topical anaesthetics

The evidence for topical anaesthetics was reported in nine RCTs,[55–63] seven[55–61] captured in three low methodological quality systematic reviews and two further RCTs[62,63] of unclear methodological quality. Pooled evidence across RCTs suggests that both EMLA cream and TEMPE spray are more effective than placebo in increasing IELT [MD 6.44 minutes, 95% CI 6.01 to 6.87 minutes ($p < 0.00001$); and 3.30 minutes, 95% CI 1.33 to 5.27 minutes ($p = 0.001$), respectively]. AEs include loss of sensation and irritation for both men and women. Application of topical anaesthetics for ≥ 20 minutes preintercourse appears to be associated with erection loss.

Selective serotonin reuptake inhibitors currently not licensed for premature ejaculation

The evidence for SSRIs other than dapoxetine was reported in 42 RCTs,[39,41,70–107,141,166] 26[39,41,70–91,141,166] captured in seven[52,64–69] low methodological quality systematic reviews and 16 further RCTs,[92–107] 14[92–94,96–100,104–107] of unclear methodological quality and two[95,103] at high risk of bias. Treatment duration was 4–12 weeks. Evidence suggests that citalopram is significantly more effective in increasing IELT than placebo (MD 4.08 minutes, 95% CI –3.40 to 4.76 minutes; MD 4.62 minutes, 95% CI 4.21 minutes to 5.03 minutes; both $p < 0.00001$). Citalopram is also significantly more effective than no treatment (MD 3.14 minutes, 95% CI 2.47 minutes to 4.35 minutes; $p < 0.00001$). Escitalopram significantly increased IELT compared with placebo (MD 1.2 minutes, 95% CI 0.79 to 1.61 minutes; geometric mean 3.5 minutes, 95% CI 1.96 to 5.04 minutes; both $p < 0.00001$). Fluoxetine significantly increased IELT compared with placebo (MD 2.41 minutes, 95% CI 2.10 to 2.73 minutes; $p < 0.00001$). There was no significant difference in IELT between fluvoxamine and placebo. Paroxetine significantly increased IELT compared with placebo (MD 5.34 minutes, 95% CI 3.79 to 6.89 minutes; $p < 0.00001$) and improved sexual satisfaction. Sertraline significantly increased IELT compared with placebo (MD 2.72 minutes, 95% CI 1.77 to 3.67 minutes;

$p < 0.00001$) and improved ejaculation control. AEs included nausea, headache, insomnia, dry mouth, diarrhoea, drowsiness, dizziness, somnolence, decreased libido and anejaculation.

Selective serotonin reuptake inhibitors licensed for premature ejaculation (dapoxetine)

The evidence for dapoxetine at 30 mg or 60 mg on demand (approved doses in the UK) came from eight RCTs[113–116,118–120,170] including one Phase II RCT[114] and six Phase III RCT[85,113,116,118,119,170] reports captured in six systematic reviews[65,67,68,108–110] of low to moderate quality, plus one further RCT of low quality. The pooled evidence across RCTs suggests that dapoxetine 30 mg (three RCTs[113,118,170]) and 60 mg (five RCTs[85,113,118,119,170]) both significantly increased IELT compared with placebo (MD 1.16 minutes, 95% CI 0.94 to 1.39 minutes; and 1.66 minutes, 95% CI 1.46 to 1.87 minutes; both $p < 0.00001$). Dapoxetine 60 mg was significantly more effective than 30 mg (MD 0.46 minutes, 95% CI 0.19 to 0.74 minutes; $p = 0.0009$). Similar effects were evident for ejaculatory control, sexual satisfaction, global impression of change and clinical benefit. There was no significant difference in IELT between dapoxetine 30 mg combined with mirodenafil (PDE5 inhibitor) and dapoxetine 30 mg alone. AEs included nausea, diarrhoea, headache and dizziness and appear to be dose dependent.

Serotonin–noradrenaline reuptake inhibitors

The evidence for SNRIs was reported in three RCTs,[121–123] one[121] captured in a low-quality systematic review, plus two further RCTs,[122,123] one[123] of unclear quality and one[122] at high risk of methodological bias. Evidence from one RCT[121] indicated that duloxetine was significantly better than placebo in increasing IELT (MD 1.52 minutes, 95% CI 0.08 to 2.24 minutes; $p < 0.00001$). Evidence from two RCTs[122,123] suggests that venlafaxine is not effective at increasing IELT compared with placebo. Duloxetine-associated side effects are reported as dry mouth and nausea, and venlafaxine caused more side effects than placebo.

Tricyclic antidepressants

The evidence for clomipramine was reported in 13 RCTs,[39,76,107,124–133] 10[39,76,124–131] captured in low-to-moderate methodological quality systematic reviews, plus three further RCTs[107,132,133] of unclear quality. Both oral and nasal administration of clomipramine is evaluated in these trials. Existing study evidence summarised by reviews suggests that oral clomipramine might be better than placebo at increasing IELT,[52,69] but the reviews are of low methodological quality and report pooled estimates based on RCT and observational data. Inhaled clomipramine 4 mg appears effective at increasing IELT compared with placebo (1.68 minutes, 95% CI 1.06 to 2.29 minutes; $p < 0.00001$). Crossover trial evidence suggests efficacy with 1 mg or 2 mg appears to be dose dependent, as do treatment-related side effects of local irritation associated with nasal administration.

Phosphodiesterase-5 inhibitors

The evidence for PDE5 inhibitors was reported in 12 RCTs,[39,55,101,120,138–145] 10[39,55,138–145] captured in five[37,134–137] systematic reviews of low to moderate methodological quality and two further RCTs[97,116] of low and unclear quality. Based on one RCT each, vardenafil[138] and tadalafil[141] both significantly increased IELT compared with placebo, (MD 3.80 minutes, 95% CI 3.30 to 4.30 minutes; and 2.59 minutes, 95% CI 1.28 to 3.90 minutes; $p < 0.00001$ and $p = 0.0001$, respectively). There was no significant difference in IELT between sildenafil and placebo in one RCT.[142] Sexual satisfaction favoured PDE5 inhibitors compared with placebo. Combined therapy (sildenafil plus sertraline or behavioural therapy) was better than sildenafil alone. Some RCTs provided evidence that PDE5 inhibitors increased IELT more than SSRIs; however, no significant difference was evident for some RCTs. AEs included flushing, headache and palpitations.

Alpha-blockers

The evidence for alpha-blockers was reported in two RCTs,[39,107] one[39] captured in low methodological quality systematic reviews and one further RCT[107] of unclear quality. IELT was not reported for either trial. Evidence from one RCT[107] suggested that terazosin, clomipramine and sertraline are all significantly better than placebo on ejaculation control, with no significant difference between active treatments. The same RCT reported no significant difference between terazosin, clomipramine and sertraline in the number of patients reporting AEs of headache, hypotension, drowsiness and ejaculation disorder.

Opioid analgesics: tramadol

The evidence for tramadol was reported in seven RCTs,[46,150–155] five[46,150–153] captured in three[147–149] low to moderate methodological quality systematic reviews and two further RCTs[154,155] of unclear methodological quality. Pooled evidence suggested that tramadol significantly increased IELT compared with placebo (MD 1.35 minutes, 95% CI 0.63 to 2.07 minutes; $p = 0.0002$) and improved sexual satisfaction. One RCT[46] suggested that tramadol combined with behavioural therapy was significantly more effective than behavioural therapy alone (MD 1.65 minutes, 95% CI 0.30 to 3.00 minutes; $p = 0.02$). One RCT[150] found no statistically significant difference in IELT between tramadol and paroxetine. Tramadol was associated with significantly more AEs than placebo, including erectile dysfunction, constipation, nausea, headache, somnolence, dry mouth, dizziness, pruritus (itching) and vomiting. Addiction to tramadol was not assessed.

Other therapies: acupuncture

The current evidence base for acupuncture comprises two RCTs[156,157] of unclear methodological quality comparing acupuncture with SSRIs (citalopram and paroxetine). Acupuncture appeared to be more effective than sham acupuncture or citalopram but paroxetine appeared to be more effective than acupuncture. The AEs associated with acupuncture are unclear and the evidence base for this treatment is limited.

Other therapies: Chinese medicine

The current evidence base for Chinese medicine comprises five RCTs[158–162] of unclear methodological quality. None was placebo controlled. These trials suggest that Chinese medicine is more effective than treatment as usual (1.57 minutes, 95% CI 1.11 to 2.03 minutes; $p < 0.00001$) but that fluoxetine is better than Chinese medicine (0.60 minutes, 95% CI 0.19 to 1.01 minutes; $p = 0.004$) in increasing IELT. AEs were not well reported. The lack of any placebo comparisons in PE trials coupled with limited evidence-based information regarding the efficacy and safety of Chinese medicine compounds limits the interpretation of results.

Other therapies: delay devices

The current evidence base for delay devices comprises one RCT[163] of unclear methodological quality. This trial indicated that a desensitising band combined with the stop–start technique increased IELT more than behavioural therapy combined with the stop–start technique. Soreness is reported with overuse but appears resolved when the device is used as instructed.

Other therapies: yoga

The current evidence base for yoga comprises one observational study (non-RCT)[164] comparing yoga with fluoxetine. This study reported that a high proportion of partners reported a satisfaction rating of yoga of 'good'. However, the IELT data suggested that fluoxetine is more effective than yoga. AEs associated with yoga were not reported. These findings are limited by non-randomised trial design and no RCTs assessing yoga for the treatment of PE were identified.

Strengths and limitations of the assessment

Strengths

Methodological considerations

This report has systematically reviewed the evidence for a range of treatments for PE. RCT evidence reported in existing reviews along with further identified RCTs was included. Our literature search covered all dates (from database inception to August 2013) in order to capture any studies missed by existing reviews in addition to those published more recently. The current evidence base includes several systematic reviews of PE treatments, many of which do not report a meta-analysis. Where meta-analyses are undertaken, methodological errors are evident. These include combining RCTs with observational studies (and not reporting which are which), double-counting participants within the meta-analyses (including the control

group from a RCT twice when different treatments are assessed), pooling data from crossover and pairwise RCTs (double counting for crossover trials), pooling between-group comparisons on questionnaire domains (subgroups) as an overall effect for the same trial (double counting), and applying a standardised MD to pool IELT effects where a MD is statistically more appropriate. This assessment report has pooled data across RCTs, when appropriate, in a meta-analysis using a MD to summarise IELT outcomes, has avoided double-counting of participants in the analysis and has considered pairwise and crossover RCT data separately. Furthermore, a formal assessment of methodological quality was undertaken. This was undertaken for both reviews from which RCT data were extrapolated and for any further RCTs identified by the searches not included in reviews.

Range of interventions assessed

The treatments evaluated in this assessment report were those relevant to the UK setting. In addition to treatments currently recommended in clinical practice, other treatments, including Chinese medicine, acupuncture, yoga and delay devices, were also evaluated, as patients might access these outside clinical practice. These treatments have not previously been reviewed in the management of PE.

Limitations

Methodological considerations

This assessment report summarises a wide range of interventions from a large volume of trial evidence and was undertaken within a limited timeframe. While RCT publications not already included in a review were obtained in full and data extracted (and checked by a second reviewer), data for RCTs reported in reviews were extracted (and checked) from the review article and not the original RCT publication. While data extraction from reviews was optimised when more than one review reported data for the same RCT, the reliability of the data extraction within the reviews cannot be guaranteed by this assessment report.

The methodological quality of the majority of existing reviews was low. Only four reviews reported independent double data extraction[36,53,135,149] (see *Appendix 4*). Reported search strategies varied in terms of the search dates and resources searched. The search strategy for this assessment report covered all dates (from database inception to August 2013) in order to capture any studies missed by existing reviews. Within this assessment report, although quality assessment was undertaken for RCTs not included in reviews, the methodological quality of individual RCTs reported in existing reviews was not assessed. Of the nine existing reviews that reported undertaking quality assessment,[35,36,38,51,53,64,65,108,110] quality scores were reported by only four,[35,51,53,64] across which the assessment method was diverse, including use of an assessment instrument not appropriate for RCTs[53] (the Newcastle–Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses).

Although the search strategy for this assessment report was comprehensive, the possibility of a publication bias cannot be discounted. Nonetheless, given the unclear methodological quality of the majority of included RCTs, coupled with the variability of treatment effects on IELT, it could be considered unlikely that any additional unpublished data would contribute significantly to the overall findings.

Nature of the available evidence

Most trials comprised men with primary PE without a concomitant condition and excluded those with erectile dysfunction. When reported, men were mainly recruited from specialist sexual health settings. For this reason, effectiveness of in men with secondary PE, PE concomitant to another condition, or not attending specialised clinics, is less certain. Trials were undertaken in a variety of European Union (EU) and non-EU countries. Variability in cultural attitudes towards PE and acceptability of the various treatments in trial populations, coupled with variability in PE definitions and IELT entry criteria, also limits the generalisability of the findings.

Within the current evidence base, there are very few RCTs of robust methodological quality that compare one treatment with another in pairwise comparisons. A network meta-analysis has not been undertaken to date. It is therefore difficult to make comparisons of efficacy between treatments. The only treatment licensed for PE in the UK is dapoxetine, which has demonstrated modest but statistically significant improvements in IELT and other outcomes, but is associated with AEs similar to those of other SSRIs. Although some other treatments (e.g. topical) have shown greater IELT improvements than dapoxetine, other treatments have not been so extensively investigated.

Treatment duration within RCTs ranged from 2 to 24 weeks. No studies reported long-term follow-up (> 6 months) of patients either continuing on or withdrawing from treatment; thus, there was no assessment of long-term safety and efficacy, or effects of treatment withdrawal.

The majority of RCTs assessed IELT and, when reported, the assessment method was mainly by stopwatch. The duration of treatment effects on IELT ranged from < 0.50 minutes to > 6.00 minutes. Many interventions also demonstrated improvements in ejaculation control, sexual satisfaction and other outcomes. However, these outcomes were often measured using different assessment scales and the reporting of outcome data was often limited. IELT is reported to have a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse.[172] There is currently no published literature which identifies a clinically significant threshold response to intervention.[23] Although the observed increases in IELT were statistically significant in favour of active treatments, it is difficult to quantify how acceptable and meaningful these changes are for men with PE, without being able to evaluate the relationship between IELT, ejaculation control and sexual satisfaction within the current RCT evidence base.

Adverse event reporting, both in reviews and in further RCTs, was limited. Although the nature of AEs associated with specific treatments could be identified, evidence surrounding proportions of patients withdrawing from treatment owing to AEs was either unclear or not reported. Furthermore, patient adherence to and acceptability of PE treatments has not yet been fully evaluated in the current evidence base.

Assessment of factors relevant to the NHS and other parties

Key considerations include the following:

- The treatment duration among RCTs ranged from 2 to 24 weeks (maximum of 12 weeks for many treatments). Thus, there is limited evidence regarding long-term safety and effectiveness of treatments.
- The effects of many treatments may be expected to end when treatment is stopped. This may be of particular concern following cessation of pharmacological agents. Behavioural modifications that are acquired through counselling might also not endure long term without continued support.
- Some AE data were available from the included RCTs, but some key safety concerns were not assessed. These include possible long-term effects of SSRIs[8] and the addiction potential of tramadol.
- Different interventions have different modes of action and patients may have a preference, for example a preference for non-pharmacological interventions, or for pharmacological agent that can be taken as needed rather than every day. Having available a range of treatment options (to be used individually or in combination) would be a useful approach to individual patient management.
- It is important to consider the balance between IELT and other effectiveness outcomes compared with AEs and inconvenience. Some patients may consider small increases of a few minutes in IELT to outweigh any treatment-related AEs, while others may not.
- In the UK, there are currently only a few specialised treatment centres for PE, and a general practitioner (GP) referral to one of these may have long waiting times. A range of treatment options should be available to GPs as a first-line approach for patients presenting with PE.

Chapter 5 Conclusions

Implications for service provision

Several interventions provided statistically significant improvements of between 1 and 6 minutes in time to ejaculation (IELT). These include pharmacological interventions (SSRIs and other antidepressants, PDE5 inhibitors, tramadol), topical anaesthetics and behavioural therapies. Many interventions also demonstrated improvements in sexual satisfaction and other outcomes. Behavioural therapy combined with pharmacotherapy was better than behavioural therapy or pharmacotherapy alone. Pharmacological and topical therapies are associated with some AEs. Trial duration was a maximum of 12 weeks for most interventions (24 weeks for dapoxetine and tramadol). Different interventions have different modes of action and individual patients may have a preference for pharmacological or behavioural interventions, so maintaining a range of options (to be used individually or in combination) may remain a useful approach in the treatment of PE.

Suggested research priorities

The suggested research priorities when evidence is most unclear are as follows.

Long-term safety and effectiveness

Assessment of long-term safety and effectiveness (> 6 months) is required to evaluate whether or not initial treatment effects are maintained long term, whether or not dose escalation is required, how soon treatment effects end following treatment cessation, and whether or not treatments can be stopped and resumed at a later time. In addition, it is important to assess the AEs associated with long-term treatment (e.g. long-term effects of SSRIs and the addiction potential of tramadol) and whether or not different doses have differing AE profiles. These research questions might be addressed by reviewing the literature surrounding the use of these treatments in other conditions (e.g. SSRIs in the management of depression). Any evidence gaps could be addressed through longer-term studies in PE; this may include observational studies or longer-term follow-up of RCT participants.

Comparison between treatments

The majority of treatments evaluated by this report provide improvements in IELT and other outcomes compared with placebo or no treatment, but are associated with AEs. The current evidence base does not include sufficient direct comparisons between treatments to inform any judgement regarding the 'best treatment'. Future research could consider a mixed treatment comparison/network meta-analysis approach and/or further head-to-head trials, as well as assessment of cost-effectiveness of the different interventions. Given that dapoxetine has been specifically developed for PE and has been extensively evaluated for this indication, head-to-head comparisons between this and other treatments might be informative. The effect of treatments used sequentially or in combination should also be further assessed. However, as patients are likely to have preferences for different types of treatment (e.g. pharmacological or behavioural), maintaining a range of options may remain a useful approach.

In terms of behavioural therapies, given the diversity of interventions in terms of technique, duration and delivery, further research is required to establish the components and intensity of intervention that are most effective. This could be addressed via further RCTs comparing different behavioural interventions in a head-to-head manner.

Clinical significance of outcomes and risk–benefit assessment

Future research should also consider an evaluation of the clinical significance of IELT increases, which may include assessment of the relationship between increases in IELT, ejaculatory control and sexual satisfaction, and whether or not increases of a few minutes in IELT are more meaningful to some patients than others. The trade-off between improvements in IELT and other clinical effectiveness outcomes compared with AEs and inconvenience should also be further assessed. Patient and partner acceptability of the different types of treatment (systemic, topical, behavioural) should also be further evaluated.

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About School of Health and Related Research

The ScHARR is one of the nine departments that constitute the Faculty of Medicine, Dentistry and Health at the University of Sheffield, Sheffield, UK. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

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Contributions of authors

Katy Cooper and **Marrissa Martyn-St James** carried out the systematic review and quality assessment of the studies and wrote the report.

Eva Kaltenthaler contributed to and checked the review.

Kath Dickinson and **Anna Cantrell** carried out the literature searches.

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Appendix 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	i (title page)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	v–vi
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and, if available, provide registration information including registration number	vi
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	5–7
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	169
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	8
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	8
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	8
Summary measures	13	State the principal summary measures (e.g. RR, difference in means)	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I2) for each meta-analysis	8

TITLE			
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	N/A
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	13, 29, 42, 71, 84, 86, 102, 118, 121, 133, 136, 142 and 143
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	174
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and CIs, ideally with a forest plot	18, 31, 44, 75, 84, 89, 107, 119, 125, 134, 138, 143 and 144
Synthesis of results	21	Present results of each meta-analysis done, including CIs and measures of consistency	23, 35, 54, 76, 97, 108, 126 and 139
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16])	N/A
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users, and policy makers)	145
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias)	147
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	149
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	vi and xxiii

Appendix 2 Literature search strategies

MEDLINE

The following strategy was developed for use in MEDLINE. This strategy was subsequently translated in accordance with the other databases searched.

MEDLINE search strategy

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

Appendix 3 Table of excluded studies with rationale

Author and Year	Reason for exclusion
Abdallah H, Abdelnasser T, Hosny H, Selim O, Al-Ahwany A, Shamloul R. Treatment of premature ejaculation by glans penis augmentation using hyaluronic acid gel: a pilot study. *Andrologia* 2012;**44**(Suppl. 1):650–3	Treatment not relevant to UK setting
Abdel-Hamid IA. Pharmacologic treatment of rapid ejaculation: levels of evidence-based review. *Curr Clin Pharmacol* 2006;**1**:243–54	Non-systematic review/treatment overview
Bandolier. Premature ejaculation treatments reviewed. *Bandolier* 2004;**11**:3	Non-systematic review/treatment overview
Basar MM, Yilmaz E, Ferhat M, Basar H, Batislam E. Terazosin in the treatment of premature ejaculation: a short-term follow-up. *Int Urol Nephrol* 2005;**37**:773–7	Treatment not relevant to UK setting
Burner M, Tahrat A. Double blind trial of atrium 300 in the treatment of sexual disorders. *Psychol Med* 1978;**10**:1165–71	Treatment not relevant to UK setting
Demirta A, Hali F, Ekmekciogl O. The effects of sildenafil, vardenafil and tadalafil on ejaculation latency time in premature ejaculators: a double blind, randomized, placebo controlled laboratory setting study. *J Sex Med* 2009;**6**:93–4	Laboratory study
Dresser MJ, Desai D, Gidwani S, Seftel AD, Modi NB. Dapoxetine, a novel treatment for premature ejaculation, does not have pharmacokinetic interactions with phosphodiesterase-5 inhibitors. *Int J Impot Res* 2006;**18**:104–10	Pharmacokinetic study
Dogan S, Dogan M. Premature ejaculation, treatment of the premature ejaculation and efficacy of selective serotonin reuptake inhibitors in the treatment of premature ejaculation. *Klinik Psikofarmakoloji Bulteni* 2007;**17**:87–99	Non-systematic review/treatment overview
El-Seweifi A. Partial penile neurectomy for management of ejaculatio praecox. *J Mens Health* 2010;**7**:282–3	Treatment not relevant to UK setting
Feige AM, Pinsky MR, Hellstrom WJG. Dapoxetine for premature ejaculation. *Clin Pharmacol Ther* 2011;**89**:125–8	Non-systematic review/treatment overview
Ginsberg DL. Gabapentin treatment of premature ejaculation. *Prim Psychiatry* 2004;**11**:20–1	Treatment not relevant to UK setting
Giuliano F, Patrick DL, Porst H, La Pera G, Kokoszka A, Merchant S, *et al.* Premature ejaculation: results from a five-country European observational study. *Eur Urol* 2008;**53**:1048–57	Non-systematic review/treatment overview
Gokce A, Halis F, Demirtas A, Ekmekcioglu O. The effects of three phosphodiesterase type 5 inhibitors on ejaculation latency time in lifelong premature ejaculators: a double-blind laboratory setting study. *BJU Int* 2011;**107**:1274–7	Laboratory study
Greco E, Polonio-Balbi P, Speranza JC. Levosulpiride: a new solution for premature ejaculation? *Int J Impot Res* 2002;**14**:308–9	Treatment not relevant to UK setting
Guan ZC, Shi BT, Wang R. Resiniferatoxin for treatment of premature ejaculation: a new medical therapy. *J Sex Med* 2010;**7**:177	Treatment not relevant to UK setting
Gurkan L, Oommen M, Hellstrom WJG. Premature ejaculation: current and future treatments. *Asian J Androl* 2008;**10**:102–9	Non-systematic review/treatment overview
Hakobyan AE, Nersisyan NR, Azatyan RE, Azizian A, Grigoryan AD. New approach to premature ejaculation treatment. *J Sex Med* 2011;**8**:175–6	Treatment not relevant to UK setting
Hoy SM, Scott LJ. Dapoxetine: in premature ejaculation. *Drugs* 2010;**70**:1433–43	Non-systematic review/treatment overview
Modi NB, Dresser MJ, Simon M, Lin D, Desai D, Gupta S. Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol* 2006;**46**:301–9	Pharmacokinetic study

Author and Year	Reason for exclusion
Morales A, Black A, Clark-Pereira J, Emerson L. A novel approach to premature ejaculation: extracorporeal functional magnetic stimulation. *Can J Urol* 2009;**16**:4458–62	Treatment not relevant to UK setting
Porst H. An overview of pharmacotherapy in premature ejaculation. *J Sex Med* 2011;**8**(Suppl. 4):335–41	Non-systematic review/treatment overview
Riley AJ, Riley EJ. Amitriptyline-perphenazine and the squeeze technique in premature ejaculation. *J Pharmacother* 1979;**2**:136–40	Treatment not relevant to UK setting
Safarinejad MR. Safety and efficacy of venlafaxine in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomised study. *Andrologia* 2008;**40**:49–55	Treatment not relevant to UK setting
Zhang GX, Yu LP, Bai WJ, Wang XF. Selective resection of dorsal nerves of penis for premature ejaculation. *Int J Androl* 2012;**35**:873–9	Treatment not relevant to UK setting

Appendix 4 Quality assessment

The Assessing Methodological Quality of Systematic Reviews[33] assessment of included reviews

Review author, review type, interventions	1. Was an a priori design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Total AMSTAR score (total number of 'Yes')
Althof 2006;[174] Althof 2012,[175] narrative, behavioural	No	No	No	No	No	No	No	No	No	No	No	0
Asimakopoulos *et al.* 2012,[134] systematic with MA, PDE5	Unclear	Unclear	No	No	No	Yes	Unclear	Unclear	No	No	Yes	2
Aversa *et al.* 2011,[135] systematic, PDE5	Unclear	Yes	No	No	No	Yes	No	No	N/A	No	Yes	3
Berner and Gunzler 2012,[36] systematic, behavioural	Yes	Yes	Yes	No	No	Yes	Yes	Yes	N/A	No	Yes	6
Burton and Liday 2011,[136] narrative, SSRIs vs. PDE5	Unclear	Unclear	No	No	No	Yes	No	No	N/A	No	Yes	2
Chen *et al.* 2007,[137] systematic, PDE5	Unclear	Unclear	No	No	No	Yes	No	No	N/A	No	Yes	2
Cong *et al.* 2012,[64] systematic with MA Fluoxetine	Unclear	Unclear	Yes	No	No	No	Yes	No	No	Yes	No	3
Hatzimouratidis *et al.* 2010, 165 guidelines, systemic, topical and behavioural	Unclear	Unclear	Unclear	Unclear	No	No	No	Unclear	N/A	No	Yes	1

Review author, review type, interventions	1. Was an a priori design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Total AMSTAR score (total number of 'Yes')
Huang *et al.* 2009,[65] systematic with MA, SSRIs – mixed	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Unclear	No	Unclear	Unclear	1
Hutchinson *et al.* 2012,[111] systematic, review of AEs and withdrawals associated with dapoxetine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kendirci *et al.* 2007,[112] communication on preclinical and clinical data, dapoxetine, communication on preclinical data	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Luo *et al.* 2012,[108] systematic with MA, dapoxetine	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Unclear	No	Unclear	Unclear	1
McCarty and Dinsmore 2012,[109] systematic, dapoxetine	Unclear	Unclear	No	No	No	Yes	No	No	N/A	No	Yes	2
McMahon *et al.* 2006,[37] systematic, PDE5	Unclear	Unclear	Yes	Yes	No	Yes	No	No	No	No	Yes	4
McMahon and Porst 2011,[68] systematic, mixed – systemic treatments	Unclear	Unclear	No	No	No	Yes	No	No	N/A	No	Yes	2

Review author, review type, interventions	1. Was an a priori design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Total AMSTAR score (total number of 'Yes')
McMahon *et al.* 2012,[169] systematic, dapoxetine	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	N/A	No	Yes	5
Melnik *et al.* 2009,[38] systematic, behavioural	Unclear	Unclear	Yes	Yes	No	No	Yes	No	N/A	No	No	3
Melnik *et al.* 2011,[35] Cochrane review, behavioural	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	7
Morales *et al.* 2007,[54] mini-review, topical anaesthetics	Unclear	Unclear	Unclear	Unclear	No	Unclear	No	No	N/A	No	Yes	1
Moreland and Makela 2005,[66] systematic, SSRIs – mixed	Unclear	Unclear	No	No	No	No	No	No	N/A	No	No	0
Pu *et al.* 2013,[51] systematic with MA, topical anaesthetics	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	No	No	No	4
Richardson *et al.* 2005;[69] Richardson *et al.* 2006,[8] systematic, mixed – systemic treatments	Unclear	Unclear	No	No	No	Yes	No	No	No	No	No	1

Review author, review type, interventions	1. Was an a priori design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Total AMSTAR score (total number of 'Yes')
Waldinger *et al.* 2004,[52] systematic with MA, mixed – systemic and topical treatments	Unclear	Unclear	No	No	No	Yes	No	No	No	No	No	1
Wang *et al.* 2007,[67] systematic, SSRIs – mixed	Unclear	Unclear	No	Unclear	No	No	No	No	N/A	No	No	0
Wang *et al.* 2010,[110] systematic with MA, dapoxetine	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	Unclear	No	Unclear	Unclear	2
Wong and Malde 2013,[147] systematic, tramadol	Unclear	Unclear	No	No	No	Yes	No	No	N/A	No	No	1
Wu *et al.* 2012,[148] systematic with MA, tramadol	Unclear	Unclear	No	Unclear	No	Yes	Yes	No	No	No	No	2
Xia *et al.* 2013,[53] systematic with MA, topical anaesthetics	Unclear	Yes	No	No	No	Yes	Yes	No	Yes	No	Yes	5
Yang *et al.* 2013,[149] systematic with MA, tramadol	Unclear	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	6

MA, meta-analysis; N/A, not applicable.

Risk of bias assessment[34] for the randomised controlled trials not included by reviews

Study, broad area	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk[a]
Ahn *et al.* 1996,[100] SSRIs – fluoxetine vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Akgül *et al.* 2008,[92] SRRIs – citalopram vs. sertraline	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Akilov *et al.* 2011,[132] TCAs – nasal clomipramine vs. placebo	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Arafa and Shamloul 2006,[97] SSRIs – sertraline vs. placebo	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Arafa and Shamloul 2007,[106] SSRIs – fluoxetine vs. escitalopram vs. paroxetine	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Athanasios *et al.* 2007,[121] SSRIs – duloxetine vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Chen 2009,[156] acupuncture – acupuncture vs. citalopram	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Culba *et al.* 2008,[101] SSRIs – fluoxetine vs. fluoxetine + PDE5 vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk
Dhikav *et al.* 2007,[164] yoga – yoga vs. fluoxetine	High risk	High risk	High risk	Unclear risk	Low risk	Low risk	High risk
Eassa and El-Shazly 2013,[154] tramadol – tramadol different doses	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Farnia *et al.* 2009,[93] SSRIs – citalopram vs. placebo	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Generali and Cada 2006,[155] tramadol – tramadol vs. placebo	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	High risk	Unclear risk
Giammusso *et al.* 1997,[103] SSRIs – paroxetine 20 mg vs. paroxetine 10 mg	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	High risk
Khelaia *et al.* 2012,[104] SSRIs – paroxetine daily vs. paroxetine on-demand vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Kilic *et al.* 2005,[122] SNRIs – venlafaxine vs. placebo	Unclear risk	Unclear risk	High risk	Unclear risk	High risk	Low risk	High risk
Leaker *et al.* 2008,[133] TCAs – inhaled clomipramine: 1 mg vs. 2 mg vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk

Study, broad area	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk[a]
Lee *et al.* 2012,[120] dapoxetine – dapoxetine adjuvant to PDE5 (mirodenafil) or placebo	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mallat *et al.* 2012,[62] topical anaesthetics – electric stimulation vs. EMLA	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Nada *et al.* 2009,[98] SSRIs – escitalopram vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Nada *et al.* 2012,[94] SSRIs – escitalopram vs. citalopram	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Pastore *et al.* 2012,[48] behavioural – pelvic floor vs. dapoxetine	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Pei and Shi 2008,158 Chinese medicine – Chinese medicine (*Wu Bei Zi* and *Xi Xin*) + sertraline + sexual counselling vs. sertraline	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Rezakhaniha and Sirosbakht 2010,[95] SSRIs – fluoxetine vs. citalopram	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk	High risk
Safarinejad 2007,[99] SSRIs – escitalopram vs. placebo	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Safarinejad 2008,[123] SNRIs – venlafaxine vs. placebo	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Shang *et al.* 2012,[96] SSRIs – citalopram vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Shao and Li 2008,[49] behavioural – behavioural therapy vs. paroxetine	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Song *et al.* 2007,[159] Chinese medicine – *Uighur medicine* vs. treatment as usual	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Steggall *et al.* 2008,[63] topical anaesthetics – lidocaine spray vs. paroxetine	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Sun et al. 2010,160 Chinese medicine – *Yimusake* tablet vs. fluoxetine	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Sunay *et al.* 2011,[157] acupuncture – acupuncture vs. paroxetine	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk

Study, broad area	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk[a]
Tuncel *et al.* 2008,[107] SSRIs – clomipramine (TCA) vs. sertraline vs. terazosin (alpha-blocker) vs. placebo	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk
van Lankveld *et al.* 2009,[50] behavioural – internet-based sensate focus vs. waiting list control	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Waldinger *et al.* 2004,[105] SSRIs – paroxetine vs. clomipramine	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk	Unclear risk
Weixing *et al.* 2012,[102] SSRIs – fluoxetine or sertraline vs. squeeze technique	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Wise *et al.* 2004,[163] delay device – desensitising band + stop–start technique vs. behavioural therapy + stop–start technique	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk
Xu *et al.* 2012,[161] Chinese medicine – *Yimusake* tablet vs. *Yimusake* tablet + trazodone (SARI antidepressant)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Zhang *et al.* 2006,[162] Chinese medicine – *Xuanju* compound vs. no treatment (both adjuvant to sensate focus)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk

a Overall risk: low risk, randomisation method, allocation concealment, blinded outcome assessment and incomplete data, all 'low risk'; high risk, inadequate randomisation (self-selection, sequential patients odd and even), in such trials allocation will likely not be concealed, and/or, incomplete outcome data 'high risk').

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