ABSTRACT

Introduction: Clomipramine is effective in treating premature ejaculation, a common form of male sexual dysfunction that affects individual's mental health and quality of life, but its optimal dosage remains controversial.

Aim: In this systematic review and meta-analysis, we aimed to evaluate the efficacy, safety, and optimal dose of clomipramine for treating premature ejaculation among men.

Methods: Eligible studies of PubMed, Embase, and Web of Science were identified from the date of inception to June 21, 2020. We conducted the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data of the study characteristics, intravaginal latency ejaculatory time (IELT), adverse events, success rate, and satisfaction rate of clomipramine vs placebo were extracted and analyzed. The risk ratio and mean difference were used for quantitatively analyzing binary outcomes and continuous outcomes. The standardized mean difference was applied to the outcome of satisfaction rate. The Mantel–Haenszel method was used for meta-analysis under random-effects model. To assess dose effect of clomipramine, a meta-regression analysis was performed.

Main Outcome Measures: The primary outcomes were the IELT and adverse events, and the secondary outcomes were the success rate and satisfaction rate of clomipramine treatment relative to the placebo.

Results: A total 14 randomized controlled trials with 710 patients were included for quantitative analysis. Clomipramine significantly increased the IELT compared with the placebo (mean difference: 1.47, 95% CI: 0.73 – 2.21). However, clomipramine was associated with higher risks of overall adverse events and adverse events in the nervous and respiratory systems. Significant dosage effects on the IELT (estimate: 0.0637, 95% CI: 0.0074 – 0.12) and a slightly increasing slope on adverse events were revealed.

Conclusion: Clomipramine increased the IELT and yielded greater satisfaction than the placebo, and the higher dose results in a superior IELT without leading to higher risk of adverse events under a dosage of 50-mg clomipramine. Wu P-C, Hung C-S, Kang Y-N, et al. Tolerability and Optimal Therapeutic Dosage of Clomipramine for Premature Ejaculation: A Systematic Review and Meta-Analysis. Sex Med 2021;9:100283.

Key Words: Clomipramine; Anafranil; Premature Ejaculation; Ejaculation Praecox; Intravaginal Ejaculatory Latency Time
INTRODUCTION

Sexual dysfunction is a complex clinical issue with biological, psychological, and social underpinnings.1 Premature ejaculation (PE), a common form of male sexual dysfunction, refers to uncontrolled ejaculation either before or soon after sexual activity. The International Society for Sexual Medicine defines PE as the inability to delay ejaculation during all or nearly all vaginal penetrations with latency time before or within 1 min of penetration for lifelong PE and within ≤3 min for acquired PE.2 Among men, the actual prevalence of PE, defined as a <1-min intravaginal ejaculatory latency time (IELT), has been reported to be approximately 2–5%.3 Sexual dysfunction can profoundly affect an individual’s life and is associated with mental health issues and a reduced quality of life,4–7 thus warranting effective interventions.

Several decades ago, behavioral therapy, including start—stop and squeeze techniques, was introduced as initial approaches for treating PE.8 However, with growing interest in sexual dysfunction, numerous studies have subsequently reported various pharmacological treatments. Recent studies have reported the beneficial effects of agents including tricyclic antidepressants, selective serotonin reuptake inhibitors, topical anesthetic agents, and sildenafil citrate.9–11 Most previous systematic reviews on medical interventions have focused on phosphodiesterase type 5 inhibitors including sildenafil and tadalafil.12–14

Open-label and controlled studies have reported that clomipramine effectively increases the IELT in individuals with PE15,16; however, its optimal dosage and its association with adverse events remain controversial. This systematic review and meta-analysis is the first, to our knowledge, to evaluate the

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Figure 1. Flow diagram of study selection.
Table 1. Characteristics of the included randomized controlled trials

| Author (year) | Area | Duration | Treatments | Total patients (n) | Age | PE definition |
|---------------|------|----------|------------|--------------------|-----|---------------|
| Choi (2019)²⁷ | Korea | 4-week run-in period without medication, 4-week baseline period, and a 12-week treatment period | Placebo | 159 | 20–65 | PEDT score greater than 9 |
| Clomipramine 15 mg | | 2–6 h before coitus | | | | |
| Kim (2018)²⁸ | Korea | 4-week washout, 4-week nonmedication run-in, and 4-week drug treatment period | Placebo | 101 | 20–65 | IELT < 2 min |
| Clomipramine 15 mg | | | | | | |
| Clomipramine 30 mg | | 2–6 h before coitus | | | | |
| Shavakhabov (2012)²⁹ | Uzbekistan | 2-week washout and an 8-week drug treatment period | Clomipramine 4 mg nasal spray | 58 | 33 (1.8) | IELT < 2 min |
| Placebo nasal spray | | 1 h before daily sleeping/coitus | | | | |
| Akilov (2011)³⁰ | Uzbekistan | 2-week washout and an 8-week drug treatment period | Clomipramine 4 mg nasal spray | 34 | 34 | IELT < 2 min |
| Placebo nasal spray | | 1 h before daily sleeping/coitus | | | | |
| Leaker (2008)³² | UK | 2-period, 2-treatment crossovers For 8 weeks | Placebo | 39 | 18–65 | IELT < 2 min |
| VR776 1-mg inhaler | | | | | | |
| VR776 2-mg inhaler | | | | | | |
| Tuncel (2008)³¹ | Turkey | 2 Months | Placebo | 90 | 20–58 | ICD 10 |
| Clomipramine 25 mg | | | | | | |
| Sertraline 50 mg | | | | | | |
| Terazosin 5 mg | | | | | | |
| Strassberg (1999)³³ | The Netherlands | 2 2-week treatment periods | Placebo | 34 | 21–73 | Approached orgasm < 2 min |
| Clomipramine 12.5 mg | | 4–6 h before coitus | | | | |
| Kim (1998)³⁴ | Korea | 4-week period per each agent with a 1-week washout | Fluoxetine 40 mg | 36 | 30–60 | IELT < 2 min |
| Sertraline 100 mg | | | | | | |
| Author (year)          | Area            | Duration                        | Treatments                       | Total patients (n) | Age       | PE definition                                      |
|-----------------------|-----------------|---------------------------------|----------------------------------|---------------------|-----------|----------------------------------------------------|
| Haensel (1996)        | The Netherlands | Crossover design included 2-3 week periods | Placebo                          | 14                  | 26–62     | DSM-IV                                            |
| Althof (1995)         | USA             | Crossover design 2-7 weeks       | Placebo                          | 15                  | 21–65     | IELT < 2 min                                      |
| Montorsi (1995)       | Italy           | Crossover study for 8 weeks      | Placebo                          | 40                  | NR        | NR                                                |
| Segraves (1993)       | USA             | 10 Coital experiences           | Placebo                          | 20                  | Placebo: 47.2 (10.2) | Ejaculation before completion of 1 min of coitus or before 8 penile–vaginal strokes |
| Girgis (1982)         | Egypt           | Crossover study for 2-6 week periods | Placebo                          | 50                  | 19–57     | NR                                                |
| Goodman (1980)        | UK              | Crossover study for 8 weeks      | Placebo                          | 20                  | 18–43     | NR                                                |

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD 10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision; IELT = intravaginal latency ejaculatory time; NR = not reported; PE = premature ejaculation; PEDT = Premature Ejaculation Diagnostic Tool.
efficacy, safety, and optimal dose of clomipramine for treating PE among men.

MATERIALS AND METHODS

This prospective systematic review began February 11, 2020, and the study protocol had been written beforehand. The primary design was registered on PROSPERO (CRD42020171420). The study group included a urologist and an experienced researcher in systematic review and meta-analysis.17–19 The urologist also had experience on conducting systematic reviews and meta-analyses.20–22 This study conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines regarding evidence selection, quality assessment, evidence synthesis, and research reporting.23

Data Selection and Search

The following basic eligibility criteria for evidence selection were predefined: (1) studies including male patients with PE and (2) placebo-controlled studies evaluating the outcomes of patients receiving clomipramine. Based on the aforementioned criteria, the relevant terms including “PE” and “clomipramine” were used in the literature search conducted in free text, Medical Subject Headings (MeSH in PubMed and Emtree in EMBASE), and abbreviations. The keywords were combined using appropriate Boolean operators, and a primary search strategy was developed without limitations regarding language and published data. The primary search strategy involved a PubMed search, which was adapted to Embase and Web of Science (Table S1). The final search was completed on June 21, 2020.

Study Selection

After potential studies were identified, 2 authors excluded irrelevant studies by screening the title and abstract in accordance with the following exclusion criteria: (1) studies recruiting patients with conditions other than PE, (2) placebo-controlled studies reporting treatments without clomipramine, and (3) gray literature not providing patient data. Disagreements between the 2 authors were resolved by the corresponding author.

Data Extraction and Quality Assessment

The same 2 authors also individually reviewed all selected randomized controlled trials (RCTs) for data extraction and risk of bias assessment. They extracted trial characteristics and outcome data, including the author name, year of publication, study area, duration of the intervention, treatment details, the number of patients and their ages, type of PE, IELT assessment, and other outcomes. The primary outcomes were the IELT and adverse events due to clomipramine treatment vs placebo treatment. The secondary outcomes were the success rate and satisfaction rate of clomipramine treatment relative to the placebo. The risk of bias of the selected RCTs were assessed using the Cochrane Risk of Bias Tool, which consists of 7 methodological items: (1) allocation generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selection report, and (7) other bias. The third author made the final decision regarding the risk of bias assessment. The GRADE methodology was used to assess the quality of the body of retrieved evidence.

Data Synthesis and Analysis

The risk ratio (RR) and mean difference (MD) were used for quantitatively analyzing binary outcomes and continuous outcomes of the RCTs. The standardized mean difference (SMD) was applied to the outcome of the satisfaction rate because various scales were used to measure satisfaction in the included studies. The Mantel–Haenszel method was used for meta-analysis. Generally, the Mantel–Haenszel method is considered preferable to the inverse variance method. All analyses were conducted using a random-effects model. The results are expressed as the RR, MD, SMD, and 95% CI values.

To assess the quality of the pooling results, this study evaluated heterogeneity and the small study effect; $P$ and the $P$ value of Cochran’s $Q$ were used to assess heterogeneity. High heterogeneity was defined as an $I^2$ value of >50% or a $P$ value of Cochran’s $Q$ of <.10 (a rigorous threshold for heterogeneity detection). The DerSimonian-Laird method was used as an estimator for tau square. The restricted maximum-likelihood method was used as an estimator for tau square when the heterogeneity was high. To determine the source of heterogeneity, the present quantitative synthesis further conducted meta-regression by using dosing of clomipramine. Meta-regression analysis in this study was performed using the mixed-effects model for both continuous study level covariates. Regression models with covariates were fit and also carried out based on the restricted maximum-likelihood. A small study effect was illustrated using the funnel plot and assessed using Egger’s test. Pooled results seemed to be affected by a small study effect when the $P$ value of Egger’s test was <.05.

RESULTS

In total, 672 studies were identified from the 3 important biomedical databases, and one study was identified through manual screening; manual screening further showed 184 studies were duplicates. Of the remaining 489 studies, 472 were excluded after the title, abstract, and article type were screened because they were not relevant to the topic ($n = 369$), they were not RCTs ($n = 75$), they were not in English ($n = 1$), or they belonged to the gray literature without details ($n = 27$). The full-text versions of the 17 remaining studies were then retrieved for further review. 3 studies met the exclusion criteria and were excluded.24–26 Finally, the data sources of the eligible studies were obtained from 14 RCTs. All RCTs were included in this study for qualitative analysis,16,27–39 and 12 studies were
included in quantitative synthesis. The flow diagram for evidence selection is displayed in Figure 1.

**Characteristics and Quality of the Included Studies**

The 14 RCTs included herein involved 710 patients with PE from Korea, Uzbekistan, the United Kingdom, Turkey, the Netherlands, the United States, Italy, and Egypt. Table 1 presents the characteristics of each trial. In these studies, clomipramine was administered for at least 2 weeks, and the longest treatment duration was 12 weeks. Most studies defined PE as an IELT of <2 min, but other studies used the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), or other definitions. 4 studies reported the PE type, with 2 studies focusing on lifelong PE, one on acquired PE and one on a mixture of both types. Patient age ranged from 18 to 73 years. 6 studies were designed as crossover studies, and 8 studies were RCTs. Most studies included herein exhibited low attrition bias and reporting bias (Table S2). Outcomes were qualified using GRADE, and outcomes showed moderate to very low quality. The GRADE tables are presented in Table S3 to S4.

**IELT of Clomipramine vs Placebo**

Of the 14 RCTs included herein, 6 studies reported data on the IELT (Figure 2). According to data from 445 patients (258 patients receiving clomipramine and 187 patients receiving placebo), clomipramine significantly increased the IELT compared with the placebo (MD: 1.47, 95% CI: 0.73–2.21, P < .0001). However, high heterogeneity ($I^2 = 85$%) was reflected in this outcome.

**Clomipramine vs Placebo: Adverse Events**

7 of 14 studies reported data on overall adverse events among patients (Figure 3). According to the data obtained from 307 patients receiving clomipramine and 207 patients receiving the placebo, clomipramine significantly increased the risk of adverse events compared with the placebo (RR: 3.52, 95% CI: 2.44–5.09, P < .0001). No heterogeneity was observed ($I^2 = 0$%) in the outcome analysis.

We performed subgroup analyses to investigate the risk of adverse events affecting various systems. Adverse events in the nervous system are presented in Figure 4, considering the mechanism of action of clomipramine. 8 studies, including 252 patients receiving clomipramine and 201 patients receiving the...
placebo, reported a higher risk of adverse events in the nervous system with clomipramine than with the placebo treatment (RR: 4.07, 95% CI: 2.41–6.86, \( P < .0001 \)). No heterogeneity was observed (I\(^2\) = 0%) in the outcome analysis. The adverse events in other systems are summarized in Table 2 and demonstrated in Figure S4 to S9. The risk of adverse events was high only for the respiratory system on treatment with clomipramine rather than the placebo (RR: 3.80, 95% CI: 1.60–9.06). No significant differences were observed in the gastrointestinal, cardiovascular, renal and urinary, reproductive, or dermatological systems. No heterogeneity was observed (I\(^2\) = 0) in all analyses.

### Dose-Dependent Effects of Clomipramine vs Placebo Treatments

To determine the dose-dependent effects on the IELT and adverse events, meta-regression analysis was performed. Meta-regression analysis of 6 studies revealed significant dosage effects on the IELT (estimate 0.0637, 95% CI: 0.0074–0.12, \( P = .0265 \); Figure S10). No dose-dependent effects on adverse events were observed (estimate 0.0074, 95% CI: −0.0284 to 0.0433, \( P = .6850 \); Figure S11) as determined through meta-regression analysis of 9 studies. However, a slightly increasing slope is evident. To determine the balance of the IELT and adverse events, 2 regression plots were overlaid through postprocessing (Figure 5). The overlaid regression plots of the IELT and adverse events under dose effects indicate that 15- to 20-mg clomipramine was associated with an approximately 2-minute IELT. The higher the clomipramine dose, the longer the IELT was. However, the risk of adverse events did not significantly differ as the dose increased from 0 to 50 mg.

### Success Rate and Satisfaction Rate of Clomipramine vs Placebo

The success rate was defined as the number of patients for whom the IELT was successfully prolonged after treatment. The results are summarized in Table 2 and demonstrated in Figure S12 to S15. 2 RCTs presented success rates with no significant difference (RR = 2.00, 95% CI: 0.99–4.05, \( P > .05 \); Table 2). However, we observed a slight trend of higher success rates among patients receiving clomipramine than among those receiving the placebo. 4 of 14 studies reported satisfaction data, which revealed a significantly higher satisfaction rate for clomipramine than for the placebo (SMD: 0.40, 95% CI: 0.09–0.70, \( P < .05 \); Table 2). However, high heterogeneity (I\(^2\) = 73%) was observed for this outcome.

### Table 2. Summary of subgroups of adverse events other than those in the nervous system and secondary outcomes

| Outcome                          | Subgroups                  | Number of studies | Effect size | 95% CI       | \( P \) value | \( I^2 \) |
|----------------------------------|----------------------------|------------------|-------------|--------------|--------------|--------|
| Adverse events                   | Respiratory system         | 6                | RR = 3.80   | [1.60, 9.06] | .003*        | 0%     |
|                                  | Gastrointestinal system    | 4                | RR = 2.11   | [0.67, 6.65] | .20          | 0%     |
|                                  | Cardiovascular system      | 2                | RR = 2.73   | [0.31, 24.17]| .36          | 0%     |
|                                  | Renal and urinary system   | 1                | RR = 1.49   | [0.06, 35.58]| .80          | Not applicable |
|                                  | Reproductive system        | 2                | RR = 2.73   | [0.31, 24.17]| .69          | 0%     |
|                                  | Dermatological system      | 3                | RR = 0.49   | [0.11, 2.22] | .36          | 0%     |
| Success rate                     | Not applied                | 2                | RR = 2.00   | [0.99, 4.05] | .051         | 0%     |
| Satisfaction rate                | Not applied                | 4                | SMD = 0.40  | [0.09, 0.70] | .01*         | 73%    |

*\( P \)-value <.05
DISCUSSION

This systematic review and meta-analysis evaluated the efficacy, safety, and optimal dose of clomipramine for treating PE among men. 14 studies were included in total. The present data indicate that compared with the placebo, clomipramine significantly increased the IELT and the risk of overall, nervous system, and respiratory system adverse events. The IELT was affected by the dose, but adverse events did not exhibit a significant dose-dependent relationship with 50-mg clomipramine treatment. Furthermore, 15- to 20-mg clomipramine treatment resulted in an approximately 2-min IELT. Treatment with <50-mg clomipramine was associated with an increased IELT, and the risk of adverse events did not significantly increase. Although clomipramine did not exhibit a significantly increased success rate relative to the placebo, the satisfaction rate for clomipramine was superior to that of the placebo.

A significantly longer IELT was observed with clomipramine use than with placebo use. However, high heterogeneity ($I^2 = 85\%$) was found in the analysis, which was mainly from one study by Leaker et al. After excluding this study, heterogeneity significantly decreased to 0%. That was the only study in which clomipramine was administered through inhalation; other treatment routes were oral or nasal sprays. Moreover, that was the only one of 3 crossover studies with a 48-h washout period; others had a minimum 1-week washout period. The “carry-over effect” is considered a primary concern with crossover trials. Treatment comparisons may possibly be biased if the residual effect of the treatment in the initial period persists into the second period when the effects of the second treatment are evaluated. Despite the fact that the first treatment had been discontinued at the end of the first period, it was challenging to assess the differences between the treatment effect and the carryover effect. To eliminate carryover effects, a washout period that is at least 5 times the half-time of the treatment with the maximum half-life in the study is suggested for the washout period. Under normal conditions, 50-mg clomipramine has a mean half-time of 20.4 h on oral administration. Consequently, an at least 5-d washout period is required for the aforementioned setting. However, Leaker et al administered 1 mg or 2 mg of VR776 via an inhaler, making it difficult to assess the half-life and concentrations of the medication. A 48-h washout period is not long enough for VR776 to be metabolized, and thus, this presumably influenced the effects of subsequent treatment, resulting in heterogeneity during statistical analysis.

Furthermore, dose-dependent effects of clomipramine treatment were also found in the subsequent meta-regression, indicating that high doses prolonged the IELT among patients with PE. Dose-dependent effects exhibited no difference in terms of race (Asian or European), treatment routes (oral, nasal spray, or inhalation), or treatment duration (2–12 weeks). Moreover, high clomipramine doses were not associated with a significantly increased risk of adverse events. We therefore suggest a higher dosage in clomipramine treatment because of the longer IELT that is achieved without increasing adverse events.

The success rates of clomipramine and placebo treatment did not significantly differ. Considering that the outcome included only 2 studies with 57 patients, the outcome was ambiguous because of the small cohort size. However, numerous studies provided data on pretreatment and post-treatment IELT, and all results indicated an increase in the IELT after clomipramine treatment. More studies with data on the number of patients with an increased IELT are required to yield more credible outcomes. The satisfaction rate was significantly higher among patients receiving clomipramine treatment rather than placebo treatment. The high heterogeneity ($I^2 = 73\%$) may be attributable to the following reasons. First, divergent satisfaction questionnaires were administered in the studies included herein. Some data were obtained by indicating whether sexual intercourse was satisfactory. Leaker et al. and Haensel et al. evaluated patient satisfaction using 5-point scale and 7-point scale questionnaires, respectively. The second factor is the psychological differences and expectations among patients.

**Figure 5.** Overlay images of 2 meta-regressions of the association between the mean difference of intravaginal ejaculatory latency time and dosage and the association between the log risk ratio of adverse events and dosage.
from different regions. The 4 studies included herein were performed in 4 different countries in Europe and Asia. Although the importance of sexual health varies by sex, age, and sexual activity,13 Flynn et al44 reported that sexual health is considered a major determinant of the quality of life among 3,515 individuals of all ages in the United States. Furthermore, they reported that race or ethnicity is a potential factor influencing a patient’s perspective of sexual health and sexual satisfaction. Different countries have different cultures and societies, with differences in sexual norms and expectations, which is potential reason for the high heterogeneity.

Despite many advantages, this study has the following limitations. First, only a few studies reported on outcome analysis. Although 14 studies were included in this meta-analysis, few reported data on IELT, success rates, and satisfaction outcome syntheses. Different diagnostic values including Premature Ejaculation Diagnostic Tool, Chinese Index of Premature Ejaculation, or International Index of Erection Function were used among studies. One study reported Premature Ejaculation Diagnostic Tool before and after clomipramine treatment and showed significant differences between placebo and 15-mg clomipramine group, which was correlated to the outcome of our study.27 To perform a higher quality meta-analysis, more studies with identical measurement tool should be included. Second, the overlaid regression plot used nervous system adverse events to determine dose effects due to clomipramine’s mechanism of action. More detailed studies on adverse events in different systems are needed for fruitful meta-regression analysis of adverse events on different systems. Third, different questionnaires were used to assess satisfaction among patients with PE. We analyzed all the data using SMD. However, the divergent questionnaires revealed high heterogeneity. More studies using identical questionnaires are required to assess patient satisfaction with much lower heterogeneity.

CONCLUSIONS

This study confirms that clomipramine prolongs the IELT and yields greater satisfaction than does treatment with a placebo. Moreover, this is the first study to analyze dose-dependent effects and the association between drug efficacy and the risk of adverse events. Below a dosage of 50-mg clomipramine, the higher dose results in a longer latency time to ejaculation without higher risk of adverse events. Therefore, we suggest clinicians to use clomipramine at the most effective dose according to individual patient tolerance.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.esxm.2020.10.011.