Pharmacological interventions for premature ejaculation: a mixed-treatment comparison network meta-analysis of randomized clinical trials

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Abstract
Premature ejaculation (PE) is the most common sexual dysfunction in men. The present study is a network meta-analysis of drugs used for treating PE. Electronic databases were searched for randomized controlled trials comparing medical interventions with either placebo or with other active drugs in patients with PE. Inverse variance heterogeneity model was used for mixed-treatment comparisons. Intravaginal ejaculatory latency time (IELT) and adverse events were the main outcome measures. A total of 44 studies were included in the meta-analysis. Dapoxetine 30 and 60 mg, tadala
tafil, sildena
tafil, paroxetine with sildena
tafil, topical lidocaine, dapoxetine 30 mg with mirodena
tafil, vardenafil, fluoxetine, and tadala
tafil, pindolol with paroxetine, tramadol, topical lidocaine with tadala
tafil, paroxetine with tadala
tafil, and topical eutectic mixture of local anesthetics were associated with a significant increase in IELT. Similarly, dapoxetine 60 mg, venlafaxine, fluoxetine, tramadol at 25, 50, and 100 mg, and combined fluoxetine and tadala
tafil were associated with an increased risk of adverse events. Dapoxetine 30 mg has a high likelihood of being the “best” in the interventional pool. Dapoxetine at 30 mg could be used as the first-line agent in the management of PE.

Introduction
Premature ejaculation (PE) is the most common sexual dysfunction in men [1]. PE has been reported to be prevalent between 9 and 83% in various populations by different methods of assessment [2]. In a study that has used a self-reporting questionnaire, nearly one-third of men reported of having PE in the United States [3]. Although many definitions of PE exist, recently, the International Society for Sexual Medicine (ISSM) defined PE “as a male sexual dysfunction characterized by ejaculation occurring always or nearly always prior to, or within one minute of vaginal penetration without patient control and with negative personal consequences” [4]. PE is an important issue to be addressed considering the negative impact on the quality of life of men as well as their associated partners [5].

Pharmacotherapies for PE include use of drugs such as dapoxetine, paroxetine, citalopram, fluoxetine, clomipramine, topical lidocaine and prilocaine, sildenafil, tadalafil, vardenafil, tramadol, and tamsulosin [6, 7]. Complementary and alternative systems of medicine (CAM) such as Chinese medicines, acupuncture, and Ayurvedic herbal medicines have also been shown to be useful for PE in limited studies [8]. Direct pairwise meta-analyses have been conducted with dapoxetine, tramadol, topical anesthetics, and phosphodiesterase inhibitors [9, 10]. However, head-to-head trials comparing all the above interventions are currently lacking and thus we do not know which agent could likely be the best therapeutic intervention for PE. A network meta-analysis (NMA) compares all the interventions available for a disease condition through both direct and indirect comparisons and estimates the probability of the agent to be the “best” in the pool [11]. We carried out the present NMA to...
compare the interventions for PE by mixed-treatment comparison approach.

**Methods**

**Information source and search strategy**

The protocol for this review was registered with PROSPERO with the registration number CRD42017067047. We completed a thorough literature search on 15 May 2017 in the following databases: Medline (through PubMed), Cochrane CENTRAL, and Google Scholar. The detailed search strategy is available as an electronic supplementary file (ESF 1). No restrictions were placed with respect to either language or publication year. Additionally, we also hand-searched the references cited in the screened literature for potential studies that could be included in the review.

**Eligibility criteria**

We included only randomized controlled clinical trials that compared one or more of the active pharmacotherapy for patients with PE either among themselves or with placebo. We included studies that defined PE by any definition, with or without erectile dysfunction (ED) and we also carried out a subgroup analysis for studies that defined PE as per ISSM criteria as well as that which included patients with ED. We excluded studies or arms that concomitantly administered any complementary and alternative therapies or psychotherapies. Intravaginal ejaculation latency time (IELT) was the primary outcome and the overall adverse events: headache and flushing were considered as the secondary outcome measures.

**Study procedure and statistical considerations**

An independent literature search was carried out by two authors with the above-mentioned search strategy and the following data were extracted for each study: trial site, year, trial methods, participants, interventions, and outcomes. The authors resolved any disagreement through discussion. We carried out the present network meta-analysis according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) [12]. We assessed the risk of bias using Cochrane risk of bias tool [13]. Publication bias was assessed using funnel plot with trim-and-fill method that identifies the number of missing studies as well as with Egger’s regression analysis. The primary outcome measure was a numerical variable and so weighted mean difference (WMD) with 95% confidence intervals was used to assess the difference between the comparisons and odds ratio (95% confidence interval) was used as the effect estimate for the comparison of adverse events. We assessed the consistency by statistics wherein a value of <3 was considered as minimal, 3–6 as modest, and >6 as gross inconsistency [14]. The above-mentioned statistics measures the relationship between direct and indirect pooled estimates. We carried out sensitivity analyses on the primary outcome measure for patients who were defined as PE as per ISSM definition; patients with ED; and studies that assessed the efficacy by vibratory stimulation and not natural sexual intercourse. In
the forest plots that were generated for each of the outcome measure, the intervention with significant pooled estimate on the top has the high probability of being the “best” among the pool of interventions. We used MetaXL for generating the pooled estimates of direct, indirect, and mixed-treatment comparison analyses through generalized pairwise modeling and Meta-Essentials software for generating funnel plots [15]. The quality of evidence for key comparisons was graded using Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) working group approach [13]. We downgraded the evidence based on the seriousness of the limitations with respect to precision, indirectness, publication bias, and inconsistency.

**Results**

**Search results**

A total of 433 articles were obtained with the above-mentioned search strategy of which 44 [16–59] were included in the qualitative review (Fig. 1). Four studies included comparisons that could not be included in the quantitative network meta-analysis as there was no common comparator through which comparisons could be analyzed and therefore 40 studies were included in the quantitative network meta-analysis. The network diagram of the interventions included in the present meta-analysis is depicted in Fig. 2. A total of 27 interventions were included in this meta-analysis. The key characteristics of the included studies are listed in a table that is available as a supplementary electronic file (ESF 2). Risk of bias assessment revealed that majority of the studies had high risk with regard to selection bias while low risk was observed in all other domains (electronic supplementary file ESF 3).

**Publication bias**

Publication bias could be assessed for the comparisons of on-demand dapoxetine 30 mg, dapoxetine 60 mg, paroxetine, sildenafil, and tramadol 50 mg with placebo. Trim-and-fill method of analysis revealed the absence of any missing studies for all the above-mentioned comparisons except for tramadol 50 mg (Electronic supplementary files 4–8). Further, Egger’s regression analysis indicated the presence of publication bias for dapoxetine 60 mg and tramadol 50 mg (P < 0.05).

**Pooled results**

**Intravaginal ejaculation latency time (IELT)**

A total of 37 studies were included for the analysis of differences in IELT between the interventions. The interventions compared include sildenafil, vardenafil, and tadalafil in the category of phosphodiesterase inhibitors; citalopram, venlafaxine, sertraline, dapoxetine, fluoxetine, and paroxetine in the category of serotonin and noradrenaline reuptake inhibitors; and tamsulosin and pinadolol in alpha blockers, tramadol, topical lidocaine, andeutectic mixture of local anaesthetics (EMLA) of lidocaine and prilocaine. Forest plot of the mixed-treatment comparison estimates between the interventions against placebo is depicted in Fig. 3. Venlafaxine and tramadol at 25, 62, and 89 mg were not observed with any significant changes in the IELT. Although tamsulosin has been the
intervention lying on the top of the forest plot with a significant pooled estimate, only one of the studies compared this agent, thus limiting the clinical significance of this intervention. Following tamsulosin, both sertraline and dapoxetine 30 mg carry equal point estimates and dapoxetine 30 mg additionally is associated with greater precision, as evident by the narrow confidence interval surrounding the point estimate. More detailed mixed-treatment comparison estimates between the key interventions are represented in Table 1. Minimal inconsistencies were observed between the direct and mixed-treatment comparison estimates (H = 2.3).

**Sensitivity analyses**

One study [16] used vibratory stimulation method to assess the efficacy of outcome measure and compared phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafl) with placebo. Exclusion of data from this study did not influence the overall interpretation of findings (Electronic supplementary file—ESF 11). Two studies [26, 27] have included patients with erectile dysfunction and the removal of data from these studies did not change the pooled estimates significantly (Electronic supplementary file—ESF 12). A total of seven studies [16–22] had defined PE as per ISSM criteria and removal of data from these studies did not change the pooled estimates of the mixed-treatment comparisons significantly (Electronic supplementary file—ESF 13).

**Grading the evidence**

Grading of the evidence was carried out for the key comparisons (those with narrow confidence intervals and thus more precision) and a summary of the same is mentioned in Table 2. Moderate quality was observed for the
Table 1 Table containing the point estimate (Weighted mean difference) with 95% confidence intervals for the direct and mixed treatment comparisons for IELT for key interventions

<table>
<thead>
<tr>
<th>Comparator intervention</th>
<th>Reference interventions</th>
<th>Dapoxetine 30 mg</th>
<th>Sertraline</th>
<th>Tamsulosin</th>
<th>Fluoxetine 60 mg</th>
<th>Dapoxetine 60 mg + Tadalafil</th>
<th>Paroxetine 30 mg + Sildenafil</th>
<th>Topical lidocaine</th>
<th>Vardenafil</th>
<th>Paroxetine 30 mg + paroxetine</th>
<th>Pindolol 50 mg</th>
<th>Topical lidocaine + Tadalafil</th>
<th>Placebo</th>
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<td>Dapoxetine 30 mg</td>
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<td>0.2</td>
<td>0.2</td>
<td>-0.1</td>
<td>-0.7</td>
<td>-0.5</td>
<td>0.5</td>
<td>-0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
</tr>
<tr>
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<td>-0.2</td>
<td>-0.6</td>
<td>-0.2</td>
<td>-0.5</td>
<td>-0.5</td>
<td>0.5</td>
<td>-0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
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<tr>
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<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
</tr>
<tr>
<td>Fluoxetine daily</td>
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<td>-0.5</td>
<td>-0.5</td>
<td>0.5</td>
<td>-0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
</tr>
<tr>
<td>Dapoxetine 60 mg</td>
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<td>-0.1</td>
<td>-0.8</td>
<td>-0.6</td>
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<td>0.6</td>
<td>-0.6</td>
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<td>1.9</td>
<td>-2.85</td>
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<tr>
<td>Tadalafil</td>
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<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
</tr>
<tr>
<td>Sildenafil</td>
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<td>-0.8</td>
<td>-0.4</td>
<td>-0.8</td>
<td>-0.8</td>
<td>0.8</td>
<td>-0.8</td>
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<td>0.8</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
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<tr>
<td>Topical lidocaine</td>
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<td>-0.2</td>
<td>-0.2</td>
<td>-0.4</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.2</td>
<td>-0.2</td>
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<td>0.2</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
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<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
</tr>
<tr>
<td>Seftaline + sildenafil</td>
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<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>0.6</td>
<td>-0.6</td>
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<td>0.6</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>0.6</td>
<td>-0.5</td>
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<td>0.5</td>
<td>-2.6</td>
<td>1.9</td>
<td>-2.85</td>
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<tr>
<td>Placebo</td>
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*aStatistically significant estimates; D Pooled estimates from direct comparisons, M Pooled estimates from mixed treatment comparisons.
comparisons of dapoxetine 30 and 60 mg on demand, while either low or very low quality was observed for the remaining comparisons.

Discussion

We conducted the present network meta-analysis to compare the medical interventions available for treating PE. A total of 44 studies were included in the meta-analysis and most of the studies had high risk of bias in most of the domains. No publication bias was detected for the comparisons of on-demand dapoxetine 30 mg, paroxetine, and sildenafil with placebo. Except for venlafaxine and tramadol at 25, 62, and 89 mg, all other interventions exhibited a significant prolongation of IELT compared to placebo. Similarly, dapoxetine 60 mg, venlafaxine, fluoxetine, tramadol at 25, 50, and 100 mg, and combined fluoxetine and tadalafil were associated with an increased risk of adverse events. Specifically, dapoxetine 60 mg was associated with an increased risk of headache and, EMLA and sildenafil with increased risk of flushing. No significant changes were observed in the pooled estimates in any of the sensitivity analyses. Moderate quality of evidence was observed for dapoxetine 30 and 60 mg compared to placebo and either low or very low grade for all other key comparisons. Dapoxetine 30 mg has a high likelihood of being the “best” in the interventional pool.

Premature ejaculation could be managed with non-pharmacological measures or using drugs or a combination of both. Non-pharmacological measures include start–stop and squeeze technique, and psychotherapy [60]. Many pharmacological agents have been evaluated for improving IELT in men with PE. But there is no consensus on which agent could likely be the best for PE. We also observed a lot of pharmacological agents to be associated with a statistically significant increase in the pooled estimates of IELT. However, the changes in IELT can be considered as clinically significant only when it is prolonged by at least 1 min [48]. In the present network meta-analysis, although tamsulosin and sertraline were observed with statistically significant pooled estimates and were placed on top of the forest plot, the lower limit of the confidence intervals for both these agents is less than 1 min. Hence, we have inferred dapoxetine at 30 mg to have a greater potential in performing better to increase IELT than other medical interventions for PE. Dapoxetine is a short-acting selective serotonin reuptake inhibitor with a rapid time taken to achieve maximum concentration in the blood. Individual clinical trials and meta-analyses have shown an increase in the IELT with dapoxetine administration either at 30 or 60 mg 1–2 h before intercourse [6]. In fact, no other drug apart from dapoxetine has been approved for the treatment of PE by any regulatory authorities and all other medications are being used as off-label indications [61]. We did not find any increased pooled estimate for dapoxetine 60 mg compared to dapoxetine 30 mg and additionally we also observed an increase in the adverse effects with dapoxetine 60 mg. Hence, we do not recommend the initiation of dapoxetine at 60 mg corroborating the advice from National Institute of Health and Care Excellence [62]. Our recommendations of dapoxetine 30 mg as a first-line agent in PE are also in alignment with the European Association of Urology guidelines [61]. Cost-effectiveness studies with dapoxetine are the need of the hour that can support or refute its use in PE [63].

This is the first network meta-analysis comparing all the medical interventions for PE in a single platform. Till date, we have included the maximum number of studies and correspondingly patients in any meta-analysis comparing drugs for PE. Publication bias was not detected for some of the comparisons and we have used inverse heterogeneity model that does not require any assumptions and is more robust than the random-effects model which has been used in previous direct meta-analyses. Sensitivity analyses were carried out for different definitions of PE, patients with ED, and the results did not deviate significantly from the overall analysis. However, the study is also limited in not having analyzed EMBASE as we did not have access to the database; we could not include quality of life as the outcome measure as there was no consistent assessment of this variable in the included studies; we could not differentiate...
Pharmacological interventions for premature ejaculation: a mixed-treatment comparison network.

Table 2 Grading the quality of evidence for key comparisons of the interventions with placebo for IELT

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Effect estimate and quality of evidence for direct comparisons</th>
<th>Effect estimate and quality of evidence for mixed-treatment comparisons</th>
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</thead>
<tbody>
<tr>
<td>Dapoxetine 30 mg on demand</td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt; 1.2 [1, 1.4]</td>
<td>Low&lt;sup&gt;b&lt;/sup&gt; 1.3 [0.9, 2.8]</td>
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<tr>
<td>Sertraline</td>
<td>Low&lt;sup&gt;c&lt;/sup&gt; 1.7 [0.8, 2.6]</td>
<td>Moderate&lt;sup&gt;d&lt;/sup&gt; 1.7 [0.8, 2.3]</td>
</tr>
<tr>
<td>Paroxetine daily</td>
<td>ND</td>
<td>Very low&lt;sup&gt;c,b,c&lt;/sup&gt; 4.8 [4.4, 5.2]</td>
</tr>
<tr>
<td>Dapoxetine 60 mg on demand</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt; 1.7 [1.3, 2.7]</td>
<td>Low&lt;sup&gt;b&lt;/sup&gt; 1.3 [1.0, 2.8]</td>
</tr>
<tr>
<td>Sildenafil on demand</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt; 2.2 [0.8, 3.6]</td>
<td>ND</td>
</tr>
<tr>
<td>Topical lidocaine</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt; 3.2 [2.5, 3.9]</td>
<td>Very low&lt;sup&gt;c,d&lt;/sup&gt; 3 [2, 4]</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>ND</td>
<td>Very low&lt;sup&gt;c,d&lt;/sup&gt; 1.9 [1, 4.9]</td>
</tr>
</tbody>
</table>

ND—Strength of the evidence could not be ascertained due to mild inconsistencies between the direct and mixed-treatment comparison estimates and serious limitations in the imprecision of estimates.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- Downgraded one level for including studies with high risk of bias.
- Downgraded one level due to first-order loop in the network.
- Downgraded one level as publication bias could not be assessed.
- Downgraded one level due to small number of total participants.
- Downgraded one level due to possibility of publication bias.

lifelong and acquired PE in the included studies due to the lack of any firm definitions from the existing literature; and duration of the final assessment of the outcome measures was different between the included studies. However, we can conclude that current evidence supports the use of dapoxetine at 30 mg as first-line treatment for PE.

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Author contributions KS had full access to all of the data in the study. KS takes responsibility for the integrity of the data, the accuracy of the data analysis, and the final decision to submit for publication. Study concept and design: KS, GS, RG, and KA; acquisition, analysis, or interpretation of data: KS, GS, RG, and KA; drafting of the manuscript: KS, GS, RG, and KA; critical revision of the manuscript for important intellectual content: KS, GS, RG, and KA; and statistical analysis: KS and GS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Pharmacological interventions for premature ejaculation: a mixed-treatment comparison network...


