Interventions to treat premature ejaculation: a systematic review short report

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Scientific summary

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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The following electronic databases were searched from inception to 6 August 2013 for published and unpublished research evidence: MEDLINE; EMBASE; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library including the Cochrane Systematic Reviews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.

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