Phosphodiesterase-5 Inhibitors for Premature Ejaculation: Systematic Review and Meta-Analysis of Placebo-Controlled Trials

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Abstract

The purpose of this analysis is to assess the efficacy and safety of phosphodiesterase-5 inhibitors (PDE5Is) for the treatment of premature ejaculation (PE). A comprehensive search was performed to ascertain from trials about PDE5Is for the treatment of PE and compare the results, including intravaginal ejaculatory latency time (IVELT), score of sexual satisfaction scale, and side effects, between the group treated with PDE5Is and that treated with placebo. Seven studies involving a total of 471 patients were included in this meta-analysis. This analysis showed that patients who were treated with PDE5Is had significantly increased IVELT (mean difference [MD] 2.60; 95% CI [1.85, 3.36]; $p < .00001$) and score of sexual satisfaction scale (MD 2.04; 95% CI [0.78, 3.30]; $p = .002$) compared with the group on placebo. More patients had side effects while taking PDE5Is, such as headache, dizziness, flushing, and nasal congestion. PDE5Is were significantly more effective than placebo in the treatment of PE. Side effects were more common among patients who were treated with PDE5Is.

Premature ejaculation (PE) is one of the most common male sexual dysfunctions. An internet-based survey conducted in the United States and Europe reported that the prevalence of PE was 22.7% (Porst et al., 2007). The International Society for Sexual Medicine (ISSM) defined PE as characterized by "ejaculation that always occurs within about 1 minute of vaginal sex from the first sexual life (lifelong PE), or a worrisome reduction in intravaginal ejaculatory latency time (IVELT), often less than 3 minutes (acquired PE); and the inability to delay ejaculation on almost all sexual experiences; and the emergence of negative personal consequences" (Serefoglu et al., 2014). IVELT was considered as the most sensitive indicator for evaluating the therapeutic effect of PE (Serefoglu et al., 2014). Patients have many treatment options to choose from, such as psychosexual therapy and pharmacotherapies (Althof, 2016; Castiglione et al., 2016; Hisasue, 2016; Serefoglu et al., 2014). Dapoxetine, a type of short-acting selective serotonin reuptake inhibitor

(SSRI), has been widely used in the treatment of PE with well-tolerated adverse events (Akhvlediani & Matyukhov, 2017; Russo et al., 2016). For patients with both PE and erectile dysfunction (ED), phosphodiesterase type 5 inhibitors (PDE5Is) were suggested as first-line therapy to improve the symptoms of ED (Montague et al., 2004).

While the possible mechanisms and effects of PDE5Is in the treatment of PE have been reported (Chen, et al., 2007; Jannini et al., 2011), the efficacy of PDE5Is in the treatment of PE is still controversial. We conducted this meta-analysis to assess the efficacy and safety of PDE5Is in the treatment of PE.

Materials and Methods

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: All patients included in the analysis were diagnosed with PE and did not suffer from ED. All subjects had a stable heterosexual

relationship with their sexual partner for at least half a year. The studies had to include comparison between PDE5Is and placebo.

The exclusion criteria are as follows: patients diagnosed with ED; patients currently having some basic disease (e.g., hepatic failure, renal failure, and diabetes) or genitourinary system disease (e.g., sexual apathy, urinary tract inflammation, and urologic neoplasm); and patients with some other issues (e.g., emotional instability, drug abuse, and surgery) that could affect sexual function. Abstracts, case reports, letters, and observational trials were not included in this analysis.

Literature Search and Data Sources

Medline (update to August 2019), Embase (update to August 2019), Cochrane Controlled Trials Register databases, and reference lists of the retrieved literature were used to find the trials that were relevant to PDE5Is and placebo for the treatment of PE. Then, the literature was screened and trials included in the meta-analysis if they met the above-mentioned criteria. The subject terms included *phosphodiesterase type 5 inhibitors, premature ejaculation, tadalafil, sildenafil*, and *vardenafil*. Two authors of the group independently completed the screening and inclusion of the documents. If the opinions were not similar, the authors discussed and arrived at the final conclusions.

Data Extraction

One author extracted the following data by reading the articles: the general data of the test (e.g., the name of the first author, publication time, country, and the study design), the characteristics of the patients (e.g., age and PE type), the interventions of the different groups (e.g., PDE5Is or placebo, dosage, usage, and duration time), and the data on effectiveness and security of PDE5Is (e.g., IVELT, score of sexual satisfaction scale, number of adverse events). All the extracted data were checked by another author.

Outcome Measurements

IVELT and score of sexual satisfaction scale were used as the primary indicators of effectiveness and the number of patients with adverse events after treatment was used as the indicator of safety. The adverse events included in this analysis were headache, dizziness, flushing, nasal congestion, and gastrointestinal upset. IVELT was measured by the sex partner with a stopwatch, starting with vaginal penetration during sexual intercourse and ending with the ejaculation. A 0–5 point scale was used to assess the sexual satisfaction of the patients before and after treatment. Adverse events that occurred during the treatment were also recorded.

Quality Assessment

The authors used the Cochrane risk of bias tool (Higgins et al., 2011) to evaluate the quality of each study. The quality items were allocation sequence generation, allocation concealment, blinding, loss to follow-up, calculation of sample size, statistical analysis, and intention-to-treat analysis. The quality assessment form was generated by discussion, as Table 1 shows.

Statistical Analysis and Meta-Analysis

The software RevMan Version 5.3.5 (Cochrane Collaboration, Oxford, UK; J. Higgins & Green) was used to complete the meta-analysis of the continuous and dichotomous data. The mean difference (MD) with 95% confidence interval (CI) was employed to compare the IVELT and the score of sexual satisfaction scale, and the odds ratio (OR) with 95% CI was used to compare the adverse events among the different groups. The I^2 test and Mantel-Haenszel chi-square test were employed to evaluate the statistical heterogeneity. The fixed effect model was

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Table 1. Quality Assessment of Individual Studies.

Study	Allocation sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Loss to follow-up	Calculation of sample size	Statistical analysis	ITT analysis
McMahon (2005)	+	+	+	+	+	+	13	Yes	ANCOVA	No
Atan et al. (2006)	+	+	–	?	?	+	0	Yes	Pearson's correlation test	No
Mattos et al. (2008)	+	+	+	+	+	+	0	Yes	ANOVA	No
Aversa et al. (2009)	+	+	+	+	+	?	2	Yes	ANOVA; multiple regression analysis	No
Gameel et al. (2013)	+	+	?	+	+	+	3	Yes	ANOVA	No
El-Hamd MA 2018 (a)	+	+	?	+	+	+	0	Yes	ANOVA	No
El-Hamd MA 2018 (b)	+	+	?	+	+	+	0	Yes	Independent t test	No

Note. Plus sign (+) = low risk of bias; question mark sign (?) = unclear risk of bias; minus sign (−) = high risk of bias; ANCOVA = analysis of covariance; ANOVA = analysis of variance; ITT = intention to treat.
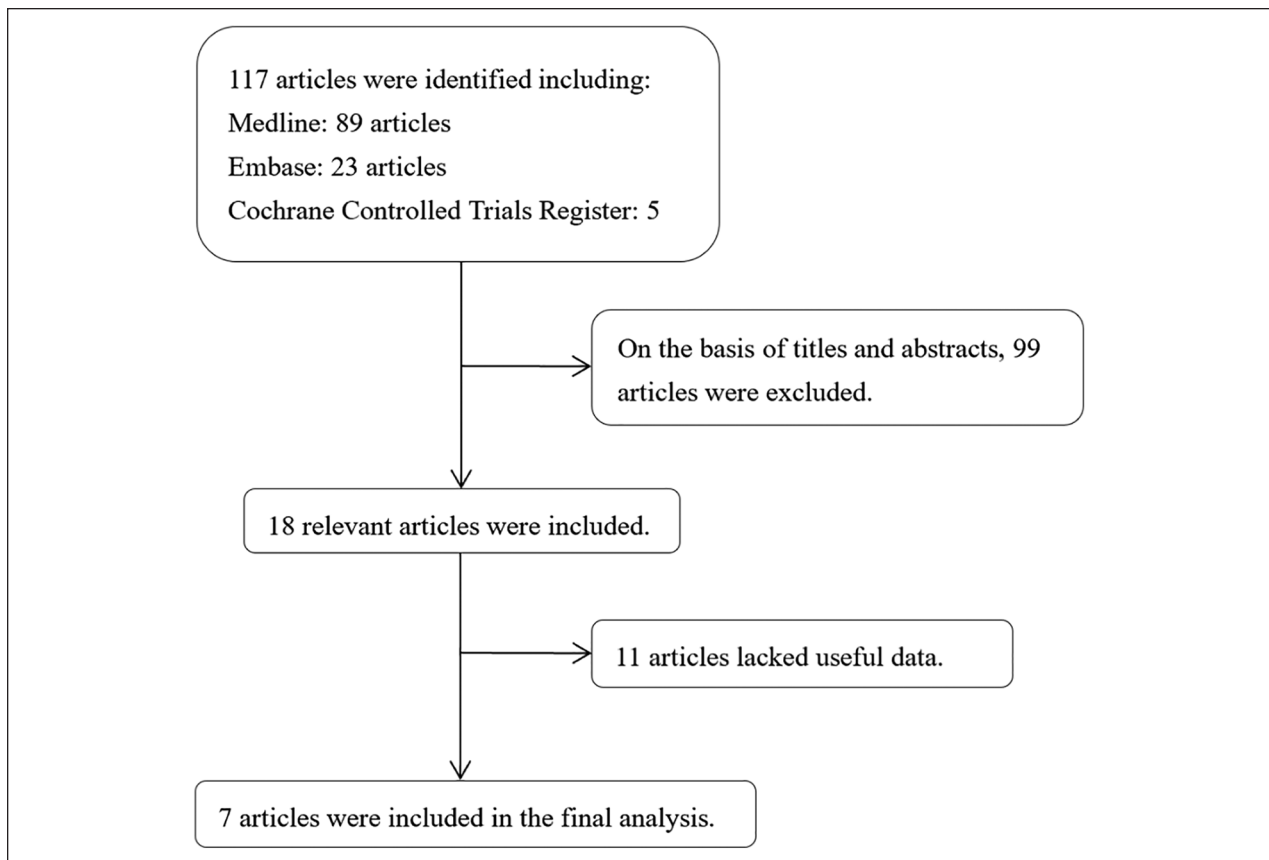
Figure 1. A flow diagram of the study selection process.

chosen if the $p > .05$; otherwise, the random effect model may be adopted. This meta-analysis does not need ethical approval and patient consent since all the data is available from previously published articles.

Results

Characteristics and Quality of the Studies

The study selection process is presented in Figure 1. One hundred and seventeen original papers were found from the commonly used database. Based on the abstract and the inclusion and exclusion criteria of this meta-analysis, 99 articles were excluded. Eleven studies were excluded without useful data. Totally, seven (Abu El-Hamd, 2018; Abu El-Hamd & Abdelhamed, 2018; Atan et al., 2006; Aversa et al., 2009; Gameel et al., 2013; Mattos et al., 2008; McMahon et al., 2005) placebo-controlled studies were included in the meta-analysis. One study (Atan et al., 2006) only contained the data about the safety of PDE5Is. The condition of the studies and characteristics of the patients are presented in Table 2.

All of the seven studies included in this meta-analysis followed the randomization process, and the scientific

sample size was identified through a calculation. The quality level of individual identified trials is presented in Table 1. However, funnel plots are not suitable to assess the publication bias in this meta-analysis and more high-quality randomized controlled trial (RCTs) are needed.

Efficacy and Safety

The indicators IVELT and score of sexual satisfaction scale were used to assess the efficacy of PDE5Is in the treatment of PE. Six studies (Abu El-Hamd, 2018; Abu El-Hamd & Abdelhamed, 2018; Aversa et al., 2009; Gameel et al., 2013; Mattos et al., 2008; McMahon et al., 2005) including 431 patients compared the indicator IVELT and 3 (Abu El-Hamd & Abdelhamed, 2018; Gameel et al., 2013; McMahon et al., 2005) RCTs (261 patients) compared the score of sexual satisfaction scale between the group treated with PDE5Is and that treated with placebo. According to the analysis, patients who were treated with PDE5Is had significantly increased IVELT compared with those treated with placebo. The pooled effect estimates across 6 RCTs (Abu El-Hamd, 2018; Abu El-Hamd & Abdelhamed, 2018; Aversa et al.,

Table 2. Study Conditions and Characteristics of the Patients.

| References	Country	Age	Design	Blinded	PE definition	PE type	Trial groups and number of patients	Comparator group and number of patients	Usage	Duration	The criterion of No ED	Outcomes
McMahon (2005)	Australia and Norway	18–65	RCT	Double blind	IVELT <2 min	Lifelong PE	Sildenafil 50–100 mg 1 hr PC (73)	Placebo (71)	OD	8 weeks	IIEF-EF ≥21	Stopwatch IVELT; IPE; sexual satisfaction scale 0–5; AEs
Atan et al. (2006)	Turkey	20–52	RCT	N M	DSM-IV	Lifelong and acquired PE	Sildenafil 50 mg 45 min PC (20)	Placebo (20)	OD	8 weeks	IIEF-EF ≥22	Ejaculation delay reported as "no change," "improvement," or "cure" by patient self-report; AEs
Mattos et al. (2008)	Brazil	24–59	RCT	Double blind	IVELT <1.5 min	Lifelong PE	Tadalafil 20 mg 1–3 hr PC (15)	Placebo (15)	OD	12 weeks	IIEF-EF ≥26	Stopwatch IVELT; AEs
Aversa A 2009	Italy	18–35	RCT	Double blind	IVELT ≤1 min >90% of IC	Lifelong PE	Vardenafil 10 mg 15–30 min PC (30)	Placebo (10)	OD	8 weeks	IIEF-EF ≥22	Stopwatch IVELT; IPE; PEDT; AEs
Gameel et al. (2013)	Egypt	26–39	RCT	Single blind	IVELT of <2 min in >75% of episodes	All had PE for >1 year	Sildenafil 50 mg 1 hr PC (30)	Placebo (27)	OD	4 weeks	IIEF-EF ≥22	Stopwatch IVELT; sexual satisfaction scale 0–5; AEs
El-Hamd (2018(a))	Egypt	24–48	RCT	Single blind	IVELT <1 min	NM	Sildenafil 50 mg 1 hr PC (30)	Placebo (30)	OD	6 weeks	IIEF-EF ≥22	IVELT; sexual satisfaction scale 0–5; PEDT; AEs
El-Hamd (2018(b))	Egypt	27–41	RCT	Single blind	IVELT <1 min	NM	Tadalafil 5 mg once a day (50)	Placebo (50)	Once a day	6 weeks	IIEF-EF ≥22	IVELT; AIPE; AEs

Note. AEs = adverse events; AIPE = Arabic Index of Premature Ejaculation; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994); IC = intercourse; IIEF-EF= score of erectile function domain of International Index of Erectile Function; IPE = Index of Premature Ejaculation; IVELT = intravaginal ejaculatory latency time; PE = premature ejaculation; PEDT = Premature Ejaculation Diagnostic Tool; NM = no mention; OD = on demand; PC = precoitus; RCT = randomized controlled trial.
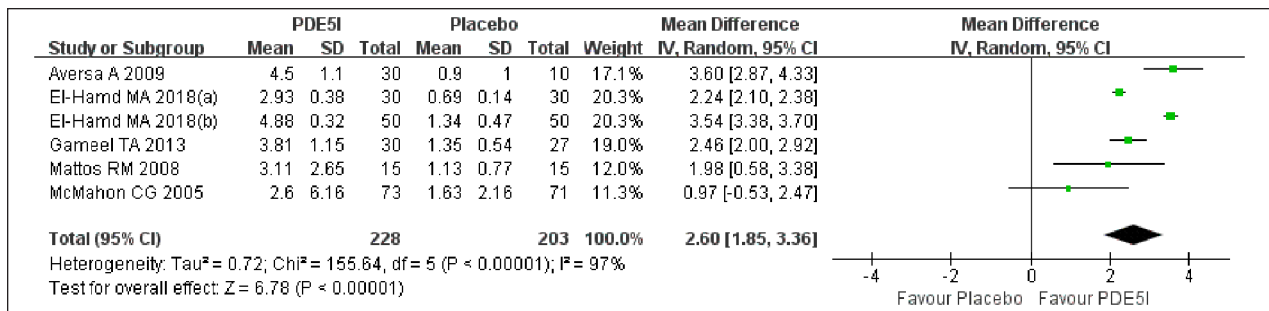
Figure 2. Forest plot shows changes in intravaginal ejaculatory latency time (IVELT; min). *SD* = standard deviation; IV = inverse variance; CI = confidence interval.
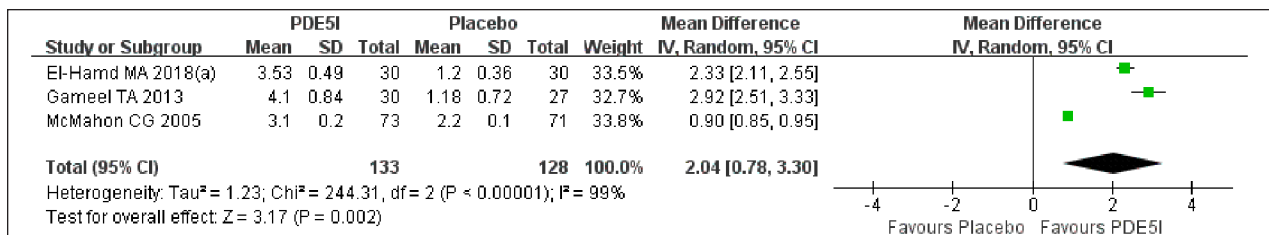
Figure 3. Forest plot shows changes in score of sexual satisfaction scale. *SD* = standard deviation; IV = inverse variance; CI = confidence interval.
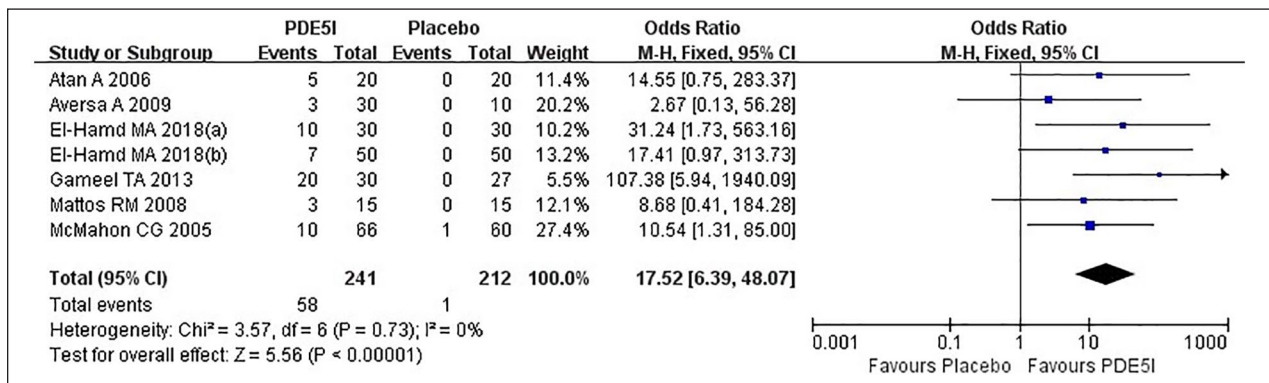
Figure 4. Forest plot shows differences between the groups for headache and dizziness. M-H = Mantel–Haenszel test; CI = confidence interval.

2009; Gameel et al., 2013; Mattos et al., 2008; McMahon et al., 2005) was 2.60 min (95% CI [1.85, 3.36]; $p < .00001$; Figure 2). In addition, the meta-analysis of sexual satisfaction scale of the two groups shows that the PDE5I group had a higher score than the placebo group (MD 2.04; 95% CI [0.78, 3.30]; $p = .002$; Figure 3).

Drug-related adverse reactions mainly included headache, dizziness, gastrointestinal upset, flushing, and nasal congestion. Adverse reactions such as headache and dizziness (OR 17.52; 95% CI [6.39, 48.07]; $p < .00001$; Figure 4), flushing (OR 11.74; 95% CI [3.88, 35.50]; $p < .0001$; Figure 5), and nasal congestion (OR 12.98; 95% CI [2.41, 69.90]; $p = .003$; Figure 6) were more

common among patients treated with PDE5Is compared with those treated with placebo. However, there was no significant difference in gastrointestinal upset (OR 2.88; 95% CI [0.62, 13.27]; $p = .18$; Figure 7).

Discussion

PE is one of the most common sexual dysfunctions that may affect the quality of sexual intercourse, leading to distress, anxiety, and frustration, even affecting the relationship between partners (Hanafy et al., 2019). Although there are many studies on PE at present, the precise pathogenesis and etiology of PE remains elusive (El-Hamd et al., 2019;
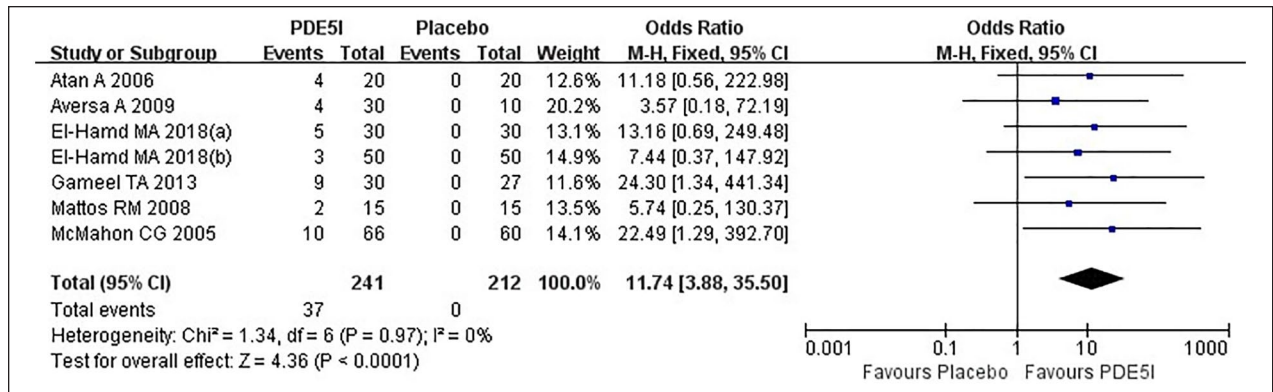
Figure 5. Forest plot shows differences between the groups for flushing. M-H Mantel–Haenszel test; CI = confidence interval.
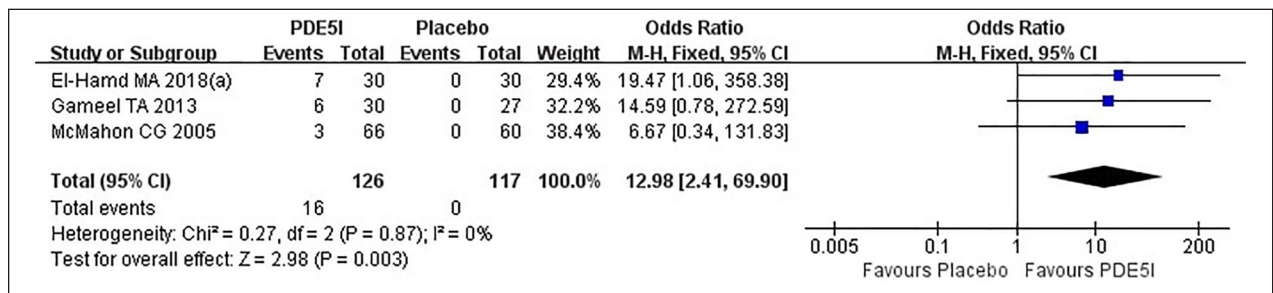

Figure 6. Forest plot shows differences between the groups for nasal congestion. M-H = Mantel–Haenszel test; CI = confidence interval.
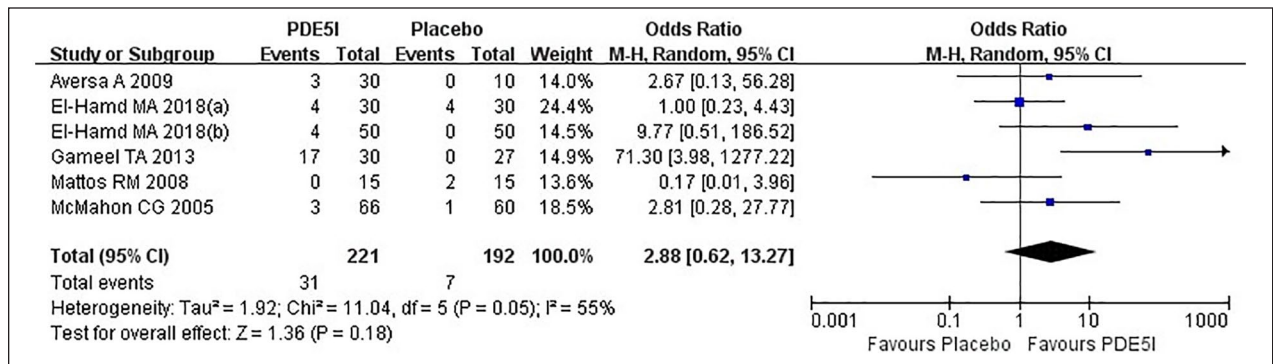

Figure 7. Forest plot shows differences between the groups for gastrointestinal upset. M-H = Mantel–Haenszel test; CI = confidence interval.

Gameel et al., 2013; McMahon et al., 2016). Psychological factors (Brody & Weiss, 2015), penile hypersensitivity (Guo et al., 2017), erectile dysfunction (Brody & Weiss, 2015), metabolic syndrome (Salama et al., 2017), polymorphisms of the serotonin transporter or its promoters (Roaiah et al., 2018), and external environmental factors (Kempeneers et al., 2018) are all considered to be related to the occurrence of PE. The ISSM (Serefoglu et al., 2014) indicated that PE was characterized by a short time to ejaculation, dissatisfaction with the ability to control ejaculation, and other negative emotions. IVELT was used as the

main comparison indicator between the different treatments of PE. Besides, three (Abu El-Hamd & Abdelhamed, 2018; Gameel et al., 2013; McMahon et al., 2005) RCTs included the indicator sexual satisfaction scale, though it was used as the second comparison indicator.

Nowadays, various methods are used for clinical treatment of PE. Although the therapeutic effect is very limited, behavioral psychosexual therapy was widely considered as the first choice for the treatment of PE (De Amicis et al., 1985; Waldinger, 2004). Medication has become the main mode of treating PE, especially SSRIs

(Lee et al., 2013), which may delay ejaculation by inhibiting the recovery of 5-HT in presynaptic membrane and increasing the amounts of 5-HT in postsynaptic membrane receptors. There are many side effects during the treatment, such as the loss of erection (use of local anesthetic), headache, dizziness, gastrointestinal upset, flushing, and nasal congestion (use of SSRIs, tramadol, etc.; Asimakopoulos et al., 2012; Sun et al., 2015). We use common adverse events as indicators of safety, including headache, dizziness, gastrointestinal upset, flushing, and nasal congestion.

PDE5Is are widely used in patients with both PE and ED to improve the symptoms of ED (Montague et al., 2004). Some articles reported that either as a single drug or as a combination drug, PDE5Is have been used to treat PE (Aversa et al., 2009; McMahon et al., 2005). Martyn-St James found that PDE5Is are significantly more effective than placebo and PDE5I combined with an SSRI is significantly more effective than SSRI alone for increasing IVELT and improving other effectiveness outcomes (Martyn-St James et al., 2017).

There is no sufficient evidence to support PDE5Is in the treatment of PE patients without ED medical history (Asimakopoulos et al., 2012). Therefore, the data was analyzed from all the included studies to confirm whether PDE5Is are feasible for the treatment of PE. And the final consequences revealed that the IVELT was significantly improved in the patients who were treated with PDE5Is compared with those treated with placebo, as also the score of sexual satisfaction scale. Meanwhile, treatment-emergent adverse events were more common among patients treated with PDE5Is, such as headache, dizziness, flushing, and nasal congestion.

Till date, for comparing PDE5Is with placebo in the treatment of PE, the number of RCTs and subjects included in this meta-analysis are the largest. And the conclusions have important clinical significance. Some limitations of this meta-analysis should be discussed. First, the definition of PE is not uniform. Atan et al. (Atan et al., 2006) used the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) to determine whether the patient has PE, while other studies mainly used the indicator IVELT to define PE. The diagnostic criterion for the included trials is IVELT <1 min (Abu El-Hamd, 2018; Abu El-Hamd & Abdelhamed, 2018), ≦1 min (Aversa et al., 2009), <1.5 min (Mattos et al., 2008), or <2 min (Gameel et al., 2013; McMahon et al., 2005). Although IVELT has different standards in different trials, the criterion of each trial is developed after scientific design and it doesn't conflict with the inclusion criteria. Second, the types of PDE5Is in this analysis included sildenafil (Abu El-Hamd & Abdelhamed, 2018; Atan et al., 2006; Gameel

et al., 2013; McMahon et al., 2005), tadalafil (Abu El-Hamd, 2018; Mattos et al., 2008), and vardenafil (Aversa et al., 2009). The trials used the corresponding dose and duration of PDE5I exposure, and the different medications had similar mechanisms, so the therapeutic effects of the different medications were similar. A high level of heterogeneity was shown in several analyses, which might result from the difference in types of PE and PDE5Is, as well as the duration of treatment and the sample sizes. Screening of the included patients is critical, and using only one indicator (score of erectile function domain of International Index of Erectile Function [IIEF-EF]) in the studies to exclude the patients with ED may lead to bias. Although we know that the inclusion of acquired PE may skew the data for PDE5Is efficacy and dilute the clinical applicability, if we analyze primary PE only, the conclusions are insufficient because of the small number of RCTs and patients. We will always pay attention to this issue, discuss it when enough relevant RCTs are published, and make relevant supplements to the current data.

The different standards involved in the studies may have resulted in biases. These limitations were unlikely to affect the result that PDE5Is can significantly improve the symptoms of PE. There is still a need for additional high-quality trials to provide more evidence.

Conclusions

This meta-analysis indicates that PDE5Is can significantly increase the IVELT and the score of sexual satisfaction scale. It is effective in the treatment of PE. Side effects were more common among those patients who treated with PDE5Is.

Declaration of Conflicting Interests

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Ethical Approval and Consent to Participate

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Supplemental Material

Supplemental material for this article is available online.

References

Abu El-Hamd, M. (2018). Efficacy and safety of daily use of tadalafil in treatment of patients with premature ejaculation: A randomised placebo-controlled clinical trial. *Andrologia*, *50*(5), e13005.

Abu El-Hamd, M., & Abdelhamed, A. (2018). Comparison of the clinical efficacy and safety of the on-demand use of paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil in treatment of patients with premature ejaculation: A randomised placebo-controlled clinical trial. *Andrologia*, *50*(1), e12829. doi:10.1111/and.12829

Akhvlediani, N. D., & Matyukhov, I. P. (2017). [The evidence for the efficiency and safety of dapoxetine in treating premature ejaculation]. *Urologiia* (5), 106–110.

Althof, S. E. (2016). Psychosexual therapy for premature ejaculation. *Translational Andrology and Urology*, *5*(4), 475–481.

Asimakopoulos, A. D., Miano, R., Finazzi Agro, E., Vespasiani, G., & Spera, E. (2012). Does current scientific and clinical evidence support the use of phosphodiesterase type 5 inhibitors for the treatment of premature ejaculation? a systematic review and meta-analysis. *Journal of Sexual Medicine*, *9*(9), 2404–2416.

Atan, A., Basar, M. M., Tuncel, A., Ferhat, M., Agras, K., & Tekdogan, U. (2006). Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. *Urology*, *67*(2), 388–391.

Aversa, A., Pili, M., Francomano, D., Bruzziches, R., Spera, E., La Pera, G., & Spera, G. (2009). Effects of vardenafil administration on intravaginal ejaculatory latency time in men with lifelong premature ejaculation. *International Journal of Impotence Research*, *21*(4), 221–227.

Brody, S., & Weiss, P. (2015). Erectile dysfunction and premature ejaculation: Interrelationships and psychosexual factors. *Journal of Sexual Medicine*, *12*(2), 398–404.

Castiglione, F., Albersen, M., Hedlund, P., Gratzke, C., Salonia, A., & Giuliano, F. (2016). Current pharmacological management of premature ejaculation: A systematic review and meta-analysis. *European Urology*, *69*(5), 904–916.

Chen, J., Keren-Paz, G., Bar-Yosef, Y., & Matzkin, H. (2007). The role of phosphodiesterase type 5 inhibitors in the management of premature ejaculation: A critical analysis of basic science and clinical data. *European Urology*, *52*(5), 1331–1339.

De Amicis, L. A., Goldberg, D. C., LoPiccolo, J., Friedman, J., & Davies, L. (1985). Clinical follow-up of couples treated for sexual dysfunction. *Archives of Sexual Behavior*, *14*(6), 467–489.

El-Hamd, M. A., Saleh, R., & Majzoub, A. (2019). Premature ejaculation: an update on definition and pathophysiology. *Asian Journal of Andrology*, *21*(5), 425–432. doi:10.4103/aja.aja_122_18

Gameel, T. A., Tawfik, A. M., Abou-Farha, M. O., Bastawisy, M. G., El-Bendary, M. A., & El-Gamasy Ael, N. (2013). On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: A randomised placebo-controlled clinical trial. *Arabian Journal of Urology*, *11*(4), 392–397.

Guo, L., Liu, Y., Wang, X., Yuan, M., Yu, Y., Zhang, X., & Zhao, S. (2017). Significance of penile hypersensitivity in premature ejaculation. *Scientific Reports*, *7*(1), 10441.

Hanafy, S., Hamed, A. M., & Hilmy Samy, M. S. (2019). Prevalence of premature ejaculation and its impact on the quality of life: Results from a sample of Egyptian patients. *Andrologia*, e13298.

Higgins, J., & Green, S. 2011 Cochrane handbook for systematic reviews of interventions, v.5.1. Cochrane Collaboration Web site. http://www.cochrane-handbook.org/.

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, KF, Weeks, L, & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, *343*(18), d5928. doi:10.1136/bmj.d5928

Hisasue, S. (2016). The drug treatment of premature ejaculation. *Translational Andrology and Urology*, *5*(4), 482–486.

Jannini, E. A., McMahon, C., Chen, J., Aversa, A., & Perelman, M. (2011). The controversial role of phosphodiesterase type 5 inhibitors in the treatment of premature ejaculation. *Journal of Sexual Medicine*, *8*(8), 2135–2143.

Kempeneers, P., Andrianne, R., Cuddy, M., & Blairy, S. (2018). Sexual cognitions, trait anxiety, sexual anxiety, and distress in men with different subtypes of premature ejaculation and in their partners. *Journal of Sex & Marital Therapy*, *44*(4), 319–332.

Lee, W. K., Lee, S. H., Cho, S. T., Lee, Y. S., Oh, C. Y., Yoo, C., Cho, J. S., Lee, S. K., & Yang, D. Y. (2013). Comparison between on-demand dosing of dapoxetine alone and dapoxetine plus mirodenafil in patients with lifelong premature ejaculation: prospective, randomized, double-blind, placebo-controlled, multicenter study. *Journal of Sexual Medicine*, *10*(11), 2832–2841.

Martyn-St James, M., Cooper, K., Ren, S., Kaltenthaler, E., Dickinson, K., Cantrell, A., Wylie, K., Frodsham, L., & Hood, C. (2017). Phosphodiesterase type 5 inhibitors for premature ejaculation: a systematic review and meta-analysis. *European Urology Focus*, *3*(1), 119–129.

Mattos, R. M., Marmo Lucon, A., & Srougi, M. (2008). Tadalafil and fluoxetine in premature ejaculation: prospective, randomized, double-blind, placebo-controlled study. *Urologia Internationalis*, *80*(2), 162–165.

McMahon, C. G., Jannini, E. A., Serefoglu, E. C., & Hellstrom, W. J. (2016). The pathophysiology of acquired premature ejaculation. *Translational Andrology and Urology*, *5*(4), 434–449.

McMahon, C. G., Stuckey, B. G., Andersen, M., Purvis, K., Koppiker, N., Haughie, S., & Boolell, M. (2005). Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *Journal of Sexula Medicine*, *2*(3), 368–375.

Montague, D. K., Jarow, J., Broderick, G. A., Dmochowski, R. R., Heaton, J. P., Lue, T. F., Nehra, A., & Sharlip, I. D.; AUA Erectile Dysfunction Guideline Update Panel. (2004). AUA guideline on the pharmacologic management of premature ejaculation. *Journal of Urology*, *172*(1), 290–294.

Porst, H., Montorsi, F., Rosen, R. C., Gaynor, L., Grupe, S., & Alexander, J. (2007). The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *European Urology*, *51*(3), 816–823; discussion 824.

Roaiah, M. F., Elkhayat, Y. I., Rashed, L. A., & GamalEl Din, S. F. (2018). Study of the prevalence of 5 HT-2C receptor gene polymorphisms in Egyptian patients with lifelong premature ejaculation. *Andrologia*, *50*(2), e12855. doi:10.1111/and.12855

Russo, A., Capogrosso, P., Ventimiglia, E., La Croce, G., Boeri, L., Montorsi, F., & Salonia, A. (2016). Efficacy and safety of dapoxetine in treatment of premature ejaculation: an evidence-based review. *International Journal of Clinical Practice*, *70*(9), 723–733.

Salama, N., Eid, A., Swedan, A., & Hatem, A. (2017). Increased prevalence of premature ejaculation in men with metabolic syndrome. *Aging Male*, *20*(2), 89–95.

Serefoglu, E. C., McMahon, C. G., Waldinger, M. D., Althof, S. E., Shindel, A., Adaikan, G., Becher, E. F., Dean, J., Giuliano, F., Hellstrom, W. J., Giraldi, A., Glina, S., Incrocci, L., Jannini, E., McCabe, M., Parish, S., Rowland, D., Segraves, R. T., Sharlip, I., & Torres, L. O. (2014). An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second international society for sexual medicine ad hoc committee for the definition of premature ejaculation. *Sexual Medicine*, *2*(2), 41–59.

Sun, Y., Luo, D., Yang, L., Tang, C., Yang, T., Hu, X., & Shen, H. (2015). Efficacy of Phosphodiesterase-5 Inhibitor in Men With Premature Ejaculation: A New Systematic Review and Meta-analysis. *Urology*, *86*(5), 947–954. doi:10.1016/j.urology.2015.06.051

Waldinger, M. D. (2004). Lifelong premature ejaculation: from authority-based to evidence-based medicine. *BJU International*, *93*(2), 201–207.