



Comparison of Safety and Efficacy Between On-demand PDE5 Inhibitor and Combined PDE5 Inhibitor with SSRI in Men with Premature Ejaculation: A Systematic Review and Meta-Analysis

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Abstract:

Introduction: Premature ejaculation is one of the most commonly encountered sexual dysfunction in men. Around 30 % of men in the world suffer from premature ejaculation. One of the most frequently given pharmacological treatments are SSRI and PDE5 inhibitor. Several studies attempted to combine the two, however the results are different from each other. Therefore, this systematic review and meta-analysis aimed to evaluate the difference of efficacy and safety between on-demand PDE5 inhibitor with the combination of PDE5 inhibitor and SSRI.

Materials and methods: This study is a systematic review and meta-analysis evaluating Randomized controlled trials analyzing the combination between the PDE5 inhibitor and its combination with SSRI. The results are measured in Intravaginal ejaculation latency time (IELT) and adverse effects. The search and screening process adheres to The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Cochrane Risk of Bias (RoB) tool is used to analyze the bias in the studies.

Results: A total of 3 RCTs, with a total of 190 patients diagnosed with premature ejaculation were analyzed in this study. The results of the analysis were statistically significant (mean difference = 1.30; 95% CI = 1.07-1.54); $p < 0.00001$, indicating that the combined on-demand PDE5 inhibitor and SSRI increased the mean IELT 1.3 minutes compared to the on-demand PDE5 inhibitor alone. Analysis of the side effects of nausea (OR = 5.16; 95% CI = 1.58-16.78; $p = 0.006$) and yawning (OR = 10.98; 95% CI = 1.32-91.02; $p = 0.03$) showed significant results.

Conclusion: The combination of on-demand PDE5 inhibitor and SSRI showed promising results in PE management compared to on-demand PDE5 inhibitor monotherapy based on the IELT with few minimal side effects, such as nausea and yawning.

Keywords: PDE5 inhibitor, SSRI, on-demand, IELT, premature ejaculation.

I. INTRODUCTION

The International Society for Sexual Medicine (ISSM) Ad Hoc Committee for the Definition of premature ejaculation (PE) defines PE as a sexual dysfunction in which ejaculation almost always or always occurs less than one minute after vaginal penetration, classified as a lifelong PE, or significant bothersome reduction of ejaculation time of three minutes or less for acquired PE. It is characterized by the inability to delay ejaculation on almost all vaginal penetrations during a sexual intercourse (1).

It is estimated that 30 to 70% of American men are suffering from PE. In Asian countries, current reports range from nine to 45% of the male population, with the lowest countries being Indonesia (9%) and China (45%). However, these reports require future investigations (2). Current management of PE consists of behavioural and pharmacological treatments. The most common pharmacological alternatives used are Selective Serotonin Reuptake Inhibitor (SSRI) drugs, such as dapoxetine and paroxetine, and Phosphodiesterase type 5 Inhibitor (PDE5i) drugs, such as sildenafil and vardenafil (3). In Europe, dapoxetine has been

approved for PE management (4). Many practitioners are recommending the drug as it is considered effective for acquired and lifelong PE (5). Even though the drug is shown to significantly improve the clinical condition of PE patients, its efficacy is considered only modest by a few reports (6). Thus, PDE5i are also investigated for its role in PE (7). Instead of promoting the benefits of using either drugs, there are a few studies which recommended combining the two drugs for maximum efficacy with tolerable side effects. However, current findings of the studies show different results of both efficacy and safety (8,9). Therefore, this systematic review aimed to analyze the results of randomized controlled trials (RCTs) evaluating the efficacy and safety of the combination of SSRI and PDE5i compared to PDE5i monotherapy.

II. RESEARCH METHODS

This review was performed according to the Preferred reporting item for systematic review and meta-analysis (PRISMA) (10,11). The protocol for this review was registered in the International prospective register of systematic reviews (CRD42020201979).

Eligibility criteria

We considered eligible all randomized controlled trials (RCTs) comparing the combination of PDE5i and SSRI versus PDE5i alone in patients with premature ejaculation that reported the Intravaginal ejaculation latency time (IELT) and treatment adverse effects. We excluded studies with the design of case reports, case-series, case-control, cohort, cross-sectional, reviews, abstracts, single-arm studies, and trials conducted on premature ejaculation patients with concomitant erectile dysfunction.

Study search and selection

A comprehensive literature search was performed from multiple databases including PubMed, Google Scholar, and ScienceDirect from their inception until March 2021 using the search strategies as demonstrated in table 1. Titles and abstracts taken from database searches were screened independently by two reviewers to assess their potential eligibility to be included. All references were collected and managed in Mendeley Desktop (12). Relevant articles were examined in full-text for eligibility criteria. Any disagreements were resolved by evaluating the full-text articles and discussion with senior authors. We demonstrated the process of study search and selection in a search flow diagram (13).

Data collection and quality assessment

To ensure standardization of data extraction from the included articles, we used piloted data extraction forms. The data collected include first author; year of publication; location of trial; number of participants; average age of participants; treatment protocols; length of the trial; and primary outcomes.

The risk of bias of the included trials was evaluated using the Risk of Bias (RoB) tools by Cochrane Collaboration (14). Each trial was evaluated in several aspects including the method of randomization, description of the blinding for the participants and investigator, incomplete data assessment, and other possible sources of bias (15).

Statistical analysis

The data were pooled as mean difference (MD) and odds ratio (OR) with 95% confidence interval (95% CI) for the assessment of IELT and adverse effects, respectively. We used the random-effects model if significant heterogeneity was found among the included trials. High heterogeneity was described as P-value ≤ 0.05 in the chi-squared test and I^2 statistic $> 50\%$.

Otherwise, we used the fixed-effects Mantel–Haenszel model. If P-value < 0.05, we consider the difference to have statistical significance (16). Review Manager 5.4 was used for data analysis.

III. RESULTS

Our initial search identified 366 records in table 1. After removing duplicates we screened 332 records and proceed by examining 20 articles in the full text for inclusion and exclusion criteria, resulting in 3 studies for qualitative and quantitative analysis with a total of 190 patients with PE (17–19).

Table 1. Systematic Search Results from Each Database

Database	Keywords	Articles
PubMed/ MEDLINE	(premature ejaculation OR PE OR sexual dysfunction) AND (PDE5i OR phosphodiesterase 5 inhibitor OR phosphodiesterase type 5 inhibitor OR sildenafil OR vardenafil OR tadalafil) AND (SSRI OR selective serotonin reuptake inhibitor OR dapoxetine OR fluoxetine OR paroxetine OR sertraline)	183
Science Direct	premature ejaculation AND (phosphodiesterase 5 inhibitor OR sildenafil OR vardenafil OR tadalafil) AND (selective serotonin reuptake inhibitor OR dapoxetine OR fluoxetine OR paroxetine) Article types: Research articles	144
Google Scholar	"premature ejaculation" PDE5i SSRI "selective serotonin reuptake inhibitor" "phosphodiesterase 5 inhibitor" sildenafil OR vardenafil OR tadalafil OR dapoxetine OR fluoxetine OR paroxetine OR sertraline	39
TOTAL		366

The PRISMA search diagram was shown in Figure 1. Basic characteristics of the included trials are summarized in table 2.

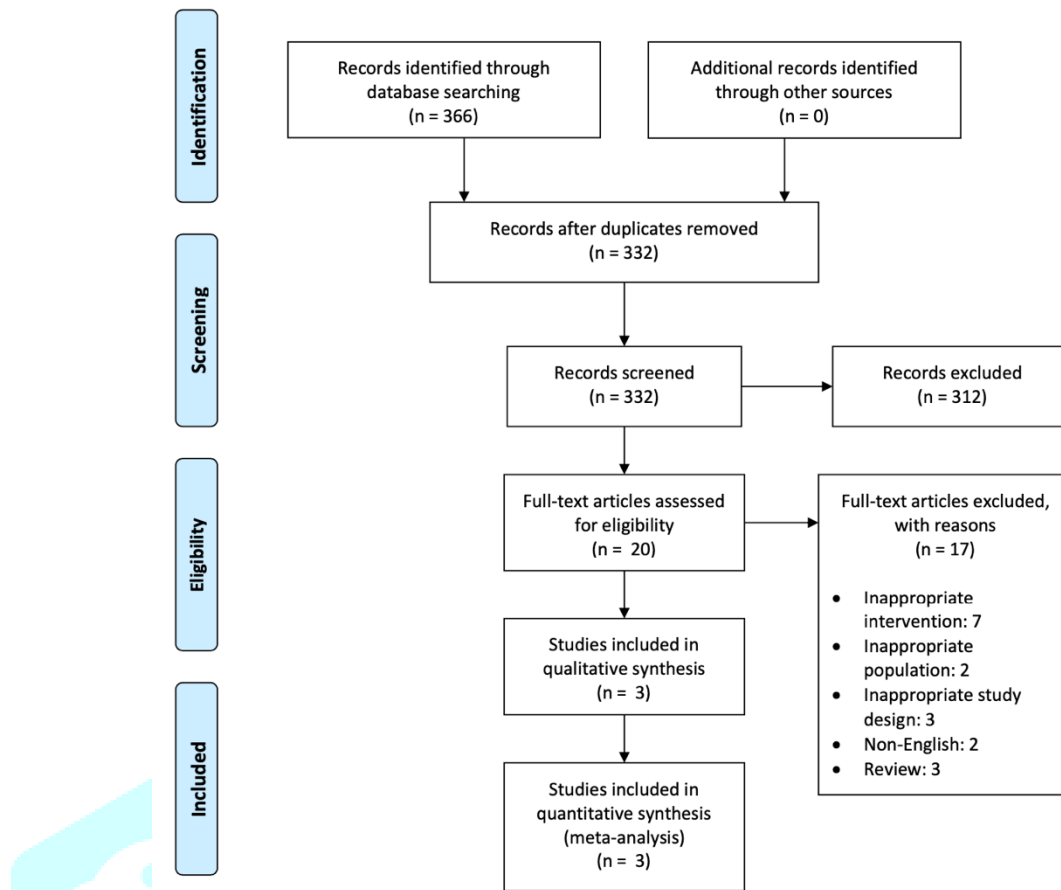


Figure 1. PRISMA flow of study selection

Table 1. Baseline Characteristics of The Included Studies

Author	Country	Study design	Treatment Group (On-demand)	Average age (years)	Participant (n)	Treatment duration	Outcome
Mattos 2008 (17)	Brasil	RCT	Tadalafil 20 mg	43,2 ± 11,3	15	12 weeks	IELT, adverse effects
			Tadalafil 20 mg + Fluoxetine 90 mg	42,81 ± 7,73	15		
Polat 2015 (18)	Turkey	RCT	Tadalafil 20 mg	27,8 ± 12,3	50	4 weeks	IELT, adverse effects
			Tadalafil 20 mg + Paroxetine 20 mg	30,5 ± 9,3	50		
Abu-el 2018 (19)	Egypt	RCT	Sildenafil 50 mg	32,8 ± 5,48	30	6 weeks	IELT, adverse effects
			Sildenafil 50 mg + Dapoxetine 30 mg	34,6 ± 6,38	30		

The RoB assessment in figure 2 and 3 showed that the trials have a low risk of bias in the aspects of selection bias, performance bias, attrition bias and, reporting bias. However, a trial by Abu-el et al has an unclear risk of bias for performance

and detection bias. Furthermore, the author did not describe the randomization process for the investigator and the blinding of outcome assessments.

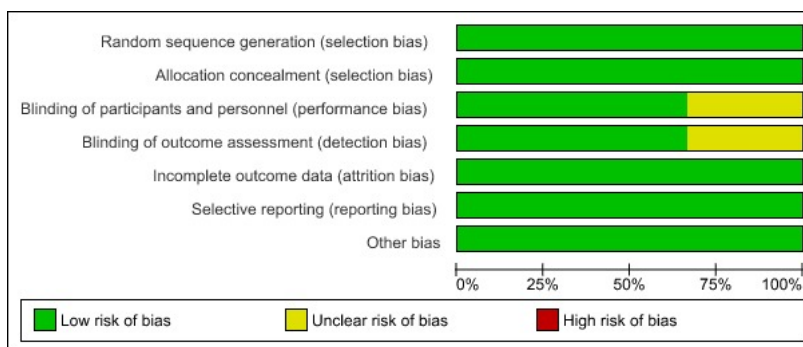


Figure 2. Risk of Bias graph of the included trials

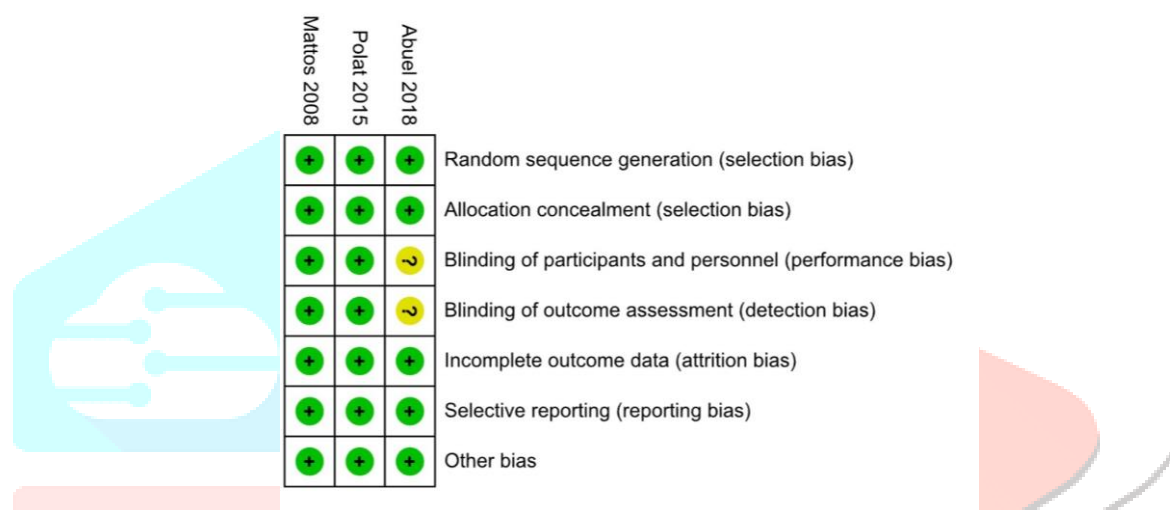


Figure 3. Risk of Bias summary of the included trials

The outcomes of IELT

The pooled analysis for IELT is summarized as a forest plot in figure 4. Our pooled analysis showed that the heterogeneity for this outcome was significant ($I^2=53$, p -value=0.12). Therefore, we used the fixed-effects model. From the pooled analysis, the mean duration of IELT in the combination of on-demand PDE5i + SSRI group was significantly longer compared to on-demand PDE5i group (MD = 1.30; 95% CI = 1.07-1, 54); $p < 0.00001$). This result indicates that the combination of on-demand PDE5 inhibitor + SSRI increases the mean IELT 1.3 minutes compared to on-demand PDE5 inhibitor alone.

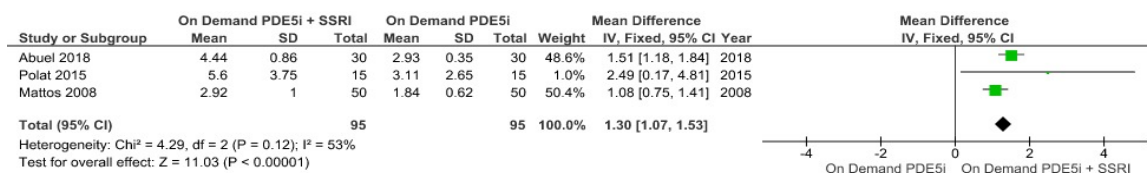


Figure 4. Meta-analysis results comparing PDE5i +SSRI versus PDE5i IELT (in minutes)

The outcomes of adverse effects

The adverse effects reported in the included trials in figure 5 were headache, flushing, palpitation, nausea, muscle soreness and frequent yawning. The overall heterogeneity for adverse effects was considerably low ($I^2 = 25\%$) with the p value = 0.18 and thus, we used the fixed-effects model. Furthermore, the heterogeneity for the headache outcome was considerably high ($I^2=61\%$).

However, the analysis showed insignificant heterogeneity (p-value=0.08) and therefore the fixed effects model was chosen. The analysis of each adverse effect was then assessed. Our pooled analyses showed that the combination of on-demand PDE5 inhibitor and SSRI had no significant differences in terms of headache, flushing, palpitation, and muscle soreness compared to on-demand PDE5 Inhibitors alone (OR = 0.58; 95% CI = 0.24-1.36; p = 0.21; OR = 0.89; 95% CI = 0.35-2.28; p = 0.81; OR = 0.82; 95% CI = 0.24-2.83; p = 0.75; OR = 5, 35; 95% CI = 0.60-47.41; p = 0.13; respectively). However, our meta-analysis showed that the combination group had a significantly higher nausea and yawning adverse effects compared to the PDE5 inhibitor alone group (OR = 5.16; 95% CI = 1.58-16.78; p = 0.006; OR = 10.98; 95% CI = 1.32-91.02; p = 0.03; respectively).

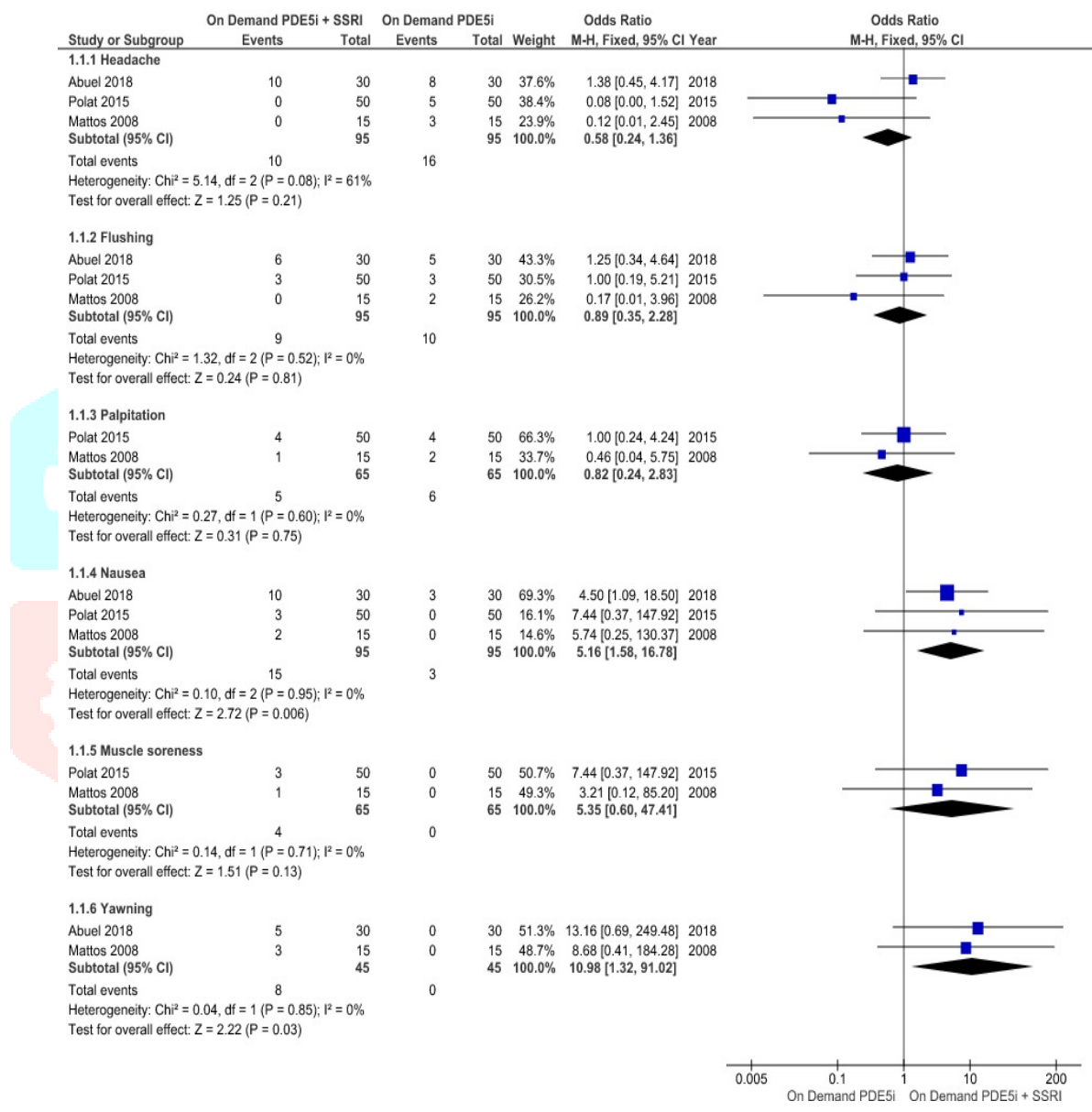


Figure 5. Meta-analysis results comparing PDE5i +SSRI versus PDE5i adverse effects

IV. Discussion

PE management is a difficult and challenging process for both the patient and the physician. Determining the etiology of each patient's condition and selecting the proper management is necessary to provide the best possible strategy for the patient. Additionally, discussing the expectation of the patient and his spouse is equally important to help develop a treatment strategy (20). Currently, most physicians tend to offer dapoxetine, paroxetine, and fluoxetine as SSRIs and tadalafil, sildenafil, and

ildenafil as PDE5is (21–24). In this review, we have obtained three RCTs, in which the PDE5i assessed were tadalafil and sildenafil, whereas the SSRIs used were fluoxetine, paroxetine, and dapoxetine(17–19).

Intravaginal ejaculation latency time (IELT)

The forest plot analysis of the three RCTs showed that the average duration of IELT is 1.3 minutes higher in the combination group compared to the PDE5i monotherapy group (MD=1,30; CI 95%=1,07-1,54; $p<0,00001$). The duration of therapy of each trial is different, ranging from four to twelve weeks. Polat et al, who administered the treatment for four weeks, reported the lowest mean IELT difference of 1.08 minutes out of the three studies. Abu-El et al reported 1.51 minutes of mean IELT difference in a six-week therapy duration. Mattos et al reported the highest mean difference of 2.49 minutes in a twelve-week treatment. The difference of mean IELT difference among studies is due to the variety of treatment duration. SSRI drugs work in both the central and peripheral nervous system. The mechanism of action of the drug increases serotonin in the synaptic cleft leading to desensitization of the 5HT1a and 5HT1b receptors (25). It works centrally by inhibiting the sympathetic pathway, thus extending the duration of erection and preventing ejaculation (26,27).

Adverse Effects

Adverse events of the use of long-term SSRI are important to be investigated as it could affect the quality of life of the patients taking the drug. Notable adverse events include psychiatric, neurologic, dermatologic, metabolic, and cognitive manifestations. Possible loss of libido is also found in several patients (9). A myriad of side effects is also found in PDE5i treatment, including headache, flushing, dyspepsia, stuffy nose, backpain, myalgia, nausea, and rash (28). In this study, the adverse effects reported include headache, flushing, palpitation, nausea, myalgia, and yawning. Based on the forest plot analysis, nausea (OR=5,16; CI 95%=1,58-16,78, $p=0,006$) and yawning (OR=5,16; CI 95%=1,58-16,78, $p=0,006$) were found to be significantly higher in the combination group. The higher occurrences of several side effects in the combination group are unsurprising as each drug produces side effects. However, the significant side effects found are mild and treatable by additional preventive behavioral and pharmacological strategies (29). The proportion of events is small compared to other side effects like headache and flushing. The overall side effects of the combination group are minimal. Additionally, the combination of the two types of drugs do not affect the pharmacokinetic of each drug, thus indicating that the combination is tolerable (30).

Study Limitations and Future Suggestions

Due to the limited amount of published RCTs, this review was not able to evaluate the comparison of specific SSRI and PDE5i drugs. Instead, we pooled the results of the RCTs into one group of combination consisting of a variety of SSRIs and PDE5is and another group of monotherapies, in which tadalafil was examined in two RCTs and sildenafil was evaluated in one RCT.

The limited number of published RCTs also have different treatment durations ranging from four to twelve weeks, causing different IELT results even though the combination group showed superiority in all treatment duration variations. An updated systematic review should be performed in the future for head-to-head comparisons of each drug or by dividing the drugs into subgroups of dapoxetine, paroxetine, and fluoxetine as SSRIs and tadalafil and sildenafil as PDE5is.

V. Conclusion

The combination of on-demand PDE5 inhibitor and SSRI showed promising results in PE management compared to on-demand PDE5 inhibitor monotherapy based on the IELT with few minimal side effects, such as nausea and yawning.

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