Selective Serotonin Reuptake Inhibitors Plus Phosphodiesterase-5 Inhibitors for Premature Ejaculation: A Systematic Review and Meta-analysis

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OBJECTIVE To evaluate the efficacy and safety of combination therapy with selective serotonin reuptake inhibitors (SSRIs) and phosphodiesterase-5 (PDE-5) inhibitors for the treatment of premature ejaculation (PE).

METHODS A systematic search of EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews was undertaken to identify articles that referred to the use of a combination of SSRIs and PDE-5 inhibitors for the treatment of PE. A meta-analysis of these clinical studies was performed. The post-treatment intravaginal ejaculatory latency time (IELT) and adverse events (AEs) were used in this meta-analysis.

RESULTS Six publications involving 971 patients were included in the meta-analysis. In the analysis, we found significantly improved IELT in the combination use group compared with the use of SSRIs (mean differences [MD], 1.01; 95% confidence interval [CI], 0.61-1.41; P <.01) or PDE-5 inhibitors alone (MD, 1.11; 95% CI, 0.79-1.43; P <.01) for PE whether or not these patients suffered from erectile dysfunction. Combined treatment was more efficacious than use of PDE-5 inhibitors alone on sexual satisfaction. Although the occurrence of drug-related AEs in the combination use group was higher than that in the use of SSRIs or PDE-5 inhibitors alone group (37.5% vs 25.63%, P <.01), the most common AEs were mild and tolerable.

CONCLUSION The combined use of SSRIs and PDE-5 inhibitors provided additive favorable effects in men with PE compared with SSRIs or PDE-5 inhibitors monotherapy and was generally well tolerated. UROLOGY 86: 758–765, 2015. © 2015 Elsevier Inc.

Premature ejaculation (PE) is the most common sexual dysfunction in men, with a prevalence ranging from 19% to over 30% in the general population.[1-3] It is characterized by a short intravaginal ejaculatory latency time (IELT); inability to delay ejaculation on all or nearly all vaginal penetrations; and negative emotional consequences, such as distress, bother, frustration, or avoidance of sexual intimacy.[4]

At present, treatment of lifelong PE is primarily based on pharmacotherapy, with only on-demand selective serotonin reuptake inhibitors (SSRIs) and topical anesthetic agents that have consistently shown efficacy in this setting.[4,5] However, many patients might not respond adequately to SSRIs, particularly those with erectile dysfunction (ED), likely because PE and ED are associated with each other.[4,6] Several recent studies have investigated the role of phosphodiesterase-5 (PDE-5) inhibitors, which are the first-line treatment of ED, reporting efficacy in the treatment of PE in the absence of ED.[7,8] It is noteworthy that PDE-5 inhibitors do not pharmacokinetically interact with SSRIs, and the combination of both is well tolerated.[9] In addition, efficacy and safety regarding the combination of PDE-5 inhibitors and SSRIs vs PDE-5 inhibitors or SSRIs monotherapy have also been investigated in the past decade.[10-13] A previous review has focused on this topic and suggested that combination therapy may be propitious to those who fail SSRI monotherapy or have concomitant ED and that it should not be the first-line treatment of PE because of the adverse drug reactions.[14] Recently, a meta-analysis of four

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studies, including 282 patients and using post-treatment IELT as the primary end point, showed an overall positive effect of the combination regimen in the treatment of PE. However, the study did not consider the side effects related to the treatment.[15] Therefore, the therapeutic role of the combination regimen is not yet fully established, particularly for men without ED.

We conducted a systematic review and meta-analysis to assess the clinical efficacy and safety of the combined use of SSRIs plus PDE-5 inhibitors vs PDE-5 inhibitors or SSRIs monotherapy in patients with PE by identifying and synthesizing the available evidence.

METHODS

Search Strategy and Inclusion Criteria

We searched the following databases: PubMed, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. The following keywords, considering all possible combinations, were used: sexual dysfunction, premature ejaculation, PDE-5 inhibitor, SSRI. We also searched the reference lists of the relevant studies. Two authors independently screened the titles and abstracts of each citation to identify potentially eligible studies. Discrepancies between the authors regarding the inclusion of studies were resolved by discussions or further consultations with a third author.

Relevant studies were required to meet the following inclusion criteria: (1) evaluate the efficacy and safety of PDE-5 inhibitors and SSRIs for the treatment of PE; (2) provide sufficient data for analysis, including the mean values and standard deviations for IELT; and (3) the full text of the study can be accessed.

Data Extraction and Quality Assessment

All relevant studies identified with the search strategy were used for the detailed assessment. Studies with insufficient data were excluded. Data were independently extracted from the included studies by 2 authors who considered the following: (1) the name of the first author and the publication year; (2) the study design and sample size; (3) the definition and classification of PE; (4) the treatment strategy and duration; and (5) efficacy outcomes and adverse events (AEs). The Jadad scoring system[16] was used to assess the quality of the randomized controlled trials, which was independently scored by 2 authors.

Data Synthesis and Analysis

Meta-analyses were performed for the 2 primary outcome parameters: IELT (in minutes) and AEs (in events per group). The Review Manager 5.2 software statistical package was used to analyze the odds ratios (ORs) for dichotomous variables and mean differences (MDs) for continuous variables. For studies that presented continuous data as means and ranges, standard deviations were calculated using the methodology described by Hozo et al.[17] Depending on whether homogeneity was accepted or rejected, we used either the fixed or the random effects model. Statistical heterogeneity was tested using the χ^2 test. If the result of an analysis exhibited a probability (P) value of $>.05$, the studies were considered to be homogeneous. Fixed effects models were used for the meta-analysis and random effects models were used in case of heterogeneity. For all statistical analyses, a 2-sided P value of $<.05$ was considered statistically significant.

RESULTS

Characteristics of Individual Studies

Based on the inclusion and exclusion criteria, 6 studies[10-13,18,19] involving 971 patients were included in the analysis. Supplementary Figure 1 displays the flow diagram of evidence acquisition. The characteristics and quality of the individual studies are presented in Table 1.All 6 studies were randomized controlled trials. Five studies had been conducted to compare the efficacy and safety of SSRI monotherapy vs combination of SSRI and PDE-5 inhibitor therapy in subjects with PE and without ED.[10-13,18] One study evaluated the efficacy and safety of dapoxetine in men with PE and ED treated with PDE-5 inhibitors.[19] All studies focused on the treatments' ability to delay the time to ejaculation.

Efficacy Assessments

Intravaginal Ejaculatory Latency Time (IELT). Five studies included in the analysis evaluated the combination of SSRIs and PDE-5 inhibitors for PE without ED, reporting IELT as the primary outcome.[10-13,18] Meta-analysis of 4 studies[10-13] revealed that post-therapeutic IELT values were significantly higher in the combined therapy group compared with the SSRIs alone group (MD, 1.01; 95% confidence interval [CI], 0.61-1.41; P <.01). There was no evidence of statistical heterogeneity between studies as assessed by the χ^2 test ($\chi^2 = 1.06$; $I^2 = 0$; $P = .79$) (Fig. 1A). The later inclusion of the study by Zhang et al[18] as a sensitivity analysis did not affect the result (random effects model: MD, 1.41; 95% CI, 0.83-1.98; P <.01); however, it introduced significant heterogeneity into the analysis ($\chi^2 = 12.04$; $I^2 = 67\%$; $P = .02$). In addition, meta-analysis of 2 studies[12,13] revealed that compared with PDE-5 inhibitor alone, the post-therapeutic IELT value was significantly higher in the combined therapy group (MD, 1.11; 95% CI, 0.79-1.43; P <.01; Fig. 1B). The variation in IELT (increase from baseline to post-treatment) in the SSRIs plus PDE-5 inhibitor group was significantly higher than that reported by patients in the SSRI or PDE-5 inhibitor alone groups (MD, 47.67; 95% CI, 35.11-60.23; P <.01; MD, 58.17; 95% CI, 51.53-64.81; P <.01, respectively; Fig. 1C).

A prospective, randomized, double-blind, placebo-controlled trial evaluated the efficacy of dapoxetine in men with PE and concomitant ED who were treated with PDE-5 inhibitors.[19] A total of 495men were randomized to placebo (n = 245) or dapoxetine (n = 250). At baseline, mean average IELT values were comparable in both groups and in subgroups based on the type of PDE-5 inhibitor (either short- or long-acting). During the 12-week study, a statistically significant increase in mean average IELT was observed in the dapoxetine group compared with the placebo group (5.2 vs 3.4 minutes, respectively), whereas similar values were observed for subjects treated with a short (5.6 vs 3.6 minutes, respectively) or long (4.8 vs 3.3 minutes, respectively) half-life PDE-5 inhibitor