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UROLOGY - REVIEW

Pharmacotherapy of premature ejaculation: a systematic review and network meta-analysis

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Abstract

Purpose The purpose of the study was to conduct a systematic evaluation of the different general prescribed drugs for premature ejaculation (PE).

Methods A systematic literature search of MEDLINE, Cochrane Central Register of Controlled Trials, and Web of Science for Systematic Reviews was performed on 1 March 2018. Intravaginal ejaculation latency time (IELT) was the main outcome. Analysis was performed under multivariate random-effects network model and efficacies of drugs were ranked with surface under the cumulative ranking (SUCRA) probabilities.

Results A total of 48 studies were reviewed and 40 of them were further enrolled into network meta-analysis. The majority of RCTs were of unclear methodological quality. Pooled evidence suggested that topical anaesthetic creams (TAs), tramadol, selective serotonin reuptake inhibitors (SSRIs), and phosphodiesterase type 5 inhibitors (PDE5is) are more effective at prolonging IELT comparing with placebo. TAs (90%) on demand (OD) and PDE5is plus SSRI (89.8%) had the highest SUCRA, which meant the most probable to be the most effective intervention.

Conclusions We recommend the initial use of dapoxetine 30 mg OD for PE because it has been tested in largest and better designed clinical trials rather than it is more effective than the other drugs studied. TAs and tramadol 50 mg OD can be used as a viable alternative to oral treatment with SSRIs. PDE5is combined with SSRIs are more effective than SSRIs monotherapy but are also associated with more side effects. PDE5is OD can be recommended to PE patients with ED.

Keywords Sexual health · Premature ejaculation · Medical treatment · Pharmacology of ejaculation

Introduction

Premature ejaculation (PE) is a common male sexual dysfunction with a reported prevalence ranging from 20 to 30% based on the relatively low number of men who present for treatment of PE [1]. Though the prevalence is high, the definition of PE has changed several times over the past few years [2, 3] which has compromised research on PE treatments. PE has a negative impact on sexual dysfunction, such as low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse [4, 5]. Besides, PE can have a detrimental effect on the relationship with the partners and may cause problems on psychological consequences, including mental distress, anxiety, embarrassment and depression [5, 6].

Available treatments of PE are varied and may include sexual education, behavioural and pharmacological interventions [7]. The European Association of Urology 2017 Guidelines on male sexual dysfunction recommend that using pharmacotherapy as first-line treatment of lifelong PE (Level of evidence: 1a). The most common pharmacological strategies for PE management include short-acting selective serotonin reuptake inhibitors (SSRIs) dapoxetine on demand (OD) (the only approved pharmacological treatment for PE) or other off-label treatments, such as long-acting SSRIs,

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topical anesthetics (TAs), phosphodiesterase type 5 inhibitors (PED5is) and tramadol. Several traditional pair-wise meta-analyses [8–10] reported that pharmacological treatments were effective comparing with placebo, but lacking evidence on which is better. It is difficult for traditional meta-analyses to explain such topic comprehensively because it can only synthesis evidence from the head-to-head trial. The network meta-analysis [11] is a newly introduced method in which it can make indirect comparison using a common comparator when a head-to-head trial is not available. It also can combine direct and indirect comparisons to simultaneously compare several treatments with preservation of randomisation in individual trials.

Intravaginal ejaculation latency time (IELT) represents the most objective criterion for assessing PE improvement according to the latest definition (IELT < 1 min), and is a primary endpoint commonly used in PE studies. Therefore, we conduct a systematic review and present a network meta-analysis of treatment effectiveness based on the IELT. The aim of our study is to explore which pharmacologic treatment for PE is better in improving IELT by summarizing evidences from Randomized Controlled Trials (RCTs).

Methods

This review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Search strategy

A systematic literature search of MEDLINE, Cochrane Central Register of Controlled Trials, and Web of Science according to PRISMA guidelines, was conducted to identify relevant studies. The timeframe spanned from the startup (from 1966, 1997 and 1900, respectively) of these databases to 1 April 2018. The search was restricted to the English language and human participants. The search strategy was developed from the Population, Intervention, Comparison, Outcome and Study design (PICOS) study framework. The search strategy used in Medline was the MeSH terms and text words, was ((((((“Therapeutics/pharmacology”[Mesh]) OR (therapeutics OR therapy OR treatment)) OR (pharmacology OR pharmacological))) AND (“Premature Ejaculation”[Mesh] OR Premature Ejaculation))) AND ((((random* OR randomized) OR ((Randomized Controlled Trial [Publication Type]) OR “Randomized Controlled Trials as Topic”[Mesh])))). The literature search was performed by two independent reviewers. Disagreements were resolved by consensus or consultation with a third reviewer.

Eligible criteria

Studies met all of the criteria listed below were included in our review. The PICOS evidence base consisted of the following: (1) Participants: patients > 18 year of age suffering from PE. (2) Interventions: pharmacologic treatment. (3) Comparisons: comparison among different drug treatments and placebo. (4) Outcomes: IELT. (5) Study design: prospective RCT. Besides, the mean with their standard deviation (SD) could be extracted (or information to calculate them). Exclusion criteria were the following: (1) full articles not in English; (2) article not reporting on any pharmacologic treatment as follows: SSRIs, Tramadol, TAs, PDE5i and their combination; (3) review, meta-analysis, meeting abstracts, comments, editorials, letters, congress reports and case reports; (4) duplicated or updated data;

Data extraction and quality assessment

The data were extracted by two independent reviewers. A third reviewer resolved any disagreement. The following information was extracted from each eligible article: summary estimates per group (mean, changes in means) with measures of variability [SD, 95% confidence interval (CI)] were extracted for continuous data if available. The primary outcome was the IELT, and the second outcome was the adverse effects reported in each study. When a SD was not provided, it was calculated with the P value or imputed from other trials included the meta-analysis using the formula: $\mathrm{SD}_{\mathrm{pooled}} = \sqrt{\frac{\sum(n_i-1)SD_i^2}{\sum(n_i-1)}}$ [13].

The quality assessments of eligible studies were evaluated using the Cochrane Risk of Bias Tool. The items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. The judgments for each entry involved were divided into three grades: “high”, “unclear” and “low”. The quality assessment was performed by two independent reviewers, and disagreements were resolved by consensus.

Statistical analyses

Regimens to be included for network meta-analysis should have been investigated at least in two trials to get pooled outcome. IELT was gauged by a standard multivariate random-effects network model [14]; the mean differences (MD) with 95% CIs of each intervention compared with control or any two interventions compared with each other were worked out. If the 95% CI was above or under

than zero, then the difference was statistically significant ($P < 0.05$).

We used the surface under the cumulative ranking curves (SUCRA) probabilities to assess the efficacy of different drugs, which was a common and popular method used in network-meta analysis [11]. SUCRA expresses a percentage of the efficacy of every intervention compared to an imaginary intervention that is always the best without uncertainty. A SUCRA value of 100% is assigned to the best treatment and 0% for the worst treatment.

Network of the included comparisons was shown through network graph. A comparison-adjusted funnel plot was used to assess the presence of small-study effect and publication bias. Inconsistency was tested by Higgins and Dias model, and $P > 0.05$ indicated a low risk of inconsistency in network meta-analysis. Sensitivity analyses were performed through only enrolling studies restricting to IELT < 2 min, studies excluding vibratory stimulation method and studies excluding patients with erectile dysfunction (ED).

All the analyses were performed with Stata 14 (Stata Corp, College Station, TX, USA) and Review Manager 5.3.

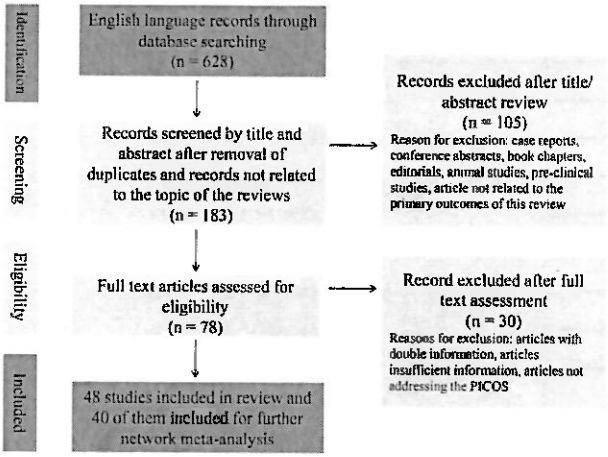


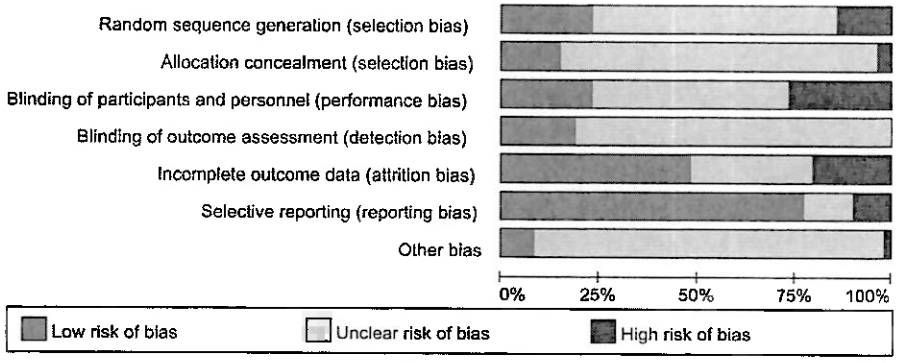
Fig. 1 Preferred reporting for systematic reviews and meta-analyses flow diagram

Results

The flowchart of study identification and inclusion process is shown in Fig. 1. Forty-eight studies were included in review and quality assessment [15–62]. Eight studies [15, 17, 24, 32, 38, 51, 58, 59] were excluded from meta-analysis because of no suitable comparator, regimen only reported once or could not extract the mean and sd of IELT. Finally, 40 studies investigating 14 interventions were included for further network meta-analysis as follows: TAs OD; tramadol (25 mg, 50 mg and 100 mg OD); fast-acting SSRI (dapoxetine 30 mg and 60 mg OD); long-acting SSRIs (sertraline 50 mg daily, fluoxetine 20 mg daily, paroxetine 20 mg daily and paroxetine 20 mg OD); PDE5is (sildenafil 50 mg OD, vardenafil 10 mg OD, tadalafil 20 mg OD) and combination of SSRIs and PDE5is OD. The detailed information for each article was showed in Supplementary Table S1. The pooled risk of bias assessment for the 48 studies is shown in Fig. 2. Supplementary Fig. S1 showed the complete risk of bias assessment for each study. In general, the quality of the reporting methodology was relative low, resulting in uncertainty regarding the risk of bias for the majority of the RCTs.

Network graph is shown in Fig. 3. Nodes were proportional to the number of patients, and edges were weighted according to the number of studies included in the comparisons. Figure 4 shows all the comparisons analysed within the network and the results of SUCRA. Pooling of MD for IELT for individual regimens compared to placebo in the network meta-analysis showed statistically significant advantages for all 14 regimens. The graph of SUCRA rank was showed in Supplementary Fig. S2. Supplementary Table S2 showed the details of side effects of each included study. We did not pool these data into network meta-analysis, because the side effects of each category of drugs were not exactly the same due to the different pharmacological actions.

Fig. 2 Overall quality assessment for the included studies



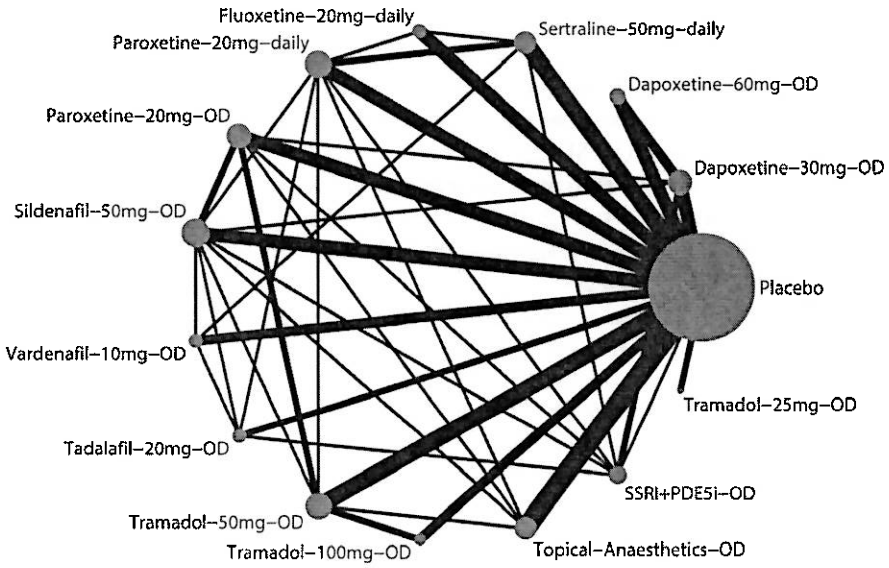


Fig. 3 Network graph of comparison included in the analysis. Nodes are proportional to the number of patients, and edges are weighted according to the number of studies included in the comparisons

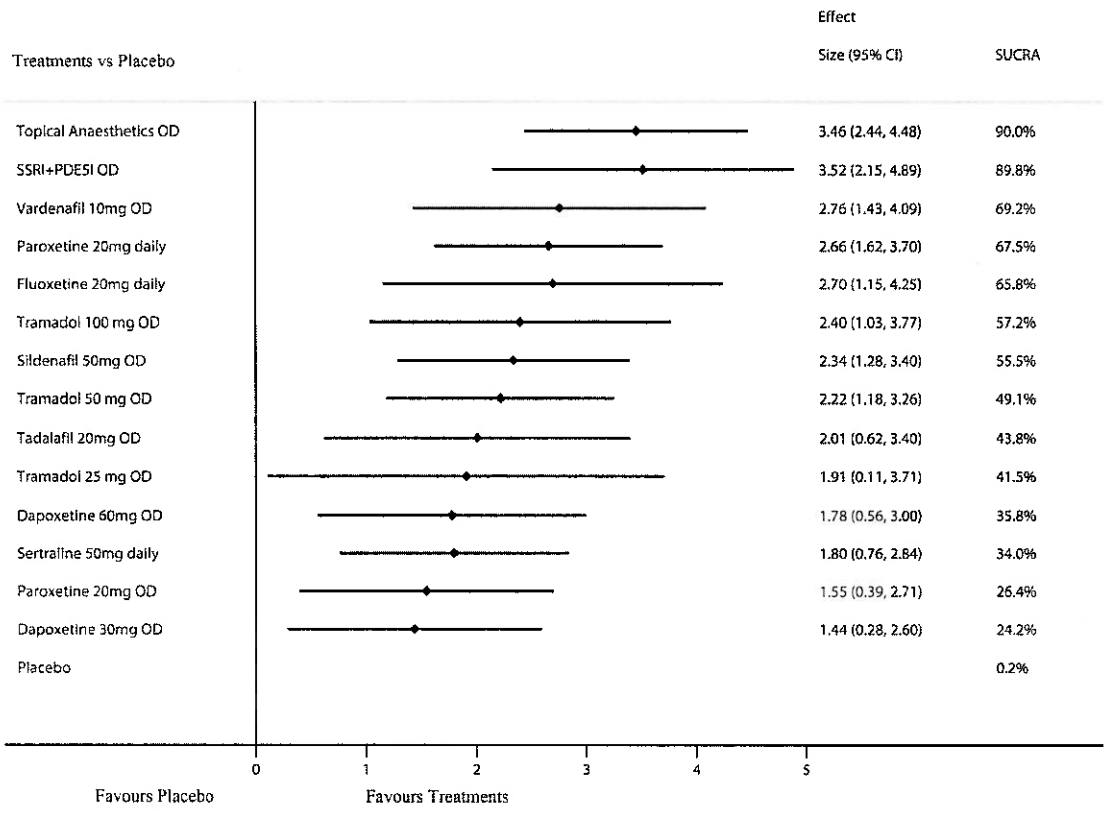


Fig. 4 Forest plot of different regimens in prolonging IELT compared to placebo for PE, and the SUCRA of each regimen included in network meta-analysis

TAs

TAs represented the historical off-label treatment for PE. A total of seven studies were included in network meta-analysis. Eutectic mixture of local anaesthetic (EMLA; AstraZeneca) cream containing lidocaine and prilocaine was tested in two studies [26, 27]. Three RCTs [34, 42, 43] prescribed topical eutectic-like mixture for PE (TEMPE;

Plethora Solutions) spray containing lidocaine and prilocaine. One RCT prescribed a lidocaine gel [53] and one reported a lidocaine spray [59]. Overall, TAs OD ranked the 1st for SUCRA (90%) which meant the most probable to be the best intervention at improving IELT. When comparing with placebo, TAs showed a significant advantage for prolonging IELT (MD 3.46; 95% CI 2.44–4.48). Treatment-related adverse events with TAs mainly included penile and vaginal numbness, possibly resulting in loss of erection and anorgasmia in female partners. All these adverse effects were reported as being tolerable (Supplementary Table S2).

Tramadol

Tramadol was a centrally acting analgesic prescribed off-label for the treatment of PE, which was mainly used to treat moderate to moderately severe pain being an opioid pain medication. Nine studies [31, 36, 45, 48, 49, 53, 54, 57, 62] with three regimens (25 mg, 50 mg and 100 mg OD) were included in our meta-analysis. All three regimens showed significant benefit comparing with placebo. Tramadol 100 mg OD had a higher SUCRA (57.2%), followed by 50 mg OD (49.1%) and 25 mg OD (41.5%) (Fig. 4). Somnolence and pruritus were the most common side effects, which occurred 100% in Eassa et al. study [51]. Other common side effects included nausea, vomiting, headache and dizziness. The incidence rates of these side effects increased with the increment of dosage (Supplementary Table S2).

Long-acting SSRIs

SSRIs were a class of compounds typically used as antidepressants and were prescribed as an effective treatment for patients with PE whether or not these patients suffer from depression. There were 18 [15–25, 30, 33, 45, 55, 56, 58, 60] published studies testing long-acting SSRIs daily use with 8 regimens were included in this review. Among these regimens, paroxetine 10 mg daily [58], fluoxetine 40 mg daily [17], sertraline 100 mg daily [17], fluvoxamine 100 mg daily [18] and citalopram 20 mg daily [24] were excluded from meta-analysis because that these regimens were reported only once.

Seven studies [22, 32, 35, 38, 53, 61, 62] with four regimens explored the efficacy of long-acting SSRIs OD use. For the same reason, fluoxetine 20 mg OD [32], fluoxetine 90 mg once weekly [35] and citalopram 20 mg OD [38] were not enrolled into meta-analysis. In summary, four regimens were finally included in further analysis (paroxetine 20 mg, fluoxetine 20 mg, sertraline 50 mg daily and paroxetine 20 mg OD).

Although all the four regimens showed significant advantages comparing with placebo, the efficacy of paroxetine 20 mg daily (67.5%) and fluoxetine 20 mg daily (65.8%) were obviously better than sertraline 50 mg daily (34%) and paroxetine 20 mg OD (26.4%) according to the rank of SUCRA (Fig. 4). SSRIs treatment-related side effects included fatigue, yawning, nausea and sleep disturbance. In addition, what need to be noted was that sudden interruption may cause SSRI withdrawal syndrome, including nausea, dizziness, headache, drowsiness and so on (Supplementary Table S2).

Short-acting SSRI

Dapoxetine hydrochloride was currently the only SSRI approved for OD treatment for PE because of its rapid absorption and short initial half-life. Two regimens (30 mg and 60 mg OD) tested in six studies [29, 40, 43, 50, 52, 61] were included in meta-analysis. Pooled evidence suggested that dapoxetine 30 mg OD and 60 mg OD both resulted in a significant increase in IELT when compared to placebo (MD 1.44; 95% CI 0.28–2.60 and MD 1.78; 95% CI 0.56–3.00, respectively). The SUCRA of 60 mg dosage (35.8%) was higher than 30 mg dosage (24.2%), which meat dapoxetine 60 mg OD had a higher probability to be a better intervention than 30 mg OD though it was not a big difference (Fig. 4). Similar to the long-acting SSRIs, the most common adverse events with dapoxetine were Nausea, headache, and dizziness. Dapoxetine 60 mg was associated with more side effects comparing with 30 mg. No discontinuation syndrome following abrupt withdrawal was observed (Supplementary Table S2).

PDE5is

PDE5is were the first-line treatment for ED and were prescribed off-label for the treatment of PE. The compounds that had been studied in PE included vardenafil, sildenafil, and tadalafil. Ten published studies [28, 33, 35, 38, 41, 46, 47, 53, 56, 61] total of three regimens, including vardenafil 10 mg OD, sildenafil 50 mg OD and tadalafil 20 mg OD, were enrolled into meta-analysis. Treatments with all three regimens were significantly more effective at improving IELT than placebo. SUCRA of vardenafil 10 mg OD (69.2%) ranked first, followed by sildenafil 50 mg OD (55.5%) and tadalafil 20 mg OD (43.8%) (Fig. 4). As for side effects, sildenafil and tadalafil were associated with greater incidence of headache and flushing compared to placebo, and tadalafil was also associated with greater incidence of dyspepsia (Supplementary Table S2).

Combination of SSRIs and PDE5is

Seven studies [32, 35, 52, 55, 56, 58, 61] reported the combination of SSRIs and PDE5is. As expected, the combination showed significantly better IELT (MD 3.52; 95% CI

2.15–4.89), and SUCRA (89.8%) ranked the second among all interventions, which was obviously higher than SSRIs and PDE5Is alone (Fig. 4). The common side effects were similar to the SSRIs and PDE5is mentioned above, but the combinations seemed to bring about higher rates of side effects, such as headache and flushing (Supplementary Table S2).

Sensitivity analyses

A total of 29 studies [18, 20, 22, 23, 26, 28–31, 33, 35, 36, 38, 40–44, 46–50, 53, 55, 57, 60–62] had defined PE as IELT < 2 min (including IELT < 1 min) criteria and were enrolled into meta-analysis. The pooled estimates of the mixed treatment comparisons did not change significantly (Supplementary Table S3). Two studies [46, 47] used vibratory stimulation method to assess the efficacy of PDE5is. Removal of data from these studies did not change the results significantly. One study [50] had included patients with ED and exclusion of data from this study did not influence the overall interpretation of findings.

Consistency, publication bias and small sample effect

The inconsistency result of network meta-analysis by Higgins model showed that P value was more than 0.05 ($\chi^2 = 23.40$, $P > \chi^2 = 0.7129$), which indicated that no evidence showed inconsistency existing in the network model. The inconsistency test was the same in Dias model. The difference between direct comparison and indirect comparison was not statistically significant ($P > 0.05$) (Supplementary Fig. S3). All the above tests showed that the network meta-analysis model was good fit for assessment in IELT. Besides, Supplementary Fig. S4 showed a comparison-adjusted funnel plot of the studies included in this meta-analysis. Most of the studies were evenly distributed inside the 95% CIs and gathered at the top, which meant a low risk of publication bias and small sample effect.

Discussion

In past decades, a plethora of pharmacological treatments had been investigated for PE. Among these interventions, TAs, tramadol, SSRIs and PDE5is were the most tested treatments. However, there was no consensus on which agent might be the best for PE. An increase in IELT was the main goal of PE therapy. Therefore, we conducted a network meta-analysis which could combine direct and indirect comparisons to simultaneously compare several treatments with preservation of randomisation in individual trials, based on IELT.

For any meta-analysis, there were three core assumptions that should be considered namely homogeneity, consistency and similarity. In our study, the main homogeneity might result from differences in inclusion criteria, active compound, dosage, usage, and treatment period. We tried our effort to reduce the source of homogeneity through removing the differences of compound, dosage and usage. The residual homogeneity indeed existed. But the approach of using a random effect model, which had taken homogeneity into account, gave more conservative results. The inconsistency and publication bias were not significant in our meta-analysis through statistical tests. Similarity was assessed by a detailed examination of the trial characteristics. In our study, all the included studies were RCTs and the quality of each study was evaluated based on Cochrane library guideline. But the quality of the reporting methodology was relative low, resulting in uncertainty regarding the risk of bias for the majority of the RCTs. In addition, regimens only reported once were excluded from meta-analysis which could help to reduce the certain bias. In our study, no significant changes were observed in the pooled estimates in any of the sensitivity analysis.

In our study, TAs OD ranked the first in SUCRA (90%), which meant the most probable to be the best intervention for PE therapy. Moreover, systemic adverse events were more prevalent with oral treatments, which might make TAs more acceptable. Likewise, the rapid action of TAs might be more acceptable comparing with planning to take oral tablet in advance. However, some limitations should be treated carefully. First, the methodological quality of the available evidence reporting TAs was relative low. Second, the inconvenience of washing and adverse events such as penile and vaginal numbness, possibly resulting in loss of erection and anorgasmia in female partners, might limit the acceptability of TAs. Third, the efficacy should be interpreted with caution, because three important studies were sponsored by industry [34, 42, 43]. And most of these studies were small sample size which might lead to larger differences in IELT outcome.

As expected, combination of SSRIs and PDE5is OD showed better IELT than single application. The SUCRA (89.8%) was the same as TAs, which meant the same probability to be the best intervention. However, similar limitations, such as relative low quality, differences in patient selection, baseline IELT, drug dosages and usage among the studies evaluated, existed for combination as a treatment option. Besides, combination was associated with more treatment-related adverse effects.

Tramadol represented a kind of opioid analgesic to treat moderate to moderately severe pain. Three regimens (25, 50, and 100 mg OD) significantly prolonged the IELT compared to the placebo and the SUCRA ranked the middle position comparing with other regimens. But the high dosage

(100 mg) did not show obviously significant advantage than low dosage (25 and 50 mg). At the same time, the regimens at low dosage were well accepted and tolerated regarding its side effects. Moreover, the lower limit of the CI for 25 mg OD was close to zero. Therefore, we recommend that tramadol 50 mg OD might be a suitable regimen for PE. Also this recommendation should be carefully weighed against the risk of drug dependence [63]. Similar limitations existed for tramadol as a treatment option mentioned above.

Daily and OD treatments had been proposed for long-acting SSRIs. Our pooled analysis showed that SUCRA of paroxetine 20 mg daily (67.5%) and fluoxetine 20 mg daily (65.8%) were obviously higher than sertraline 50 mg daily (34%) and paroxetine 20 mg OD (26.4%), which meant that the first two regimens had higher probability to be better treatments than the rest of two regimens. Side effects of these regimens were the similar. So the two regimens namely paroxetine 20 mg daily and fluoxetine 20 mg daily were recommended when SSRIs were applied in clinical practice according to our study. Similarly, this result should be interpreted with caution owing to low quality of single trial and differences in patient selection, baseline IELT, drug dosages and usage among the studies evaluated.

Our network meta-analysis suggested that PDE5is were significantly more effective than placebo and that PDE5is combined with SSRIs were significantly more effective than SSRIs monotherapy. SUCRA of three regimens vardenafil 10 mg OD (69.2%), sildenafil 50 mg OD (55.5%) and tadalafil 20 mg OD (43.8%) took the middle place among all interventions. When comparing with SSRIs, increase in IELT of PDE5is was not significantly different. Two [46, 47] of four studies testing vardenafil used vibratory stimulation method to assess the efficacy, which might large the difference between vardenafil and placebo. In our sensitivity analyses, removal of data of these two studies, the results did not change significantly. However, these findings should be interpreted with caution, given the high levels of statistical heterogeneity that were evident across RCTs and the clinical heterogeneity of recruited participants along with the unclear methodological quality of the existing RCT evidence base. In consideration of that PDE5is were the golden standard for the treatment of ED, we recommended that PDE5is could be chosen first for PE patients with ED.

Dapoxetine was the only oral drug approved for PE in adult males. Until now, dapoxetine had the largest efficacy and safety database for use in men with PE. The pharmacology of dapoxetine made it adequate for on-demand treatment in most patients in terms of IELT improvement, leading to convenience and acceptance for the patients. Our pooled evidence suggested that dapoxetine 30 mg and 60 mg OD were both significant efficacy compared to placebo. 60 mg OD had a not obviously better SUCRA than 30 mg OD, but was associated with more side effects. However, dapoxetine 30 mg OD ranked the last place in our study. All of the first four biggest sample size studies included in out meta-analysis were dapoxetine, which might help to explain its low ranking. Because smaller studies have generally shown positive results, and smaller studiers always mean single-center studies which were reported showing larger treatment effects than multicenter studies [64]. Based on the largest efficacy and safety database, we recommended that dapoxetine 30 mg OD could be the initial treatment for PE.

There were several limitations that should not be ignored. First, though prolonging IELT was the main goal for treating PE, ejaculatory control and sexual satisfaction were also important for evaluation of therapeutic effect. However, most of studies did not report the relationship between IELT, ejaculation control and sexual satisfaction. Therefore, it was difficult for us to quantify how acceptable and meaningful of IELT improvements for PE treatments. In addition, the changes in IELT could be considered as clinically significant only when it was prolonged by at least 1 min. For example, an increase in IELT from 30 to 50 s was probably statistical significance, but not clinically significant according to the latest definition of PE (IELT < min). Although every RCT showed no difference in baseline IELT among intervention groups, the baseline IELT was not the same among studies because of the different inclusion criteria. Second, treatment periods were not the same among included studies which could influence the therapeutic efficacy. Third, few studies distinguished between lifelong PE and acquired PE, for which the IELT cutoff differed. Likewise, inclusion criteria differed by the fact that the definition of PE had changed several times over the past few years. Such methodological drawbacks limited systematic interpretation of the treatment efficacy for PE. Fourth, bias caused by certain methodological deficiencies and not well-designed RCTs included in the analysis still existed in our study. Fifth, though we systematically reviewed the drug treatment-related side effects, we did not investigate them through network meta-analysis method because of different side effects among different kinds of drugs and the limited data, which were also important for drug comparison. Sixth, some studies discussing other uncommon regimens (reported only once) were excluded in our network meta-analysis. However, further analysis should be performed when the data are enough in the future. Finally, we tried our effort to reduce the source of homogeneity through removing the differences of compound, dosage and usage, the residual homogeneity indeed existed because of the patient selection, baseline IELT, methodological deficiencies and relative low quality of RCTs.

Conclusion

As for pharmacotherapy of PE, all regimens show efficacy in prolonging IELT comparing with placebo. We recommend the initial use of short-acting SSRI dapoxetine 30 mg OD for PE because it has been tested in largest and better designed or described clinical trials rather than it is more effective than the other drugs studied in our network meta-analysis. With regard to long-acting SSRIs, paroxetine 20 mg daily and fluoxetine 20 mg daily are more effective than sertraline 50 mg daily and paroxetine 20 mg OD. TAs has the highest probability to be the best intervention and it should be validated in future large and well-designed RCTs. At present, TAs can be used as a viable alternative to oral treatment with SSRIs. We find evidence to suggest that PDE5is combined with SSRIs are more effective than SSRIs monotherapy but are also associated with more side effects. Given the golden standard role in treating ED, we recommend PDE5is OD (vardenafil 10 mg, sildenafil 50 mg or tadalafil 20 mg) to PE patients with ED. Tramadol appears effective in the treatment of PE and 50 mg OD maybe the suitable regimen acting as an alternative to SSRIs. However, all of these results should be interpreted with caution because of the limitations in our study.

Author contributions ZJ and XW: project development, data collection and management, manuscript writing and revising, data analysis; DY: data collection, data analysis and revising; HL: data collection, data analysis; KW: project design and development, data interpretation, manuscript editing and revising. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors of this article as well as all the included studies declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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