Selective serotonin reuptake inhibitors for premature ejaculation: a systematic review and network meta-analysis

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ABSTRACT
Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed for the treatment of premature ejaculation (PE). We systematically reviewed the evidence base for SSRIs in the management of PE, by summarising evidence from randomised controlled trials (RCTs) and presenting a network meta-analysis of treatment efficacy. We searched bibliographic databases including MEDLINE to August 2013. RCTs in adult men with PE that evaluated SSRIs were eligible for inclusion. The primary outcome was intravaginal ejaculatory latency time (IELT). A total of 41 RCTs that evaluated an SSRI against a comparator were included. With the exception of fluvoxamine, all SSRIs were associated with a significant increase in IELT compared with placebo. Paroxetine was associated with the greatest increase in IELT compared with placebo. However, the comparative evidence between different SSRIs is currently limited due to the lack of head-to-head trials.

METHODS
The following databases were searched from inception to 6 August 2013 for published and unpublished research evidence: MEDLINE; Embase; CINAHL; CDSR, CCRT, DARE and the HTA database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science. Existing systematic reviews were also checked for eligible studies. 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[1]. A Bayesian network-meta analysis (NMA)/mixed treatment comparison of direct and indirect evidence was undertaken using WinBUGS[2] Version 14 to estimate the relative efficacy across SSRIs (e.g., SSRI α vs. SSRI β). A random-effects treatment difference model with parameters estimated by Markov Chain Monte Carlo simulation was used. Treatment effects were estimated with reference to placebo. Non-informative prior distributions were used throughout the model. Convergence of the model to its posterior distribution was assessed[3]. Model fitting was checked by comparing the total residual deviance close to the total number of data points included in the analysis. A rankogram was also used to present the rank probabilities of each treatment being most effective[4]. The assumption of consistency when direct and indirect evidence was combined was checked using the node-splitting approach[5]. The quality of evidence for the outcome of IELT was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.[6]

RESULTS
• The searches identified 2,283 citations. Fifty-five full-text articles were obtained as potentially relevant. A total of 41 RCTs that evaluated an SSRI against a comparator (placebo, no therapy, another SSRI, or another agent) were included.
• Only one RCT was considered to be at low risk of bias on all domains of the risk of bias assessment. Three RCTs were assessed as being at high risk of attrition bias (>30%). The remainder of RCTs were considered at unclear risk of bias mainly due to lack of reporting of information to inform the risk of bias assessment.
• IELT outcome data were available for the NMA from 20 of the 41 included RCTs.
• The reporting of other efficacy outcomes (e.g., sexual satisfaction, ejaculatory control) was much more varied, both in the assessment method and the outcome data available.
• Across the majority of RCTs, outcome data for adverse event reporting was disparate in terms of limited reporting of types of adverse events and patient numbers.
• NMA results were consistent with the direct comparisons in that all SSRIs were associated with a significant increase in IELT compared with placebo with the exception of fluvoxamine (Figure 1). Paroxetine was associated with the greatest increase in IELT compared with placebo (mean difference 5.22 minutes [95% CrI 3.77 to 6.72]). Paroxetine was estimated to have 89% probability of having the greatest effect on IELT increase, followed by citalopram (11%).
• The GRADE quality of evidence for NMA comparisons were downgraded from ‘high’ to ‘moderate’ due to lack of direct evidence. NMA comparisons between: fluvoxamine vs. escitalopram, dapoxetine 30mg vs. escitalopram, dapoxetine 60mg vs. escitalopram, dapoxetine 30mg vs. fluvoxamine, and fluoxetine vs. sertraline, were further downgraded to ‘low’ due to imprecision (95% CrI crossing zero effect). No comparison was downgraded due to suspected publication bias due to the limited number of RCTs for some SSRIs available to assess this.
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RESULTS CONTINUED

CONCLUSIONS

• NMA evidence suggests that, with the exception of fluvoxamine, SSRIs are more effective than placebo at increasing IELT in men with PE. Compared with placebo, the treatment effects on IELT that were observed ranged from 0.53 minutes (fluvoxamine, not significant) to 5.34 minutes (paroxetine).

• From the narrative synthesis, adverse events associated with SSRIs appear to be nausea, headache, insomnia, dry mouth, diarrhoea, drowsiness, dizziness, somnolence, decreased libido and anejaculation. However, evidence surrounding the seriousness and tolerability of adverse events associated with SSRIs is unclear.

• From the narrative synthesis, measures of sexual satisfaction appear improved with citalopram, dapoxetine, fluoxetine, and measures of sexual satisfaction and ejaculation control appear improved with dapoxetine and sertraline.

• The majority of RCTs of SSRIs in the treatment of PE are of unclear risk of bias, mainly due to limited reporting regarding blinding of the outcome assessment.

• The current evidence base does not include sufficient direct comparisons between different SSRIs and between SSRIs and other active treatments to inform definitive judgement regarding the “best treatment”.

• The trade-off between IELT and other effectiveness outcomes versus adverse effects and inconvenience should also be further evaluated. Furthermore, patient adherence to and acceptability of SSRIs in the treatment of PE has not yet been fully evaluated.

REFERENCES


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Figure 1. SSRIs vs. comparator - forest plot of IELT outcomes (minutes) from network meta-analysis – random-effects