Systematic Review and Meta-Analysis

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Comparative efficacy and safety of phosphodiesterase-5 inhibitors with selective serotonin reuptake inhibitors in men with premature ejaculation

A systematic review and Bayesian network meta-analysis

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Abstract

Background: We performed the network meta-analysis (NMA) and systematic review involved all evidence from relevant trials to compare the efficiency and safety of various types of selective serotonin reuptake inhibitors (SSRI) and phosphodiesterase-5 inhibitors (PDE5i) in patients with premature ejaculation (PE).

Methods: We conducted comprehensive searches of peer-reviewed and grey literature. PubMed, the Cochrane Library Central Register of Controlled Trials, Embase were searched for randomized controlled trials published up to June 1, 2017. The primary outcome was intravaginal ejaculation latency time (IVELT) and adverse effects (AEs). We performed pairwise meta-analyses by random effects model and network meta-analysis by Bayesian model. We used the GRADE framework to assess the quality of evidence contributing to each network estimate.

Results: Of 3046 titles and abstracts initially identified, 17 trials reporting 5739 participants were included. Considering IVELT in the NMA, paroxetine plus sildenafil and sildenafil alone are both superior to placebo (MD: 1.75, 95% CrI: 0.05 to 3.78; MD 1.43, 95% CrI 0.003 to 2.81). Sildenafil is superior to sertraline (MD: 1.63, 95% CrI: 0.10 to 2.79). Considering AEs, placebo demonstrated obviously lower risk comparing to paroxetine, sildenafil and paroxetine plus sildenafil (OR 0.20, 95% CI: 0.05 to 0.52; OR 0.23, 95% CI: 0.04 to 0.80; OR 0.45, 95% CI: 0.01 to 0.92). Compared with tadalafil plus paroxetine, dapoxetine showed significantly less AEs (OR 0.23, 95% CI 0.02 to 0.96).

Conclusions: Our study concluded that although paroxetine plus sildenafil and sildenafil alone both demonstrated significant IVELT benefit compared with placebo, significant increase of AEs risk was also observed. Furthermore, sildenafil alone was superior to sertraline in efficacy with comparable tolerability.

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Kun Jin, Linghui Deng, and Shi Qiu: These authors have contributed equally to this work. We synthesize the best available evidence to inform premature ejaculation treatment strategies.

In the absence of head-to-head trials, this is the first systematic review and network meta-analysis to provide a comprehensive estimate of relative efficacy and safety of premature ejaculation treatment strategies.

We include only English-language peer-reviewed random randomized controlled trials making it possible that some relevant articles were not included.

The considerable amount of heterogeneity between included studies was not fully explained by the variables examined.

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Abbreviations: AEs = adverse effects, CI = confidence intervals, CrI = credibility intervals, IVELT = intravaginal ejaculation latency time, MD = mean difference, NMA = network meta-analysis, OR = odds ratio, PDE5i = phosphodiesterase-5 inhibitors, PE = premature ejaculation, RCT = randomized controlled trials, SSRI = selective serotonin reuptake inhibitors.

Keywords: phosphodiesterase type 5 inhibitor, premature ejaculation, selective serotonin reuptake inhibitor

1. Introduction

Premature ejaculation (PE) is a common adult male sexual disorder, with the prevalence rates of 20% to 30%.[1] According to the newly International Society for Sexual Medicine (ISSM) Guidelines, PE is defined as "Ejaculation that always occurs less than 1 min of vaginal penetration from the first sexual experience (lifelong PE), or a clinically significant and bothersome reduction in latency time, often ≤ 3 min (acquired PE)".[2] It is associated with 'marked distress or interpersonal difficulty[3] affecting sexual enjoyment and confidence, relationships of both partners and other aspects of an adult man's life.[4,5] Intravaginal ejaculation latency time (IVELT) is regarded as the most common and useful treatment standard, for the reason of its sensitivity in measuring the efficacy of PE treatment.[6,7]

At present, medication therapy of PE includes selective serotonin reuptake inhibitor (SSRI) therapy (citalopram, sertraline, fluoxetine, dapoxetine or paroxetine), phosphodiesterase type 5 inhibitor (PDE5i) therapy (tadalafil or sildenafil), topical desensitizing agents (prilocaine or lidocaine) and other agents (tramadol or pindolol). Reports showed that oral intake of SSRI appeared as effective for patients with PE,[8] resulting from its function of increasing the time IVELT. Except for efficacy, SSRI is recommended by AUA and International Society of Sexual Medicine guidelines because of its character of well-tolerated (eg, less anorexia, anejaculation, gastrointestinal upset and reduced libido).[9]

The choice of first line treatment is best addressed by direct comparisons of treatment regimens in high quality studies, but such studies considering SSRI combined with PDE5i do not yet exist for PE. Previous systematic reviews and meta-analyses have relied on direct comparisons: dapoxetine in different dose versus placebo,[10,11] SSRI plus PDE5i versus placebo,[12] SSRI, PDE5i versus the combination of SSRI plus PDE5i,[13] SSRI versus PDE5i,[14] tramadol versus placebo,[15] SSRI, PDE5i, tramadol versus placebo.[16] These reviews restricted to the overall variety (eg, SSRI, PDE5i or combination of SSRI plus PDE5i). Two meta-analysis had limitations as they focused on only a select number of interventions (dapoxetine or tramadol), which limited the evidence to a fraction of that available. Furthermore, in the absence of head-to-head trials, their relative efficacy and safety were unknown. We performed a pairwise meta-analysis and Bayesian network meta-analyses (NMA), comparing the relative efficacy and safety of PE treatment strategies.

2. Methods

2.1. Search strategy

Medline, Embase, the Cochrane central register of controlled trials, and the reference lists of the retrieved studies were searched to identify RCTs studies. A search strategy using the medical subject heading and text keywords: "premature ejaculation" was used (see online supplementary appendix 1, http://links.lww.com/MD/C673). The latest search was completed on 31 August, 2017. The previous published systematic reviews and reference lists of retrieved publications were also reviewed for additional studies. Ethical approval was not necessary for our study because all the participants were from others' RCT and our NMA did not involve information collection of patients.

2.2. Study selection

Following the principles of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), we established the inclusion criteria before searching.[17] Two reviewers (KJ and SQ) included all prospective randomized controlled trials (RCT) comparing one or more common pharmaceutical treatment with SSRIs combined with PDE5I, SSRIs monotherapy, PDE5I monotherapy or placebo for the PE patients. Studies that met the following criteria were finally included:

(1) trials were conducted in a homogenous group of PE patients;

(2) the interventions compared included at least 2 of the 4 treatment options;

(3) the outcomes included IVELT, satisfactory score and/or adverse effects (AEs);

(4) full-text original articles. Studies were excluded if they were non-English, review, non-randomized intervention, and study design.

We also excluded crossover trials and quasi-randomized studies. If duplicate studies were found, only the publication with the most complete data was used. Using the reference manager software Endnote, we identified and remove the duplicate records. Next step, 2 members (KJ and SQ) of our team independently scanned each title and abstract. If necessary, 2 study team members performed independent full-text reviews. After scanning all potentially relevant articles, 2 members of our study team discussed to consensus. Any discrepancies in the study inclusion were resolved by consulting the senior authors (QW).

2.3. Data extraction

Data were extracted by 2 reviewers (S.Q and K.J) from original trial using a specifically designed form that collected information on first author, publication year, the number of patients, definition of PE, patient characteristics (age, acquired/lifelong PE), details of treatment options and outcomes. We chose IVELT as the primary outcome, defined as the time that intercourse lasts from initiation of vaginal penetration to ejaculation. It was mainly measured by a stopwatch and expressed in minutes. Secondary outcomes were satisfactory score and AEs, each patient recorded their satisfaction with sexual intercourse before and post the treatment. We mainly concentrated on the change in posttreatment of IVELT and satisfactory score over the baseline. The AEs reported in each treatment intervention mainly including headache and dizziness, fatigue, decreased libido, gastrointestinal upset, palpitation, nasal congestion, erectile dysfunction and flushing. Disagreements were resolved by a third reviewer (Q.W).

2.4. Assessment of risk of bias

Two reviewers (K.J and S.Q) assessed studies quality using the methodology and categories on the basis of the Cochrane

Collaboration Handbook.[18] Concisely, the tool for assessing risk of bias includes 7 specific domains: random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain is assigned a judgement relating to the risk of bias for that study classified as low risk, high risk, or unclear. We presented risk of bias graphs by Review Manager 5.3 software.

2.5. Data synthesis and statistical analysis

We performed pair-wise meta-analysis in random effects model initially. We expressed the results as mean difference (MD) with 95% confidence intervals (CI) for continuous outcomes (variation of IVELT or Satisfactory Score), and the odds ratio (OR) with 95% confidence intervals (CI) for discontinuous outcomes (AEs). The Cochran Q test and the I^2 statistic were used to evaluate the statistical heterogeneity among studies. A P value of .05 or less for the Q test or an I^2 greater than 50% was suggestive of substantial study heterogeneity. Random-effects Bayesian NMA was performed for indirect and mixed comparisons using Markov chain Monte Carlo methods in WinBUGS version 1.4.3.[19] We report the resultant effect as MD/OR with corresponding 95% credibility intervals (CrIs). We evaluated the relative ranking probability of each strategy and obtained the hierarchy of competing interventions using surface under the cumulative ranking curve (SUCRA).[20] We employed the node-splitting method to assess the presence of inconsistency.[21]

2.6. Quality of evidence

Two researchers (K.J and S.Q) independently evaluated the quality of each pair of comparison. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology[22] was performed to rate the quality of evidence. In this approach, direct evidence from RCTs starts at high quality and can be downgraded based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and publication bias to levels of moderate, low and relatively low quality.[23]

3. Result

3.1. Literature search and study characteristics

The primary literature search yielded 1241 citations in total, of which 675 articles met the criteria that identified according to their titles and abstracts. The study selection process is shown in Figure 1. Among these consequences, 130 studies were screened for the inclusion after the full test analyses. 113 articles were

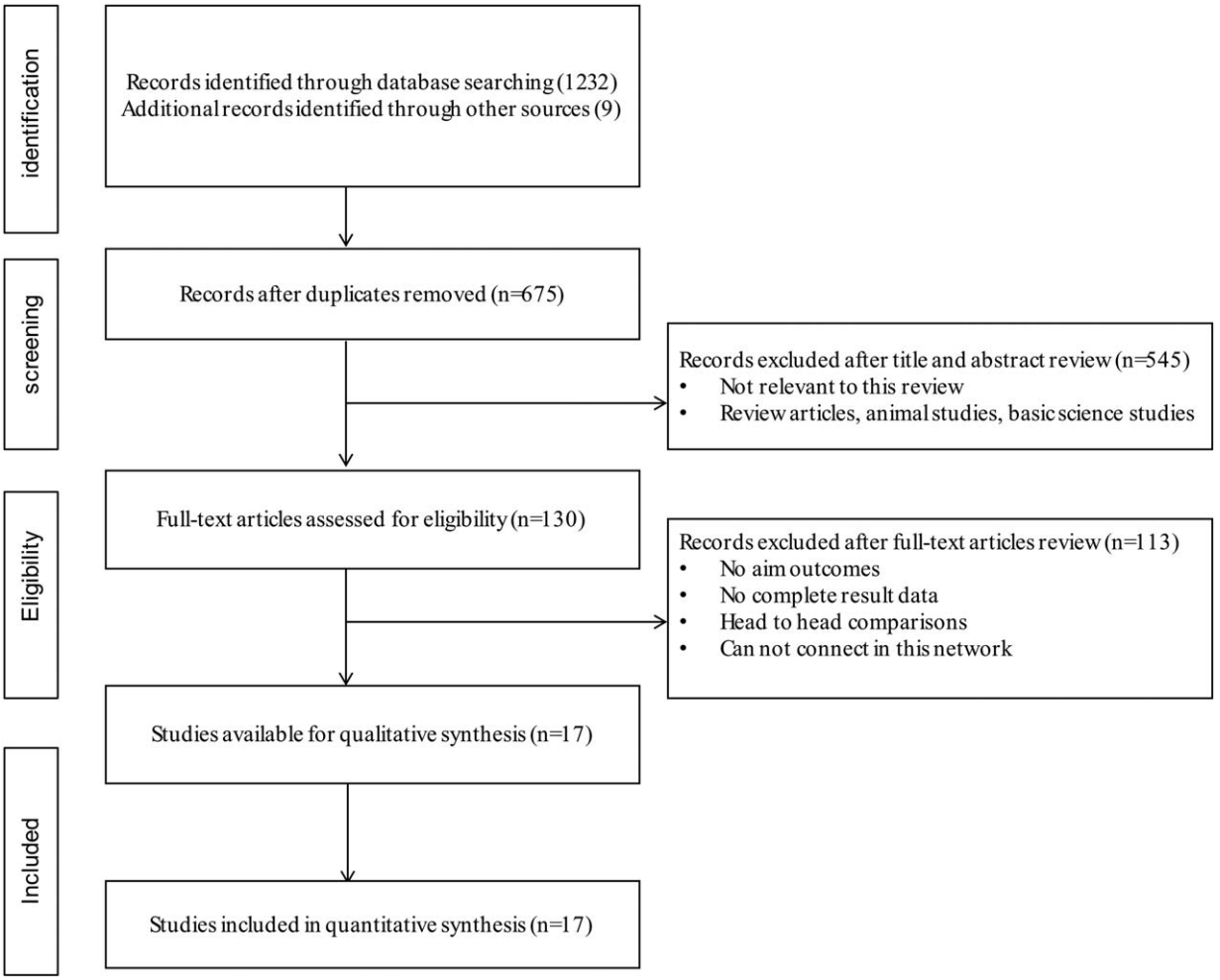

Figure 1. Flowchart of studies inclusion.

excluded for the reason of researches with single-armed experimental group, no randomized study design, crossover or quasi-randomized studies, no relevant outcome reported and no relevant treatment. In the end, 17 eligible articles were left to fit our analysis.[9,24–39]Table 1 summarizes the characteristics of these 17 RCTs covering 5739 adults aged from 18–77. All participants in the trials were diagnosed premature ejaculation or with IVELT of about 0.5–1.5 min more than 1 year. Overall, 7 single medication (paroxetine, dapoxetine, fluoxetine, sertraline, tadalafil, sildenafil, placebo) and 5 combined medications were included (tadalafil plus sildenafil, dapoxetine plus mirodenafil, tadalafil plus fluoxetine, paroxetine plus sildenafil, sildenafil plus fluoxetine). The network plot had a polygonal network configuration with mixed connections (Fig. 2 and online supplementary appendix 2, http://links.lww.com/MD/C673).

3.2. Quality assessment

The details of quality assessment are as measured by the Cochrane Collaboration risk-of-bias tool (see online supplementary appendix 3, http://links.lww.com/MD/C673). Quality assessment were measured by Cochrane risk-of-bias tool. Details of these 17 studies are shown in Figure 3. Five studies[24,26,28,33,35] showed low risk in random sequence generation, and 4 studies[9,26,29,35] showed low risks in allocation concealment. Risk of participant blinding is high in 3 studies[24,25,32] and low in 9 studies.[9,26–30,33–35] Only 1 study[9] demonstrated high risk of outcome assessment blinding, while 9 studies[24,26–30,33–35] showed low risk. Four studies[24,25,29,34] were found low risk in incomplete outcome data, accompanied with 9 studies[9,26–28,30–33,35] in high risk. High risk in selective reporting were discovered in 7 studies. [17–19,25–26,28–29] Risk of other source of bias were all low in 13 studies.[9][24–35]

Table 1

Study characteristic and baseline characteristics of included studies.

Study	location	Age	Participants (N)	Intervention/Control (N)	Treatment duration	Follow-up	Dosage	Usage
Moudi et al 2016[24]	Iran	17–49	100	Paroxetine 50	30 days	3 months	10 mg	Daily
				Tadalafil + Paroxetine 50		6 months	10 mg + 10 mg	Daily
Polat et al 2014[25]	Turkey	20–41	150	Paroxetine 50	1 month	1 month	20 mg	Daily
				Tadalafil 50		2 months	20 mg	On demand
				Paroxetine + Tadalafil 50			20 mg + 20 mg	On demand
Gameel et al 2013[9]	Arab	26–39	85	Sildenafil 30	4 weeks	4 weeks	50 mg	On demand
				Paroxetine 28			20 mg	On demand
				Placebo 27			NR	On demand
Lee et al 2013[26]	Korea	30–70	76	Dapoxetine 31	12 weeks	4 weeks	30 mg	On demand
				Dapoxetine + Mirodenafil 45		12 weeks	30 mg + 50 mg	On demand
McMahon et al 2013[27]	USA	19–74	429	Dapoxetine 221	12 weeks	14 weeks	60 mg	Not reported
		21–71		Placebo 208			60 mg	
Buvat et al 2009[28]	France	39.6	1162	Dapoxetine 388	24 weeks	4 weeks	30 mg	Not reported
		40.5		Dapoxetine 389		12 weeks	60 mg	
		40.1		Placebo 385		24 weeks	NR	
Mattos et al 2008[29]	Brazil	24–59	60	Tadalafil + Fluoxetine 15	12 weeks	12 weeks	20 mg + 90 mg	On demand
				Tadalafil + Placebo 15			20 mg + 90 mg	On demand
				Fluoxetine + Placebo 15			90 mg + 20 mg	1/week
				Placebo 15			110 mg	On demand
Kaufman et al 2008[30]	USA	NR	480	Dapoxetine 313	9 weeks	9 weeks	60 mg	On demand
				Placebo 167			60 mg	On demand
Hosseini et al 2007[31]	Iran	21–43	91	Fluoxetine 48	4 months	2 months	20 mg	On demand
				Sildenafil + Fluoxetine 43		4 months	20 mg + 50 mg	On demand
Wang et al 2007[32]	UK	20–51	108	Paroxetine 49	3 or 6 months	3 months	20 mg	Daily
				Sildenafil 59		6 months	50 mg	On demand
Pryor et al 2006[33]	USA	18–65	2618	Paroxetine 876	12 weeks	12 weeks	30 mg	Daily
				Paroxetine 870			60 mg	Daily
				Placebo 872			NR	Daily
McMahon et al 2005[34]	UK	18–65	126	Sildenafil 66	8 weeks	8 weeks	50–100 mg	On demand
				Placebo 60			100 mg	On demand
Zhang et al 2005[35]	China	18–42	72	Sertraline 36	12 weeks	12 weeks	50 mg	Daily
				Sertraline + Sildenafil 36			50 mg + 50 mg	Daily
Salonia et al 2002[36]	Italy	19–47	69	Paroxetine + Sildenafil 36	6 months	3 months	20 mg + 50 mg	Daily + On demand
				Paroxetine 33		6 months	20 mg	Daily
Waldinger et al 2001[37]	Netherlands	18–65	36	Paroxetine 12	6 weeks	1 week	20 mg	Daily
				Sertraline 12		2 weeks	50 mg	Daily
				Placebo 12		3 weeks		
						4 weeks		
						5 weeks		
						6 weeks		
Yilmz et al 1999[38]	Turkey	22–56	40	Fluoxetine 20	1 month	1 month	20 mg	Daily
		24–58		Placebo 20			20 mg	Daily
Biri et al 1998[39]	Turkey	21–54	37	Sertraline 22	4 weeks	4 weeks	50 mg	Daily
				Placebo 15			50 mg	Daily

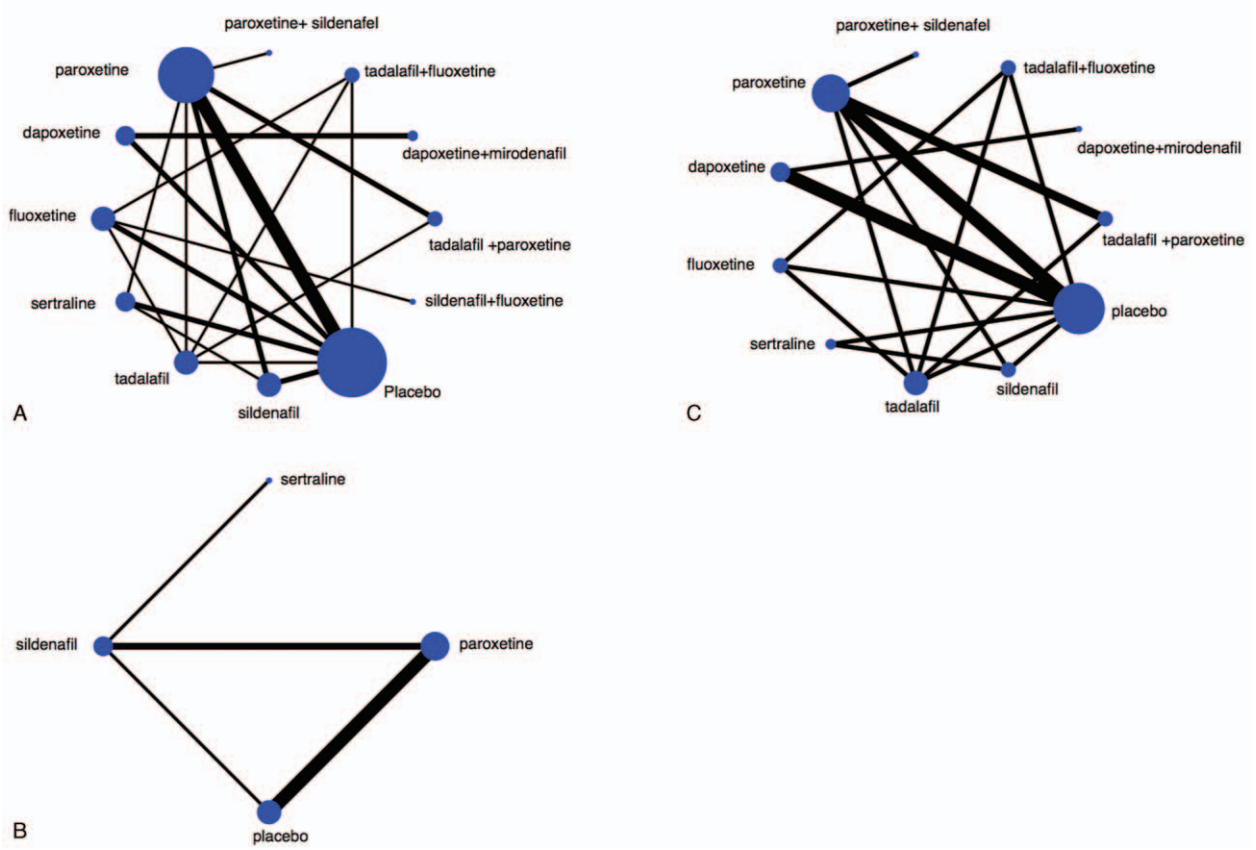

Figure 2. Evidence network for (A) IVELT; (B) Satisfactory score; (C) Adverse effects. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of randomised-controlled trials (RCTs) that contributed to each direct comparison is indicated on the line between nodes.

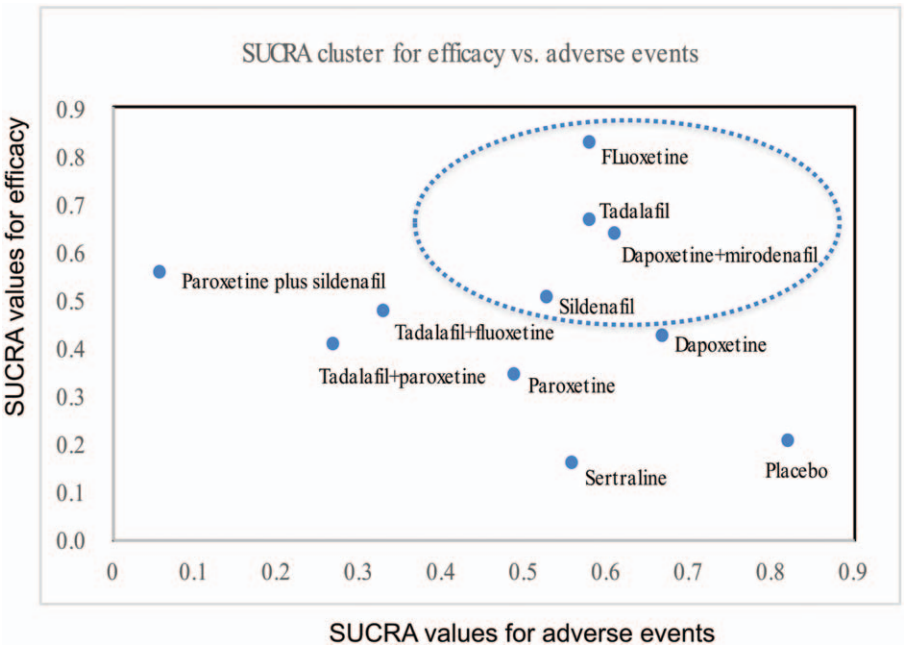

Figure 3. Scatterplot including SUCRA value for efficacy and SUCRA value for AEs.

In addition, 4 studies[36–39] were difficult to assess the bias for the reason of lacking complete methodology descriptions.

3.2.1. IVELT. Seventeen studies[9,24–39] including 5739 patients were included in this analysis. In the pairwise meta-analysis, compared with placebo, paroxetine demonstrated a significant increase of IVELT (MD 0.89, 95% CI 0.86 to 0.93, $P < .001$). But there was a high heterogeneity with the I^2 index of 99%. Another significant improvement of IVELT was found in sertraline compared with placebo (MD 0.56, 95% CI: 0.50 to 0.62, $P < .001$). Considering the result of NMA, paroxetine and sertraline both showed no significant difference compared with placebo (MD 0.68, 95% CrI -0.33 to 1.89; MD -0.19, 95%, CrI -1.49 to 1.68). Two comparisons without contrast of pairwise led to significant difference in therapy: paroxetine plus sildenafil versus placebo (MD 1.75, 95% CrI 0.05 to 3.78) and sildenafil versus sertraline (MD 1.63, 95% CrI 0.10 to 2.79). Moreover, sildenafil was significantly superior to the placebo (MD 1.43, 95% CrI 0.003 to 2.81); However, in the pairwise meta-analysis, no significant difference was witnessed (MD 1.38, 95% CrI -0.55 to 2.32). No significant differences were found between other agents. SUCRA analysis suggested sildenafil plus fluoxetine (85%), fluoxetine (80%), tadalafil (64%), dapoxetine plus mirodenafil (60%), paroxetine plus sildenafil (58%) and sildenafil (53%) as the 6 treatments with the highest probability of IVELT amelioration (see online supplementary appendix 4, http://links.lww.com/MD/C673).

3.3. Satisfactory score

Five studies[9,30,32–33,36] including 3363 patients were incorporated in the analysis. In the pairwise meta-analysis, the therapy benefit of sildenafil was significantly better than paroxetine (MD 0.82, 95% CI 0.54 to 1.11, $P = .038$). Compared with placebo, paroxetine could satisfy patients more obviously (MD 0.56, 95% CI 0.48 to 0.63, $P = .09$). Correspondingly, in the NMA, sertraline, sildenafil and paroxetine were associated with significantly better satisfactory score than placebo (MD 4.62, 95% CrI 3.74 to 5.72; MD 1.52, 95% CrI 1.10 to 2.41; MD 0.61, 95% CrI 0.38 to 1.07). Compared with paroxetine, sertraline and sildenafil were associated significant improvement (MD 4.01, 95% CrI 3.16 to 5.08; MD 0.91, 95% CrI 0.50 to 1.56). Sildenafil demonstrated significant benefit to sertraline (MD 3.10, 95% CrI 2.37 to 3.83). The SUCRA were 100%, 66%, 33%, 0% for sertraline, sildenafil, paroxetine and placebo, respectively.

3.4. Adverse events

Considering pairwise meta-analysis, paroxetine is inferior to placebo (OR 6.10, 95% CI 2.81 to 13.25, $P < .001$). Dapoxetine had a higher possibility of causing side effects compared with placebo (OR 2.40, 95% CI 2.00 to 2.89, $P = .007$). Seventeen studies consisting of 5379 patients were included in the NMA. Compared with tadalafil plus paroxetine, dapoxetine showed significantly less AEs (OR 0.23, 95% CI 0.02 to 0.96); Placebo demonstrated obviously lower risk of AEs comparing to paroxetine, sildenafil and paroxetine plus sildenafil (OR 0.20, 95% CI 0.05 to 0.52; OR 0.23, 95% CI 0.04 to 0.80; OR 0.45, 95% CI 0.01 to 0.92). Paroxetine plus sildenafil (6%), dapoxetine plus mirodenafil (27%) and tadalafil plus paroxetine (33%) were the 3 interventions with the highest probability of causing AEs.

3.5. SUCRA cluster

Figure 3 shows a scatterplot including SUCRA value for efficacy on the *y*-axis and SUCRA value for AEs on the *x*-axis. Cluster analysis demonstrates the division of treatments into 2 distinct groupings. One cluster of interventions, which includes fluoxetine, tadalafil, sildenafil and dapoxetine plus mirodenafil, has higher SUCRA values for both outcomes compared with the other grouping. (Fig. 3)

3.6. Network consistency

There was no inconsistency in the NMA estimates when we used the node-splitting approach and the differences between direct and indirect estimates in closed loops were insignificant which unable the assessment of network coherence. The total residual deviance for IVELT improvement (37.2, df = 36.4), satisfactory score (12.7, df = 12.3) and adverse events (28.5, df = 26.7) implied a good model fit.

4. Discussion

Several causes, including organic and psychogenic factors, are speculated to the possible mechanisms of PE, but the exact causes are still unclear. According to animal and human psychopharmacological studies, central serotonergic neurotransmission is related to lifelong PE,[9] for example, 5-hydroxytryptamine-2C receptor hyposensitivity and/or 1A receptor hypersensitivity, as proposed mechanisms.[38–42] There is no standard therapy because of no exact mechanism. The results of this NMA demonstrate important differences in IVELT and AEs between various interventions for PE. Our findings suggest a possible IVELT advantage of sildenafil and paroxetine plus sildenafil compared to placebo. Compared 1 treatment to the other, no differences were found. Notably, their benefits must be weighed against possible harms or adverse effects.

McMahon et al reported a possible explain of IVELT increase: The reduction in post-ejaculatory refractory time and confidence observed among men may lead to improved IVELT in the longer term.[34] For the same problem, McMahon CG suggested that the proposed mechanisms of action of sildenafil in managing PE was relevant to improving the erection and down-regulating the erectile threshold, which making the arousal easier.[41] On the contrary, Abdel-Hamid et al contributes this phenomenon to the pathway of nitric oxide (NO)-cGMP, through suppressing the contraction of the seminal vesicle, vas deferens, prostate and urethra and decreasing the control of the central sympathetic to smooth muscle, thus increases the IVELT.[25] In a well-designed, randomized, double-blind, placebo-controlled study, compared with placebo, sildenafil has following advantages: enhancing the consciousness of ejaculatory control, sexual satisfaction and confidence; reducing depression, anxiety and the duration of reaching a second erection after ejaculation.[34] Abdel-Hamid IA et al estimated that sildenafil can increase the baseline IVELT as much as 5 times sertraline,[43] our NMA showed consistent result that sildenafil was associated with 1.63 times IVELT than sertraline. There are several possibilities that may cause the difference in multiple: patient selection, baseline IVELT, and drug dosages. One study showed that sildenafil is superior than the all other treatment methods in the aspects of IVELT control and overall satisfaction ($P < .0001$).[43] In the randomized experiment conducted by Gammel, on-demand use of sildenafil provided the best overall sexual satisfaction scores, and exerted a better outcome than paroxetine and local penile anaethetics.[9] But our

NMA showed differently from the result: Sertraline ranked superior to Sildenafil. However, satisfaction criteria varied in various studies, besides, there is no exact and accurate criterion to measure satisfaction of the partner. Among the studies, various methods were used to assess satisfaction. For the reason that satisfaction is a subjective feeling, a standard assessment should be made to defined in order to determine patient post-treatment satisfactory and partner satisfactory.

Sildenafil can cause some tolerant side effects, including nausea, diarrhea, dizziness, headache, insomnia, dyspepsia, and so on, of which nausea and dizziness are the main AEs leading to withdrawal in 1 meta-analysis.[10] All the RCTs included in the NMA showed that SSRI, PDE5I and other medication caused more side effects than placebo. In accordance with this conclusion, our NMA work demonstrated that sildenafil caused more side effects than placebo.

Waldinger et al reported that SSRI was demonstrated to be effective in relieving PE, with paroxetine bringing about the most remarkable delay in ejaculation compared with baseline values, probably due to activation of the 5-HT2c receptor that then inhibit the function of the 5-HT1a receptors or keeps a dynamic balance between the 2-receptor functions (5-HT1a and 5-HT2c).[40–41] In our NMA, the combination of paroxetine plus sildenafil was associated with 1.75 times IVELT than placebo. However, the combination therapy was comparable to paroxetine or sildenafil alone in promoting the IVELT. In the study conducted by Salonia et al[37] the result estimated that the IVELT improved in patients using combined therapy, which is corresponding to our NMA results. Three previous meta-analysis[12–14] all showed that therapy with SSRIs plus PDE5i for PE was associated with a significantly greater increase in mean IVELT compared with SSRI or PDE5i alone. The probable reason is that the mechanism of SSRI differs from that of PDE5i, 2 types of medicine take effect in different targets, and pharmacodynamics of them can't influence each other. Owing to this, the side effects are more likely to occur, which is corresponded with our NMA. Another meta-analysis recommended dapoxetine at 30 mg as the first-line agent.[44] However, paroxetine plus sildenafil showed more IVELT than dapoxetine in the NMA, but the author negate the result for lack of pair-wise comparison of the 2 therapies. In the overall consideration, sildenafil plus paroxetine precedes monotherapy except for a little more tolerated side effects. IVELT and side effects have to be considered when using combination of 2 drugs.

There are some limitations in our NMA: First, the criterion of PE is not defined, causing the baseline of IVELT different. This gap may lead to the improvement of IVELT more notable, exaggerating the efficacy of medicine or making the result inaccuracy. The second limitation is that there are not enough studies, and non-English articles were excluded, causing high risks of typeI and typeII errors. Third, the duration of treatment and follow-up are various, no clear data has determined the best duration. And short-term of treatment may conceal the efficacy of some medicine. Fourth, the dosage and usage can affect the therapeutic result and occurrence rate of side effects. In 1 meta-analysis,[9] doubling dosage or on demand use improve IVELT more obviously, causing more side effects at the same time. Furthermore, it is unclear whether the combination of paroxetine plus sildenafil can still be tolerated in the long-term treatment, and whether it can cause new complications. More researches are needed to make up for the deficiency above.

5. Conclusion

IVELT and side effects have to be considered when using combination of 2 drugs. Our study indicated that although paroxetine plus sildenafil and sildenafil alone both demonstrated significant IVELT benefit compared with placebo, significant increase of AEs risk was also observed. Furthermore, sildenafil alone was superior to sertraline in efficacy with comparable tolerability, but no conclusion can be drawn in terms of the comparison of the combined treatment based on current evidence. Further investigations focusing on long-term effectiveness and acceptability of treatments, and investigate the optimal timing and thresholds for treatments are warranted to draw a final conclusion.

Table 2

Table 2

Statistically significant results of network meta-analysis.

Comparisons	No. of studies	No. of participants	Pairwise meta-analysis mean difference/odds ratios (95% CI)	Network meta-analysis mean difference/odds ratios (95% CrI)	Heterogeneity I^2	*P* value	Quality of evidence
IVELT							
Paroxetine plus Sildenafil vs Placebo	0	–	–	1.75 (0.05 to 3.78)	–	–	Low
Sildenafil vs Sertraline[36]	1	36 vs 36	–	1.63 (0.01 to 2.79)	–	–	Low
Sildenafil vs Placebo	2	96 vs 87	1.38 (−0.55 to 3.32)	1.43 (0.003 to 2.81)	0%	.85	Low
Satisfactory Score							
Sertraline vs Paroxetine	0	–	–	4.01 (3.16 to 5.06)	–	–	Low
Sildenafil vs Paroxetine[9,36]	2	77 vs 89	−0.82 (−1.11 to −0.54)	0.91 (0.50 to 1.56)	0%	.38	Low
Paroxetine vs Placebo[9,30,33]	4	1217 vs 1066	0.56 (0.48 to 0.63)	0.61 (0.38 to 1.07)	54%	.09	Moderate
Sildenafil vs Sertraline[36]	1	36 vs 36	–	3.10 (2.37 to 3.83)	–	–	Low
Sertraline vs Placebo	0	–	–	4.62 (3.74 to 5.72)	–	–	Low
Sildenafil vs Placebo[9]	1	30 vs 27	–	1.52 (1.10 to 2.41)	–	–	Low
Adverse effect							
Dapoxetine vs Tadalafil plus Paroxetine	0	–	–	0.23 (0.02 to 0.96)	–	–	Low
Placebo vs Paroxetine plus Sildenafil	0	–	–	0.45 (0.01 to 0.92)	–	–	Low
Placebo vs Paroxetine[30,33]	3	2059 vs 1911	0.16 (0.08 to 0.36)	0.20 (0.05 to 0.52)	94%	<.00001	Moderate
Placebo vs Sildenafil[34]	1	60 vs 66	–	0.23 (0.04 to 0.80)	–	–	Low

95% CI = 95% Confidence Intervals; 95% CrI = 95% Credible Intervals; , IVELT = intravaginal ejaculation latency time; Quality of evidence as judged based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. First, we rated quality of evidence for direct comparisons; second, we rated quality of evidence for indirect estimates (starting at the lowest rating of the 2 pairwise direct estimates that contribute as first-order loops to the indirect estimate, which can be rated down further for imprecision or intransitivity), and then third, rating the quality of evidence for the network combining direct and indirect estimates. In this step, if direct and indirect estimates from second-order comparisons are similar, the higher of the ratings was assigned to the network meta-analysis estimates.

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Author contributions

QW and LY conceived this review. KJ, XT, SQ, and LHD identified reports of trials and extracted data. KJ provided statistical advice and SQ did all statistical analyses. JKL and LHD checked for statistical inconsistency and interpreted data. LY, XT, YGB, and SQ contributed to data interpretation. KJ drafted the report and all other authors (QW, LY, SQ, LHD, ZHT, YGB, and JKL) critically reviewed the article. All authors read and approved the final manuscript.
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