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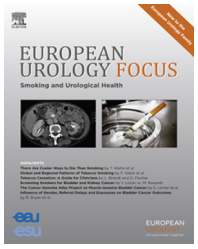

Review – Sexual Medicine

Phosphodiesterase Type 5 Inhibitors for Premature Ejaculation: A Systematic Review and Meta-analysis

Marrissa Martyn-St James [a,*], *Katy Cooper* [a], *Shijie Ren* [a], *Eva Kaltenthaler* [a], *Kath Dickinson* [a], *Anna Cantrell* [a], *Kevan Wylie* [b], *Leila Frodsham* [c], *Catherine Hood* [d]

[a] *School for Health and Related Research, University of Sheffield, Sheffield, UK;* [b] *Porterbrook Clinic, Sexual Medicine, Sheffield, UK;* [c] *Institute of Psychosexual Medicine, London, UK;* [d] *St. George's Hospital, London, UK*

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Abstract

Context: Phosphodiesterase type 5 inhibitors (PDE5-Is) are prescribed off-label for the treatment of premature ejaculation (PE).
Objective: To systematically review the evidence from randomised controlled trials (RCTs) for PDE5-Is in the management of PE.
Evidence acquisition: Medline and other databases were searched through September 2015. Quality of RCTs was assessed. Intravaginal ejaculatory latency time (IELT) data were pooled in a meta-analysis. Heterogeneity was assessed.
Evidence synthesis: Fifteen RCTs were included. The majority were of unclear methodological quality. Pooled IELT evidence suggests that PDE5-Is are significantly more effective than placebo (231 participants, $p < 0.00001$), that there is no difference between PDE5-Is and selective serotonin reuptake inhibitors (SSRIs; 405 participants, $p = 0.50$), and that PDE5-Is combined with an SSRI are significantly more effective than SSRIs alone (521 participants, $p = 0.001$); however, high levels of statistical heterogeneity are evident ($I^2 \geq 40\%$). Single-RCT evidence suggests that sildenafil is significantly more effective than the squeeze technique, but both lidocaine gel and tramadol are significantly more effective than sildenafil. Sildenafil combined with behavioural therapy is significantly more effective than behavioural therapy alone. Sexual satisfaction and ejaculatory control appear to be better with PDE5-Is compared with placebo and with PDE5-Is combined with an SSRI compared with an SSRI alone. Adverse events are reported with both PDE5-Is and other agents.
Conclusions: PDE5-Is are significantly more effective than placebo and PDE5-Is combined with an SSRI are significantly more effective than SSRIs alone at increasing IELT and improving other effectiveness outcomes; however, heterogeneity is evident across RCTs. The methodological quality of the majority of RCTs is unclear.
Patient summary: We reviewed phosphodiesterase type 5 inhibitors (PDE5-Is) for treating premature ejaculation. We found evidence to suggest that PDE5-Is are effective compared with placebo and that PDE5-Is combined with an SSRI are more effective than an SSRI alone. Adverse events are reported with PDE5-Is and other agents; however, the quality of the evidence is uncertain.
Trial registration: PROSPERO registration number CRD42013005289

* Corresponding author. School for Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK.
E-mail address: m.martyn-stjames@sheffield.ac.uk (M. Martyn-St James).

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1. Introduction

Premature ejaculation (PE) is commonly defined by short ejaculatory latency and perceived lack of ejaculatory control, both related to self-efficacy, and by distress and interpersonal difficulty [1]. PE can be either lifelong (ie, primary; present since first sexual experiences) or acquired (ie, secondary; beginning later) [2]. The International Society of Sexual Medicine's Ad Hoc Committee for the Definition of Premature Ejaculation defines PE as a male sexual dysfunction characterised by ejaculation within about 1 min of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time to $\leq$3 min (secondary PE), the inability to delay ejaculation, and negative personal consequences [3].

The treatment of PE should attempt to alleviate concern about the condition and to increase sexual satisfaction for the patient and the partner [4]. Available treatment pathways for the condition are varied, and treatments may include both behavioural and pharmacological interventions. Phosphodiesterase type 5 inhibitors (PDE5-Is) are prescribed for the condition off-label. A number of randomised controlled trials (RCTs) and observational studies have compared PDE5-Is with placebo, no therapy, behavioural therapy, or pharmacological agents. Previous reviews have summarised this evidence [5–9]; however, none to date has presented a meta-analysis of only RCT evidence.

The aim of this study was to systematically review the evidence for PDE5-Is in the treatment of PE by summarising evidence from RCTs and presenting a meta-analysis of treatment effectiveness.

2. Evidence acquisition

The review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

2.1. Searches

Medline and other bibliographic databases were searched from inception to 30 September 2015. Details of all sources searched and full search terms are reported elsewhere [11]. All citations were imported into Reference Manager software (version 12; Thomson ResearchSoft, Carlsbad, CA, USA), and any duplicates were deleted.

2.2. Eligible studies

RCTs in adult men with PE that evaluated a PDE5-I alone or in combination with another therapy were eligible for inclusion. Single-arm randomised crossover-design studies (participants randomised to different intervention periods) were excluded to avoid double counting of participants in the meta-analysis. Theses and dissertations were not included. Non-English publications were included if sufficient data could be extracted from an English-language abstract or tables.

The primary outcome was intravaginal ejaculatory latency time (IELT). Other outcomes included sexual satisfaction, control over ejaculation, relationship satisfaction, self-esteem, quality of life, treatment acceptability, and adverse events (AEs).

2.3. Data extraction, quality assessment, and data synthesis

One reviewer performed data extraction of each included study. All numerical data were then checked by a second reviewer.

Methodological quality of RCTs was assessed using the Cochrane Collaboration risk-of-bias assessment criteria [12]. We classified RCTs as having overall *low* or *high* risk of bias if they were rated as such for all three of the following key domains: (1) allocation concealment, (2) blinding of outcome assessment, and (3) completeness of outcome data (attrition <30%).

If possible, between-group differences were pooled across RCTs in a meta-analysis using Cochrane RevMan software (version 5.2) [13]. Random-effects models were applied if the I^2 value was >40%. Between-group effect estimates were considered significant at $p < 0.05$. Assessment of publication bias, assessed by visual inspection of funnel plots, was planned if $\geq$10 RCT comparisons were available.

3. Evidence synthesis

3.1. Search results

The searches identified 2391 citations. Of these, 2369 citations were excluded as titles or abstracts. Twenty-two full-text articles were obtained as potentially relevant. The study-selection process is fully detailed in the PRISMA flow diagram in Supplementary Figure 1. A total of 15 RCTs that evaluated a PDE5-I (with or without a combined therapy) against a comparator were included.

Details of the included RCTs are presented in Table 1.

3.2. Risk-of-bias assessment of randomised controlled trials

The majority of RCTs were considered to be at unclear risk of bias mainly because of lack of reporting of information to inform the risk-of-bias assessment. Four RCTs were described as single-blind or open-label and were considered to be at high risk of performance bias [14–17]. One RCT was considered to be at high risk of selective reporting because although IELT and secondary outcomes were assessed, IELT outcomes were not reported and secondary outcomes were minimally reported (no data) [14]. One RCT was considered to be at overall high risk of bias because group allocation sequence was according to patient presentation at the clinic [17]. One RCT was considered to be at overall high risk of bias because numbers of participants withdrawing at 6 mo were imbalanced, with >30% in one group and no indication of whether these participants were included in the analysis [16]. We were unable to assess two RCTs fully because the body text was in the Chinese language; these studies were judged as having overall unclear risk [18,19]. Only one RCT

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