A network meta-analysis on comparative efficacy and tolerability of on-demand therapy for premature ejaculation

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ABSTRACT

Introduction: The use of pharmacotherapy as a first-line treatment for premature ejaculation (PE) is recommended by EAU guidelines. However, no study had analyzed multiple treatment comparisons among available on-demand therapy. Therefore, we aimed to perform a network meta-analysis (NMA) to characterize the comparative efficacy and tolerability of on-demand therapy for PE.

Methods: We systematically searched randomized controlled trials (RCTs) in several databases at any period up to November 2019. NMA was performed to estimate efficacy and tolerability outcomes using intravaginal ejaculation latency time (IELT) and overall adverse effects (AEs), respectively. We ranked each outcome using the surface under the cumulative ranking curve (SUCRA) and presented the two outcomes as a clustered ranking plot.

Results: A total of 19 RCTs comprising 5950 patients were included in this NMA. All active treatments showed significant improvement compared to placebo. Among the available on-demand treatment, the combination of SSRI plus PDE5i showed the highest efficacy (MD: 3.06; 95%CI 1.84-4.29) followed by tramadol 100 mg and vardenafil 10 mg (MD 2.9, 95%CI 1.63-4.16; MD 2.36, 95%CI 1.2-3.52, respectively). Based on the SUCRA, the combination of SSRI plus PDE5i had the highest score (91.7%) in efficacy, while dapoxetine 30 mg had the highest score (73.3%) in terms of tolerability.

Conclusion: The combination of SSRI plus PDE5i was the treatment of choice for individuals who prioritize efficacy. For those who prioritize tolerability, dapoxetine 30 mg and vardenafil 10 mg became alternative treatments. Various on-demand therapy options require careful discussion with patient expectations of treatment effects.

Keywords: premature ejaculation, sexual dysfunction, on-demand therapy, phosphodiesterase type 5 inhibitor, selective serotonin reuptake inhibitor

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INTRODUCTION

Premature ejaculation (PE) is regarded as a common male sexual dysfunction that affects one out of four men.¹ The International Society for Sexual Medicine (ISSM) has classified PE into two definitions: lifelong PE as ejaculation that occurred after vaginal penetration shorter than one minute and acquired PE as a significant reduction in latency time shorter than 3 minutes.² This condition may require careful attention since its detrimental effects on men's quality of life as well as their partners.³ Despite the detrimental consequences, a study suggested that men with PE are less likely to seek medical attention than the other sexual dysfunction like erectile dysfunction (ED).⁴

There are several approaches to treat PE, including behavioral and pharmacological therapy. However, behavioral therapy found to be ineffective in lifelong PE, and thus pharmacological therapy is recommended as the first-line treatment according to European Urological Association (EAU) guideline.⁴ Various off-label pharmacological therapy for PE are proposed with daily and on-demand dosing options. Daily dosing appeared to provide stronger delayed ejaculation effects, but along with increased short-term and long-term adverse effects. While on-demand dosing offered usage flexibility and lowered adverse effects but with lower efficacy.⁵

Although there are several off-label treatments available, dapoxetine on-demand is the only drug approved for PE in many countries.⁶ However, it is not clear whether dapoxetine on-demand is better than other off-label treatment while head-to-head trials are limited. Network meta-analysis (NMA) is useful in gathering evidence from the limited trial comparison because its extended meta-analysis can combine direct and indirect comparison to estimate treatment effect within a single statistical model.⁷ Therefore, we aim to conduct an NMA to compare the efficacy and tolerability of on-demand therapy for PE.

METHODS

Literature search
A comprehensive literature search was conducted through several electronic databases, including PubMed, Clinical trial, and Cochrane library at

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any period up to November 2019 following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements. To identify potentially relevant articles, we used the following MeSH terms (serotonin uptake inhibitors OR dapoxetine OR paroxetine OR fluoxetine OR sertraline OR phosphodiesterase 5 inhibitors OR sildenafil OR vardenafil OR tramadol) AND (premature ejaculation).

**Eligibility criteria**
We included randomized controlled trial (RCT) or randomized crossover-controlled trial (RCCT) comparing on-demand treatment for adults diagnosed with PE according to ISSM or DSM-IV criteria without any restriction of language. The exclusion criteria were (1) non-randomized studies; (2) studies reported irrelevant outcomes to our interest; and (3) study without full-text access.

**Data extraction and quality assessment**
Data from each study, including author, publication date, study design, details of the intervention, number and characteristics of participants, diagnosis criteria of PE, and outcomes of the study were extracted using a piloted form. The primary outcomes were the treatment efficacy and tolerability measured by the mean difference of intravaginal ejaculation latency time (IELT) in minutes and the overall number of adverse effect (AE), respectively. Two independent reviewers (N.Y. and Y.A.) extracted the data in duplicate, and a third reviewer (Y.A.A.) resolved any disagreements. We assessed the quality of each RCT using the risk of bias tool developed by Cochrane Collaboration that evaluated seven domains, including random sequencing process, intervention allocation process, blinding of the participant, blinding of the outcome, assessment on incomplete data, assessment on selective reporting, and assessment on other potential sources of bias.

**Data synthesis and analysis**
We performed both pairwise meta-analysis and NMA to evaluate the efficacy of multiple treatments comparison. The standard pairwise meta-analysis was conducted using the random-effects model if there was heterogeneity found. The NMA was performed using the frequentist model on the assumption of a common heterogeneity for all comparisons. To assess transitivity, we compared the distribution of demographic variables including age, IELT at baseline, and treatment duration that could act as effect modifiers across treatment comparisons. Analysis of loop design inconsistency was used to evaluate inconsistency, measured using the inconsistency factor (IF) with 95% confidence intervals (CI). The inconsistent loop was defined as the loops with the presence of IF with 95% CI other than zero. The NMA was presented as odds ratio (OR) and mean difference (MD) for binary outcomes and continuous outcomes, respectively. Each outcome was ranked using the surface under the cumulative ranking curve (SUCRA), and we provided a clustered ranking plot to demonstrate the trade-off between efficacy and tolerability. All statistical analyses were conducted using STATA 16.0. (College Station) and Review Manager 5.3 (Cochrane Collaboration).

**RESULTS**

**Literature search and study characteristics**
We identified a total of 585 articles from the initial search process. After the duplication removed, we screened 482 articles according to the studies titles and abstracts. We manage to accessed 57 potentially eligible articles for full-text eligibility. Among those articles, 38 were excluded, and 19 RCT were found to be eligible to be included in this NMA. The characteristics of these 19 RCTs were summarized in table 2. The study search and selection process were summarized in Figure 1. The overall participants included in the trial were diagnosed with premature ejaculation with IELT in less than 2 minutes. A total of 12 drugs were compared, eight of those were monotherapy (dapoxetine, paroxetine, sertraline, tadalafil, vardenafil, tramadol, sildenafil, and placebo) and the others were the therapy combination of SSRI plus PDE5i. The average study sample size was 119 participants, and the means age was 39.8 years old. Overall, 3975 participants were assigned to the active treatments group, and 1975 were assigned to the placebo group. The overall result for the risk of bias assessment was a low-moderate risk, summarized in Table 3. Figure 2 showed the network plot of on-demand treatment comparison. The node size was corresponding to the number of assigned participants, and the network line was corresponding to the number of studies. In the analysis of efficacy, 15% of the loops were inconsistent (3 of 20 loops), and 0% of the loops were inconsistent for tolerability (0 of 18 loops), the loop inconsistency results were summarized in the Figure S7.

**Network meta-analysis**
According to the NMA, all on-demand therapies were showed significant improvement compared to the placebo, except for sertraline 50 mg (MD 0.47; 95% CI -1.97, 2.92) and tramadol 25 mg (MD 1.63; 95% CI -0.17, 3.43). The MDs between on-demand
Table 1  PICO of the study

| Population | Patients with premature ejaculation |
| Intervention | Oral on-demand drug for PE |
| Control | Placebo and other on-demand drugs for PE |
| Outcomes | IELT and overall AEs |

Table 2  Characteristic of the included studies

| Study                | Design | On-demand intervention dose | Participant (n) | Mean age (years) | PE Definition | Study protocol |
|---------------------|--------|-------------------------------|----------------|-----------------|---------------|---------------|
| McMahon et al. 2005 | RCT    | Placebo, Sildenafil 50mg      | 60             | 42.85           | DSM-IV, IELT < 2 min | 8 weeks       |
| Pryor et al. 2006  | RCT    | Placebo, Dapoxetine 30mg, Dapoxetine 60mg | 672            | 40.5            | DSM-IV, IELT < 2 min | 12 weeks      |
| Mattos et al. 2008 | RCT    | Placebo, Tadalafil 20mg       | 15             | 45.4            | DSM-IV, IELT < 1.5min | 12 weeks      |
| Buvat et al. 2009  | RCT    | Placebo, Dapoxetine 30mg, Dapoxetine 60mg | 339            | 40.1            | DSM-IV, IELT < 2 min | 24 weeks      |
| Mathers et al. 2009 | RCCT  | Vardenafil 10mg, Sertraline 50mg | 44             | 38              | IELT < 1.5 min | 6 weeks       |
| Aversa et al. 2009 | RCCT  | Placebo, Vardenafil 10mg      | 10             | 24              | DSM-IV, IELT < 1.5 min | 16 weeks      |
| McMahon et al. 2010 | RCT    | Placebo, Dapoxetine 30mg, Dapoxetine 60mg | 342            | 40.9            | DSM-IV, IELT < 2 min | 12 weeks      |
| Gokce et al. 2010  | RCCT   | Placebo, Vardenafil 10mg      | 17             | 33.5            | IELT < 1 min | -             |
| Gokce et al. 2011  | RCT    | Placebo, Sildenafil 50mg, Tadalafil 20mg, Vardenafil 10mg | 20             | 29              | IELT < 1 min | -             |
| Pastore et al. 2012 | RCT    | Dapoxetine 30mg, Dapoxetine 60mg | 8              | 30              | ISSM, IELT <1 min | 12 weeks      |
| Kaynar et al. 2012 | RCCT   | Placebo, Tramadol 25mg        | 30             | 38.6            | IELT < 1.5 min | 8 weeks       |
| Gameel et al. 2013 | RCT    | Placebo, Paroxetine 20mg, Sildenafil 50mg, Tramadol 50mg | 27             | 32.8            | IELT < 2 min | 4 weeks       |
| Lee et al. 2013    | RCT    | Dapoxetine 30mg, SSRI + PDE5i | 31             | 50.7            | PEDT | 12 weeks      |
| McMahon et al. 2013 | RCT    | Placebo, Dapoxetine 60mg      | 208            | 48.7            | IELT < 2 min | 18 weeks      |
| Kahn et al. 2013   | RCT    | Placebo, Tramadol 100mg       | 30             | 37.5            | DSM-IV | 8 weeks      |
therapies ranged from 0.47 to 3.06. The combination of SSRI plus PDEi showed the highest efficacy (MD 3.06; 95% CI 1.84, 4.29), followed by tramadol 100mg (MD 2.9; 95% CI 1.63, 4.16), and vardenafil 10 mg (MD 2.36; 95% CI 1.2; 3.52). The treatment efficacy based on SUCRA demonstrated that SSRI plus PDEi ranked first (91.7%), followed by tramadol 100 mg (88.2%), and vardenafil 10 mg (75.6%).

NMA results for IELT was summarized in figure 3. In terms of AE, our searches identified a total of 18 RCTs eligible to be included. Figure 4 provided forest plots of overall AE on each treatment dosage compared to the placebo (ORs ranged from 1.5 to 16.18). All treatment showed significantly higher AE compared to placebo, except for sertraline 50mg (OR 1.5; 95% CI 0.15, 14.68), tadalafil 20 mg (OR 2.06; 95% CI 0.77, 5.48), vardenafil 10mg (OR 3.14; 95% CI 0.84, 11.73), and tramadol 25 mg (OR 16.18; 95% CI 0.81, 323.31). The treatment tolerability based on SUCRA showed that dapoxetine had the highest score (73.3%), followed by sertraline (71.9%), and tadalafil (68.9%).

Clustered ranking plot of efficacy and tolerability
Figure 5 present the clustered ranking plot based on the SUCRA in the form of Cartesian coordinates. The x-axis characterized the ranking for efficacy, and the y-axis characterized the ranking for tolerability. The farthest upper-right coordinate represented the treatment with the highest efficacy along with the lowest AE, and thus suggested the best choice.
of treatment. SSRI plus PDE5i were coordinated in the farthest upper-right area, which indicates that the combination was a better choice compared to the other on-demand drugs. Dapoxetine 30mg showed the highest tolerability compared to the other treatment, but with low to moderate efficacy.
DISCUSSION

According to the latest EAU guideline, the recommendation for management of PE was tailored based on their subtype. In acquired PE, the primary strategy of the treatment was to treat the underlying disease that caused PE. While in lifelong PE pharmacological intervention was chosen to be the first-line treatment.

Currently, dapoxetine was the only oral drug that has been approved in many countries. However, there were various drugs proposed as the off-label treatment for PE, including SSRI, PDE5i, tramadol, and alpha-1 blockers. Pharmacological treatment for PE is available with daily and on-demand dosing options. In this study, we were focusing on trials that evaluated the efficacy and tolerability of drugs available with on-demand dosing since it offered usage flexibility for the patients along with lower AEs. This study provided NMA to identify direct and indirect comparisons investigating the best choice of treatment available.

Our results for efficacy demonstrated that all on-demand therapies were showed significant improvement compared to the placebo, except for sertraline 50 mg. A combination of SSRI plus PDE5i showed the highest efficacy among all treatment. These results were consistent with the previous meta-analysis by Qin et al. that showed the combination of SSRI plus PDE5i had a stronger efficacy than SSRI alone. Tramadol ranked as the second-highest efficacy among all on-demand treatments. This result supported the previous meta-analysis by Wu et al. that demonstrated tramadol could delay ejaculation and increase IELT up to 3 minutes compared to placebo. However, our analysis indicates that tramadol had the lowest tolerability among all treatments. Tramadol was a central opioid-based analgesic that carries a high number of side effects with the potential for abuse and dependency. Therefore, careful consideration is needed before prescribing this therapy. Based on the SUCRA for efficacy, vardenafil 10 mg ranked third, thus indicated that PDE5i has good efficacy in treating PE. Currently, PDE5i has widely approved treatment for ED but not for PE. Various studies have shown that PDE5i might have a role in treating PE. McMahon et al. proposed some of PDE5i mechanism, including reduced performance anxiety, reduced sympathetic tone, and nitric oxide release.

In terms of tolerability, our NMA showed that dapoxetine was best drug with tolerable side effects. This result might reflect the reason for dapoxetine to be widely approved for the treatment of PE in many countries. After weighing the efficacy and tolerability, our NMA demonstrated that the combination of SSRI plus PDE5i had a significant advantage compared to other on-demand therapies. This might be due to the fact that both drugs work in different mechanisms and different drug targets.

This study had some limitations. First, in terms of transitivity, the duration of treatment protocol among trials was varied, this difference might provide variety on the treatment efficacy and side effects that lead to reduced network connectivity in NMA and therefore lower the statistical power. Second, we found some evidence of inconsistency in loop design analysis that might result in biased treatment efficacy. Third, we found a low to moderate risk of bias of the included studies.

CONCLUSION

This study showed that the combination of SSRI plus PDE5i was found to be the best treatment for PE. For those who prioritize tolerability, dapoxetine 30 mg and vardenafil 10 mg became alternative treatments. Various on-demand therapy options require careful discussion with patient expectations of treatment effect.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to the material presented in this article.

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AUTHOR CONTRIBUTION
N.Y. and Y.A.A. design the concepts of study. N.Y. and Y.A. did the literature search, acquired trials, and extracted data. N.Y. performed all data analyses, checked for statistical inconsistency. N.Y., Y.A., and Y.A.A. contributed to original manuscript writing. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL
The following are available online at doi:10.17605/OSF.IO/EYWTH. Figure S1: PRISMA Flow Diagram, Figure S2: Risk of bias assessment, Figure S3: Pairwise meta-analysis result, Figure S4: Network league table, Figure S5: Funnel Plot of included study, Figure S6: SUCRA result, Figure S7: Loop inconsistency result.

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