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REVIEW

Efficacy and safety of on-demand dapoxetine combined with phosphodiesterase-5 inhibitor compared to monotherapy dapoxetine as a treatment of premature ejaculation without erectile dysfunction: A systematic review and meta-analysis

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Summary

Background: *Premature Ejaculation (PE) affects about 30% of the male population. The European Association of Urology (EAU) guidelines state that monotherapy dapoxetine on-demand has been successfully used to treat PE throughout Europe. Several studies have stated that when dapoxetine and phosphodiesterase-5 inhibitor (PDE-5i) are used combined, sexual enjoyment and Intravaginal Ejaculation Latency Time (IELT) are increased more than when dapoxetine is taken alone. However, further investigation is needed to determine whether PDE-5i and dapoxetine can be safely consumed together.*

Methods: *This study was conducted using 5 randomized controlled trials (RCTs), which systematically extracted from online databases namely Science Direct, PubMed, Google Schoolar and Cochrane Library. Included studies were assessed using Cochrane Risk of Bias (RoB) 2.0 for RCTs. The data analysis was performed using RevMan software 5.1 of the Cochrane Collaboration.*

Results: *Five RCTs with a total of 498 potent men with PE from the period 2013-2024 showed pooled mean difference of dapoxetine + PDE-5i was found significantly associated with higher post-treatment IELT scores compared to monotherapy dapoxetine (MD 1.08; 95% CI 0.34-1.83; P = 0.004; I^2 = 95%; 4 RCTs). The pooled mean difference of dapoxetine + PDE-5i also showed statistically significant association with higher post-treatment Sexual Satisfaction Scale (SSS) scores compared to monotherapy dapoxetine (MD 0.76; 95% CI 0.49-1.04; P < 0.00001; I^2 = 68%; 2 RCTs). Among 10 adverse effects (headacahe, flushing, nausea, dizziness, fatigue, nasal congestion, palpitation, vomitting, sleep disturbance, and constipation), the use of combination therapy is presenting significantly higher incidence of headache, flushing, nasal congestion compared to monotherapy dapoxetine (RR 3.00; 95% CI: 1.91-4.71; P < 0.00001; I^2: 0%; 5 RCTs), (RR 15.78; 95% CI: 5.48-45.45; P < 0.00001; I^2: 24%; 5 RCTs), (RR 9.00; 95% CI: 1.17-69.01; P = 0.03; I^2: 0%; 2 RCTs), respectively.*

Conclusions: *This study demonstrates the combination of dapoxetine and PDE-5i significantly improves post-treatment scores of IELT and sexual satisfaction compared to dapoxetine monotherapy. Despite an increased risk of certain side effects, the overall tolerability of the combination therapy remains favorable.*

KEY WORDS: *Dapoxetine; PDE-5i; Combined; Premature Ejaculation.*

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INTRODUCTION

Premature Ejaculation (PE) is characterized by a short *intravaginal ejaculatory latency time* (IELT) and an inability to control ejaculation, frequently results in interpersonal issues, anxiety, and psychological distress. PE presents as the most common male sexual dysfunction, affecting about 30% of men worldwide (1). With etiologies ranging from neurological reasons like serotonergic neurotransmission disruptions to psychosocial triggers like anxiety and relationship problems, this condition can present as either acquired or lifelong. According to the *International Society for Sexual Medicine* (ISSM), acquired PE is defined as a decrease in IELT to less than three minutes following a period of normal sexual function, while lifelong PE is defined as ejaculation that consistently occurs within one minute of vaginal penetration since the beginning of sexual activity (1, 2).

Historically, PE was managed through counseling and behavioral therapy, but new developments in pharmaceutical treatments have provided more targeted treatment options. *Selective serotonin reuptake inhibitors* (SSRIs) are the primary pharmacological care for PE, with dapoxetine as the first and only SSRI authorized for on-demand usage in PE treatment (3). The *European Association of Urology* (EAU) guidelines state that monotherapy dapoxetine on-demand has been successfully used to treat PE throughout Europe. Dapoxetine delays ejaculation by raising serotonin levels in the synaptic clefts and re-establishing equilibrium between 5-HT1A and 5-HT2C receptor activity.

Despite its efficacy, many patients report suboptimal improvements in IELT and sexual satisfaction when treated with dapoxetine monotherapy (3, 4). Several studies have stated that when dapoxetine and *PDE-5 inhibitors* (PDE-5i) are used together, sexual enjoyment and IELT are increased more than when dapoxetine is taken alone. PDE-5i, which were first created to treat erectile dysfunction, increase nitric oxide signaling, which causes the vas deferens and corpus cavernosum's smooth muscles to relax. A longer IELT is facilitated by this mechanism, which also reduces performance anxiety and promotes improved erectile function (2, 4).

Many studies and trials have stated that combination therapy improves IELT and sexual satisfaction while retaining a manageable safety profile. But, there have been reports of mild adverse effects which are similar to those seen with monotherapy. However, the specific therapeutic function of PDE-5i in the management of PE is still not well defined, highlighting the urgent need for additional study in this field to enhance treatment approaches and enhance patient outcomes (1, 3).

This systematic review and meta-analysis aim to provide evidence on the clinical efficacy and safety of on-demand dapoxetine combined with PDE-5i compared to dapoxetine monotherapy.

Materials and methods

This systematic review and meta-analysis was conducted following the guidelines outlined in the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) framework. Adherence to the PRISMA guidelines ensured a rigorous and transparent approach to study identification, selection, and data synthesis. This PICO (*Population, Intervention, Comparator, Outcomes*) framework is used to ensure a structured and rigorous methodology. The population of interest consisted of men who were diagnosed with PE based on the *International Society for Sexual Medicine's* (ISSM) criteria without having *erectile dysfunction* (ED). Patients were diagnosed with PE if, either from the beginning of their sexual experiences or after a distressing shift in ejaculatory latency, they consistently experienced ejaculation before or within one minute of vaginal penetration. Furthermore, in order to be included, a person had to be unable to postpone ejaculation during the majority of vaginal penetrations and experience unfavorable personal outcomes like frustration, distress, or avoiding sexual closeness. The intervention evaluated in this study was on-demand combination therapy of dapoxetine and PDE-5i, and the comparator group included patients receiving on-demand dapoxetine monotherapy, which is currently a standard pharmacological treatment for PE or dapoxetine + placebo.

Outcomes were categorized into primary and secondary measures. The primary outcomes included post-treatment score of IELT and *Sexual Satisfaction Scale* (SSS). IELT was recorded using a stopwatch by patients before and at the conclusion of the treatment period. Patients were provided with clear instructions on the measurement protocol, starting from intromission to ejaculation. Moreover, the SSS was used to measure sexual satisfaction, which ranged from 0 (severe dissastisfaction) to 5 (extreme pleasure). Meanwhile, the secondary outcomes focused on adverse effects associated with drug administration. Patients reported symptoms such as headache, flushing, dizziness, and other potential side effects.

Search strategy and eligibility criteria

The primary review question for this systematic review and meta-analysis was: "*Does the combination of on-demand dapoxetine and PDE-5i improve IELT and SSS compared to dapoxetine monotherapy in men with premature ejaculation without erectile dysfunction compared to dapoxetine monotherapy?*"

A thorough search of the Cochrane Library, PubMed, ScienceDirect, and Google Scholar databases was conducted from October 2024 to December 2024. A Medical Subject Headings (MeSH) terms, such as "*Dapoxetine*" AND "*PDE5 Inhibitor*" OR "*Sildenafil*" OR "*Tadalafil*" AND "*Premature Ejaculation*" were used in the search approach. In order to find more relevant studies, the references of pertinent papers were also manually searched. To guarantee correctness, results were deduplicated and imported into the Mendeley Reference Management system.

Inclusion and exclusion criteria

Randomized controlled trials (RCTs) that examined the efficacy and safety of on-demand dapoxetine monotherapy in comparison to dapoxetine combined with PDE-5i for the treatment of PE were included. According to the ISSM criteria, male sexual dysfunction is defined as follows: (i) ejaculation that consistently occurs within one minute of vaginal penetration or after a distressing reduction in ejaculatory latency; (ii) an inability to delay ejaculation on most vaginal penetrations; and (iii) negative personal consequences like distress, frustration, or avoidance of intimacy. Participants in the studies had to have a diagnosis of PE and to be active heterosexual individuals.

Exclusion criteria were applied to ensure the specificity and quality of the included studies. Studies were excluded if they involved participants with erectile dysfunction, as determined by a score of less than 22 on the *International Index of Erectile Function* (IIEF), or if they included individuals with comorbid conditions such as diabetes, chronic prostatitis, severe hepatic, renal impairment, or neurological disorders. Patients who had taken PE medication within the three months before enrolling in the trial were also excluded. Additionally, studies that did not compare the combination therapy with monotherapy, case reports, conference abstracts, and studies with insufficient data for meta-analysis were excluded.

Data extraction

A standardized electronic data extraction form created in Microsoft Excel was used to extract the data. Study features including the first author, the year of publication, the study design, the sample size were extracted. Details of the intervention, such as the dosage of PDE-5i and dapoxetine and duration of follow-up, were also documented, along with information about the comparator.

Two independent reviewers performed the data extraction process to ensure accuracy and reliability. Third reviewer was consulted or a consensus-based discussion was used to settle any disagreements or conflicts between the reviewers. The integrity of the dataset utilized for

analysis was guaranteed, and the chance of errors was reduced.

Risk of bias of included studies

The risk of bias in the included studies was independently assessed at the outcome level by two reviewers using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. Every domain received a risk of bias rating of low, some concerns, or high. The reviewers consulted with senior reviewers or a third reviewer to settle any disputes about how to evaluate the study's quality.

Data analysis

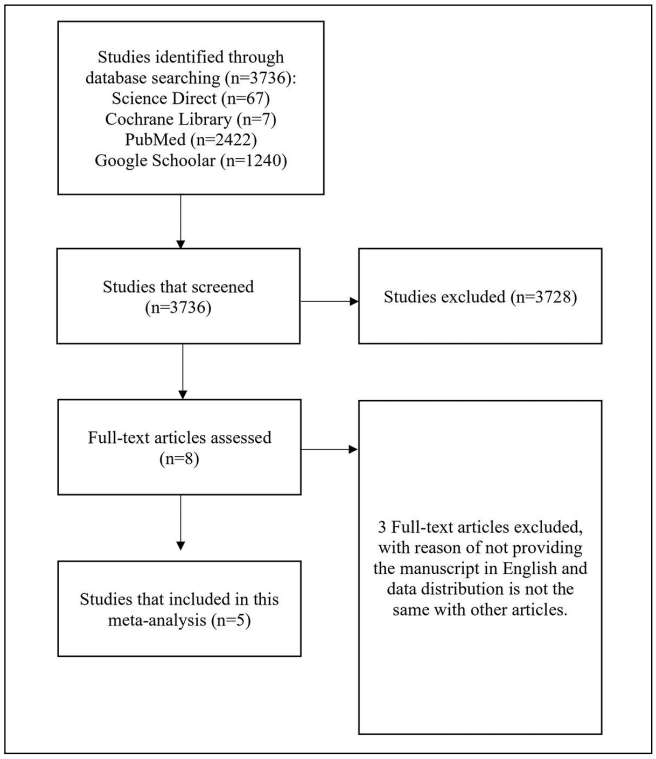
Review Manager (RevMan) software version 5.4 (Cochrane Collaboration) was used for data synthesis and meta-analysis. The pooled *mean difference* (MD) and associated 95% *confidence intervals* (CIs) were computed for continuous outcomes, such as improvement of IELT and SSS scores. The results were summarized using *risk ratios* (RRs) with 95% CIs for binary outcomes, including side effects like headache, nasal congestion, and sleep disturbance. If at least two research reported on the same result, a meta-analysis was carried out. The chi-square test was used to evaluate study heterogeneity, and the I^2 statistic was used to quantify the heterogeneity. Heterogeneity was defined as low if I^2 was less than 50%, and high if greater than 50%. A fixed-effects model was used if there was insufficient heterogeneity ($I^2 < 50\%$), otherwise, a random-effects model was implemented.

Results

Study selection

A total of 3,736 studies were identified through a comprehensive database search, which included *Science Direct* (n = 67), *Cochrane Library* (n = 7), *PubMed* (n = 2,422), and *Google Scholar* (n = 1,240). 3,728 papers were eliminated following title/abstract screening and duplication removal because they were irrelevant or had insufficient data. The predetermined inclusion and exclusion criteria were used to evaluate the eligibility of 8 full-text articles. Furthermore, 3 studies were excluded after full-text assessment and 5 studies were included in the quantitative synthesis as shown in Figure 1.

Figure 1.
Flow chart of study selection.



Study characteristics

The included studies as shown in Table 1 were varied in definitions of PE, intervention protocols, durations, and definition of ED as the criteria. Most trials used IELT as a diagnostic criterion for PE, with thresholds ranging from less than one minute to two minutes (1, 3, 4, 5). One study used the *Premature Ejaculation Diagnostic Tool* (PEDT) with a score ≥ 11 to identify lifelong PE.2

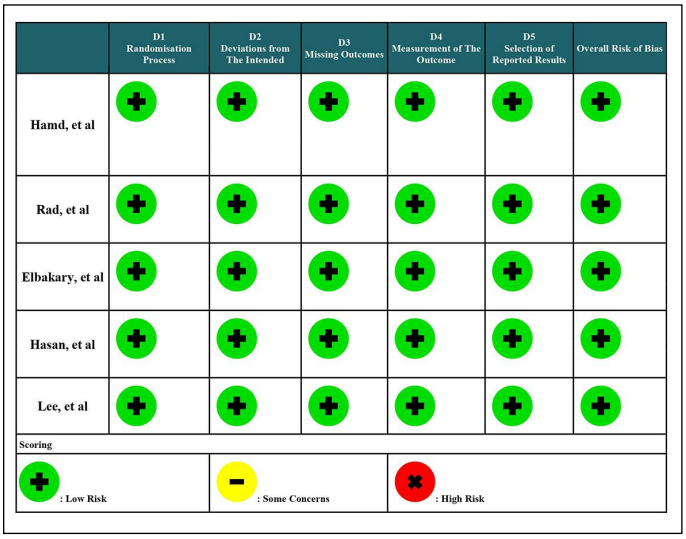
Combinations of dapoxetine (30 mg) and PDE-5i, including sildenafil (50 mg), tadalafil (5 mg or 10 mg), and mirodenafil (50 mg), were part of the intervention regimens. These combinations were compared to dapoxetine monotherapy or, in one study, to dapoxetine plus placebo. Across the investigations, treatment durations varied from four to twelve weeks, and sample sizes varied from

Table 1.
Characteristics of included studies.

Author, year	Design	PE definition	Type of PE	Drug, dosage (patients qmount)	Duration	No ED definition
Hamd, 2017 (1)	RCT	IELT < 1 min	NA	Dapoxetine 30 mg + Sildenafil 50 mg (n = 30) *vs* Dapoxetine 30 mg (n = 30)	6 weeks	IIEF ≥ 22
Rad, 2021 (5)	RCT	IELT < 2 mins	NA	Dapoxetine 30 mg + Tadalafil 10 mg (n = 30) *vs* Dapoxetine 30 mg (n = 30)	4 weeks	NA
Elbakary, 2022 (4)	RCT	IELT 1-2mins	NA	Dapoxetine 30 mg + Sildenafil 50 mg (n = 40) *vs* Dapoxetine 30 mg (n = 40)	12 weeks	IIEF Scoring
Hasan, 2024 (3)	RCT	IELT < 1 min	Lifelong and Acquired PE	Dapoxetine 30 mg + Tadalafil 5 mg (n = 89) *vs* Dapoxetine 30 mg (n = 91)	12 weeks	IIEF > 22
Lee, 2013 (2)	RCT	PEDT ≥ 11	Lifelong PE	Dapoxetine 30 mg + Mirodenafil 50 mg (n = 62) *vs* Dapoxetine 30 mg + Placebo (n = 56)	12 weeks	IIEF > 22

RCT: Randomized Controlled Trial; IELT: Intravaginal Ejaculation Latency Time; PE: Premature Ejaculation; IIEF: International Index of Erectile Function; NA: Not Available.

Figure 2.
Risk of bias of included studies.



30 to 110 patients per group. The IIEF score, which most studies require to be ≥ 22, was one of the validated measures used in the trials to make sure participants did not have erectile dysfunction.

Risk of bias of included studies

All of the included studies have a low overall risk of bias as shown in Figure 2. A high degree of scientific rigor in terms of randomization protocols, adherence to interventions, thorough outcome reporting, and suitable assessment methodologies is suggested by this consistency throughout the included studies. The absence of concerns related to missing data or selective reporting further strengthens the validity of the synthesized findings from these trials.

Post-Treatment IELT

Figure 3 illustrates the pooled effect of dapoxetine combined with PDE5i compared to dapoxetine monotherapy on IELT. The overall MD was 1.08 (95% CI: 0.34-1.83; P = 0.004), indicating a significant higher value in post-treatment IELT for the combination therapy. Variability between trials was suggested by the high heterogeneity (I^2 = 95%; Chi^2 = 64.20, P < 0.00001) that was found. With a mean difference of 1.47 (95% CI: 1.34-1.60), *Hasan et al.* (2024) (3) had the highest weight (34.9%) among the included studies, while *Lee et al.* (2013) (2) had the lowest weight (5.0%) and reported an MD of 2.20 (95% CI: -0.89-5.29), with broader confidence intervals indicating less precision.

Post-treatment SSS

Figure 4 shows that the combination of dapoxetine and PDE5i produced noticeably higher SSS scores after treatment, compared to dapoxetine monotherapy. With a pooled MD of 0.76 (95% CI: 0.49-1.04; P < 0.00001), the combination therapy significantly increased sexual pleasure. The studies' moderate heterogeneity (I^2 = 68%; Chi^2 = 3.14, P = 0.08) indicated considerable variation but general consistency in the effect's direction.

Headache

The forest plot in Figure 5 presents the incidence of headaches as an adverse effect associated with the use of dapoxetine combined with PDE5i compared to dapoxetine monotherapy. With a pooled RR of 3.00 (95% CI: 1.91-4.71; P < 0.00001), the combination therapy group had a noticeably increased chance of experiencing headaches. *Hasan et al.* (2024) (3) reported a risk ratio of 3.32 (95% CI: 1.87-5.92) and contributed the greatest weight (56.5%) among the included studies. A smaller sample size resulted in wider confidence intervals for even higher RR of 5.00 (95% CI: 1.19-20.92) reported by *Hamd et al. (2017)* (1).

Figure 3.
Forest plot of post-treatment IELT.

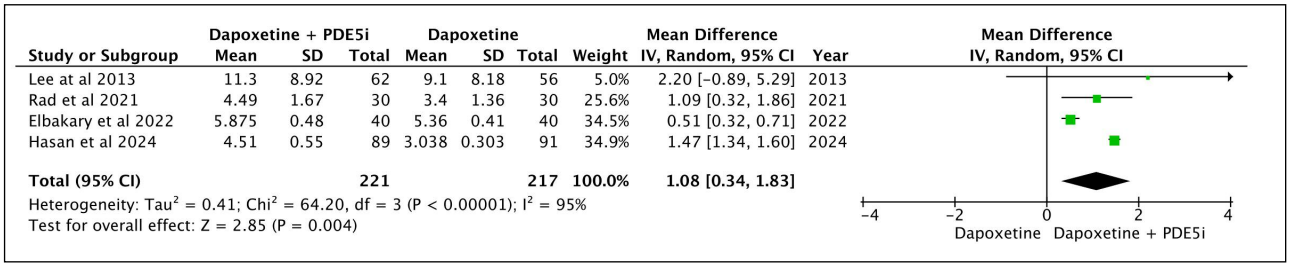


Figure 4.
Forest plot of post-treatment SSS.

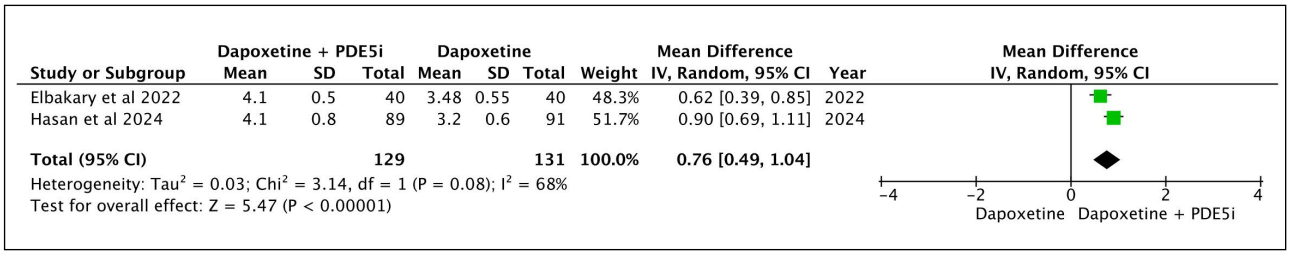
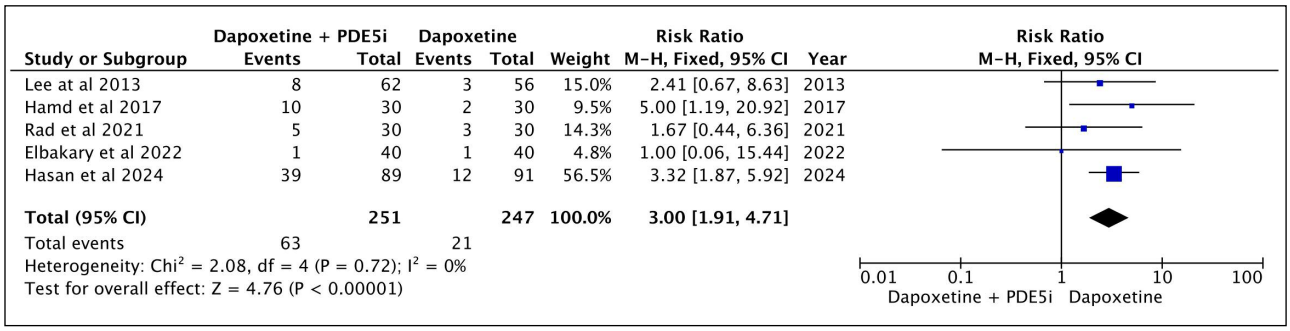


Figure 5.
Forest plot of headache as one of the adverse effect



Heterogeneity across the studies was minimal (I^2 = 0%; Chi^2 = 2.08, P = 0.72), suggesting a consistent direction of effect across trials. While the combination therapy was more effective in improving IELT and sexual satisfaction, the findings underline an increased risk of headaches as a potential side effect.

Flushing

The forest plot in Figure 6 presents the incidence of flushing as an adverse effect associated with the use of dapoxetine combined with PDE5i compared to dapoxetine monotherapy. With a pooled RR of 15.78 (95% CI: 5.48-45.45; P < 0.00001), the combination therapy group had a noticeably greater incidence of flushing. A significantly enhanced risk was highlighted in *Hasan et al. (2024)* (3), which contributed the most weight (27.9%) and reported the highest risk ratio of 40.90 (95% CI: 5.75-291.13). Due to smaller sample sizes or fewer incidents, other studies, such as *Lee et al. (2013)* (2) and *Rad et al. (2021)* (5), similarly revealed higher risk ratios, albeit with broader confidence ranges. Heterogeneity across studies was low (I^2 = 24%; Chi^2 = 5.24, P = 0.26), indicating consistency in the reported effect sizes.

Nausea

Figure 7 illustrates the incidence of nausea as a side effect of dapoxetine combined with PDE5i compared to dapoxetine monotherapy. The pooled RR was 1.24 (95% CI: 0.91–1.68; P = 0.17), indicating no statistically significant difference in the likelihood of nausea between the two groups. The largest contribution to the analysis came from *Hasan et al. (2024)* (3), which carried a weight of 64.1% and reported an RR of 1.18 (95% CI: 0.82-1.69). Other studies, such as *Hamd et al. (2017)* (1) and *Rad et*

Figure 6.
Forest plot of flushing as one of the adverse effect.

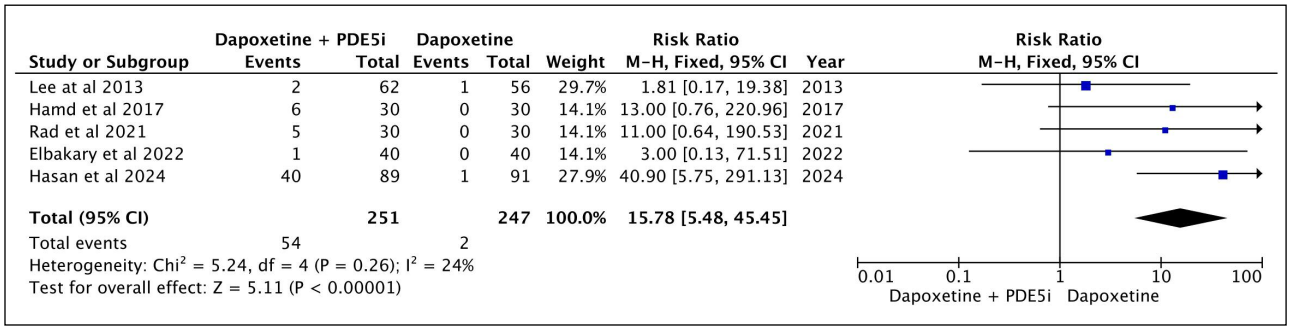
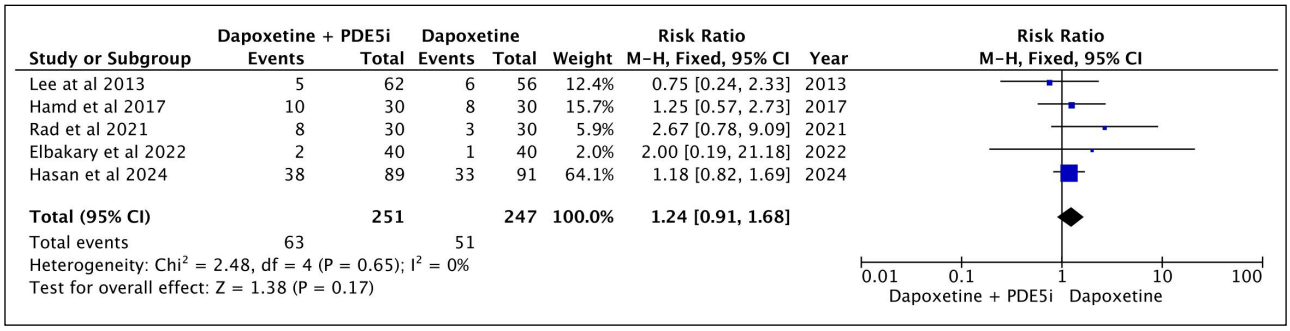


Figure 7.
Forest plot of nausea as one of the adverse effect.



al. (2021) (5), showed varying risk ratios, with *Hamd et al.* reporting a slightly higher RR of 1.25 (95% CI: 0.57-2.73). Heterogeneity among the studies was minimal, with an I^2 of 0% (Chi^2 = 2.48, P = 0.65), suggesting consistency in the findings across trials.

Dizziness

The forest plot in Figure 8 depicts the occurrence of dizziness as an adverse effect when comparing dapoxetine combined with PDE5i to dapoxetine monotherapy. There was no significant difference between the two treatment groups, as indicated by the pooled RR of 1.06 (95% CI: 0.68-1.68; P = 0.79). *Hasan et al.* (2024) (3) provided the majority of the analysis's weight, reporting an RR of 0.97 (95% CI: 0.57-1.67), indicating that the two groups' incidences of dizziness were similar.

There was very little variation (I^2 = 0%; Chi^2 = 0.61, P = 0.89), suggesting that the included studies' findings were all consistent.

Fatigue

Figure 9 examines the incidence of fatigue as an adverse effect associated with dapoxetine combined with PDE5i compared to dapoxetine monotherapy. There was no statistically significant difference between the two groups, as indicated by the pooled RR, which was 1.14 (95% CI: 0.70-1.87; P = 0.60). The majority of the analysis's weight (73.3%) came from *Hasan et al.* (2024) (3), who reported an RR of 1.19 (95% CI: 0.68-2.08). Other studies, including *Rad et al. (2021)* (5), reported extremely few or no occurrences, therefore their contributions were smaller. The included studies were consistent, as evidenced by the low heterogeneity (I^2 = 0%; Chi^2 = 1.64, P = 0.65).

Nasal congestion

Figure 10 examines the incidence of nasal congestion as an adverse effect associated with dapoxetine combined with PDE5i compared to dapoxetine monotherapy. With a pooled RR of 9.00 (95% CI: 1.17-69.01; P = 0.03), the

Figure 8.
Forest plot of dizziness as one of the adverse effect.

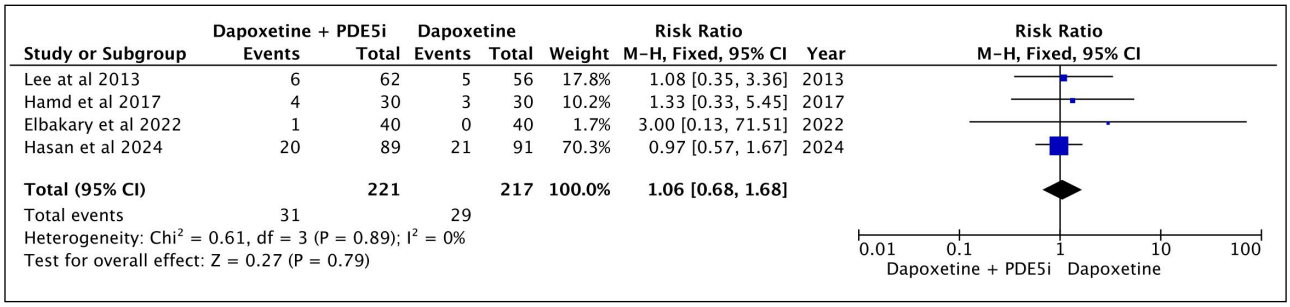


Figure 9.
Forest plot of fatigue as one of the adverse effect.

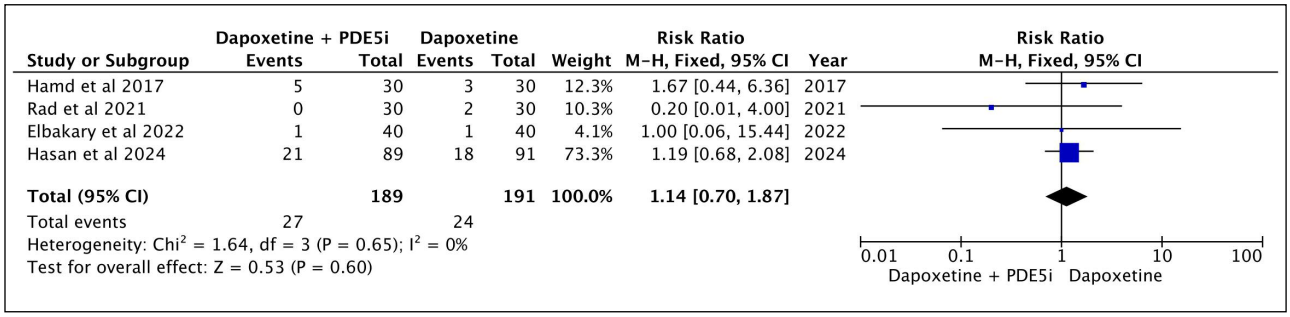
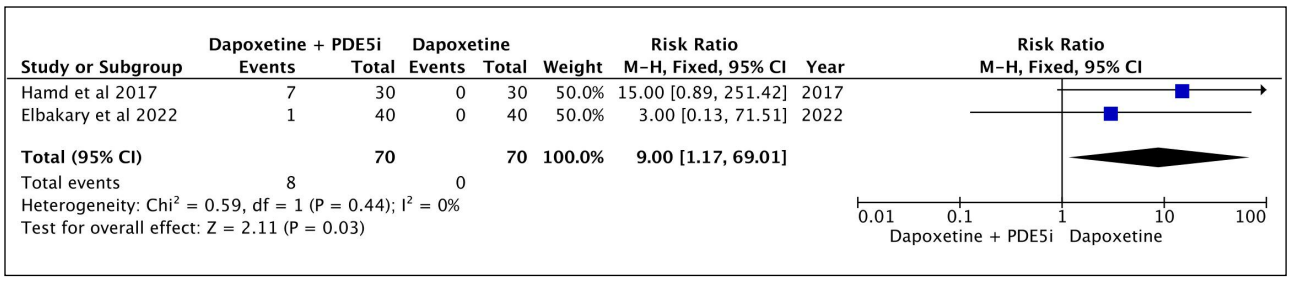


Figure 10.
Forest plot of nasal congestion as one of the adverse effect.



combination therapy group had a statistically significant higher incidence of nasal congestion. *Elbakary et al. (2022)* (4) and *Hamd et al. (2017)* (1) both contributed equally to the analysis (50 percent weight each), with RR of 3.00 (95% CI: 0.13-71.51) and RR of 15.00 (95% CI: 0.89-251.42), respectively. There was minimal heterogeneity (I^2 = 0%; Chi^2 = 0.59, P = 0.44), indicating that the results were homogenous and consistent throughout the investigations.

Palpitation

The forest plot in Figure 11 analyzes the occurrence of palpitations as an adverse effect of dapoxetine combined with PDE5i versus dapoxetine monotherapy. The pooled RR was 1.97 (95% CI: 0.69-5.66; P = 0.21), indicating no statistically significant difference in the risk of palpitations between the two treatment groups. *Hasan et al. (2024)*(3) contributed the majority of the weight (79.0%), reporting an RR of 1.53 (95% CI: 0.45-5.25). Heterogeneity was negligible (I^2 = 0%; Chi^2 = 0.46, P = 0.50), reflecting consistency in the findings across studies.

Vomiting

The forest plot in Figure 12 evaluates the incidence of vomiting as an adverse effect in patients treated with dapoxetine combined with PDE5i compared to dapoxetine monotherapy.

The pooled RR was 4.00 (95% CI: 0.46-34.78; P = 0.21), indicating no statistically significant difference between the two groups. Both *Hamd et al. (2017)* (1) and *Rad et al. (2021)* (5) contributed equally to the analysis (50% weight each). Heterogeneity was minimal (I^2 = 0%; Chi^2 = 0.05, P = 0.82), reflecting homogeneity across studies.

Sleep disturbance

The prevalence of sleep disturbances as a side effect of dapoxetine with PDE5i as opposed to dapoxetine monotherapy is investigated in the Figure 13. The combined therapy was associated with insignificantly incidence of sleep disruptions, as indicated by the pooled RR of 2.15 (95% CI: 0.51-9.08; P = 0.30). *Rad et al. (2021)* (5) demonstrated a higher RR of 4.33 (95% CI: 1.37-13.67) with a weight of 52.1%, with *Hamd et al. (2017)* (1) providing 47.9% weight and recording an RR of 1.00 (95% CI: 0.28-3.63). The results showed moderate heterogeneity (I^2 = 64%; Chi^2 = 2.79, P = 0.09), indicating some variation.

Figure 11.
Forest plot of palpitation as one of the adverse effect.

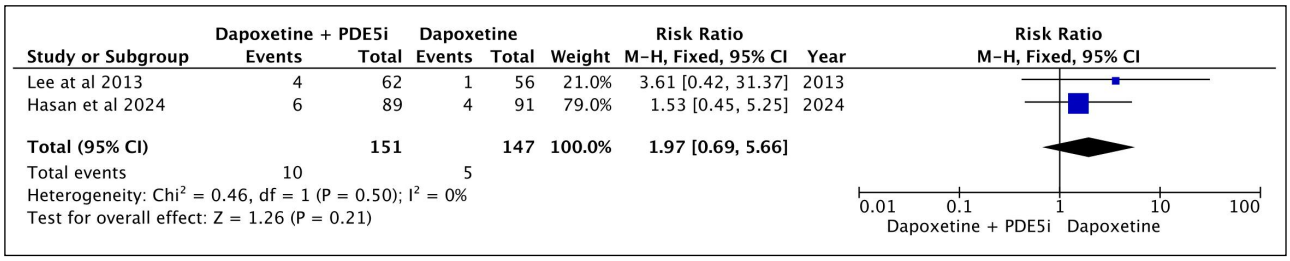


Figure 12.
Forest plot of vomiting as one of the adverse effect.

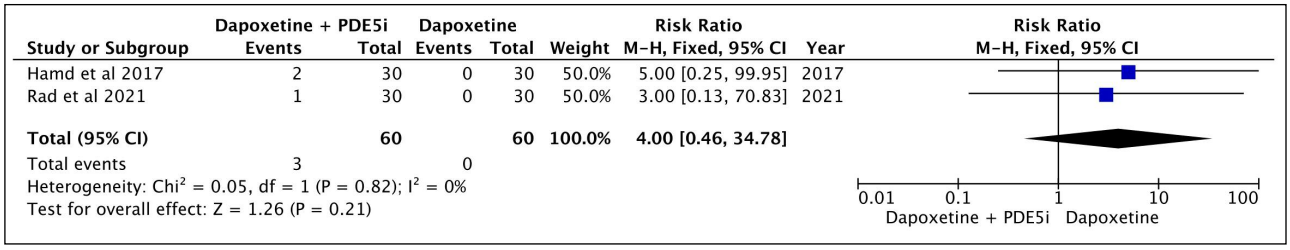


Figure 13.
Forest plot of sleep disturbance as one of the adverse effect.

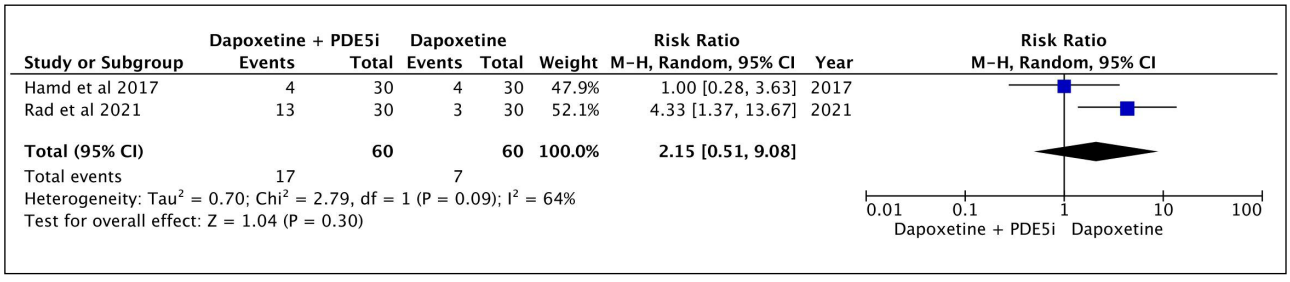
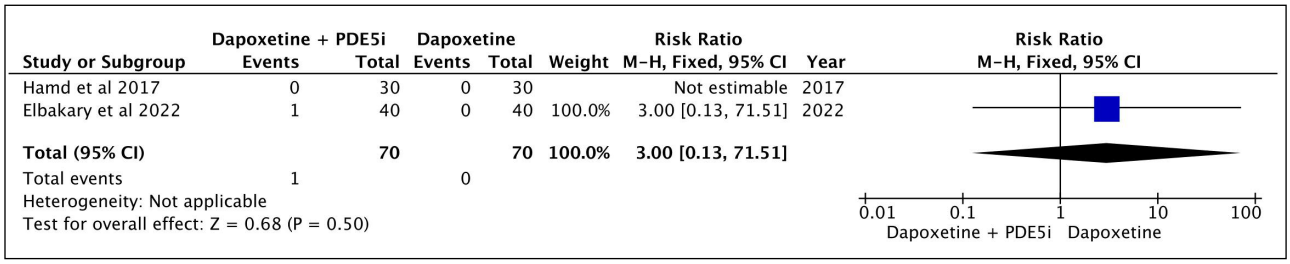


Figure 14.
Forest plot of constipation as one of the adverse effect.



Constipation

The prevalence of constipation as a side effect of dapoxetine with PDE5i as opposed to dapoxetine monotherapy is investigated in the Figure 14. Between the two groups, there was no statistically significant difference, as indicated by the pooled RR of 3.00 (95% CI: 0.13-71.51; P = 0.50). With a reported RR of 1.00 (95% CI: 0.06-71.51), *Elbakary et al. (2022)* (4) was the only study that provided data for this outcome. In contrast, *Hamd et al. (2017)* (1) did not record any incidents in either group, so the RR for that study could not be estimated. Heterogeneity was not relevant because of the small number of occurrences and studies that were considered.

Discussion

This meta-analysis highlights that the combination of dapoxetine and PDE5i significantly results in higher post-treatment scores of IELT and SSS compared to dapoxetine monotherapy, with pooled MD of 1.08 (95% CI: 0.34-1.83; P = 0.004) for IELT and 0.76 (95% CI: 0.49-1.04; P < 0.00001) for SSS. These findings align with the hypothesized synergistic effect of the two drugs, which target both psychological and physiological factors contributing to PE. One study also mentioned that more than half of the patients were unsatisfied with monotherapy of dapoxetine (6). Supporting this, other RCTs have shown that the combination of fluoxetine and tadalafil results in significantly higher IELT compared to either drug alone, further suggesting that PDE5i may be effective in managing PE in patients without erectile dysfunction (7).

Dapoxetine, a SSRI, was the first FDA-approved drug specifically designed for on-demand management of PE. It functions by reducing the activity of the 5-HT1A receptor, activating the 5-HT2C receptor, and blocking the serotonin transporter. The 5-HT1A and 5-HT2C receptors are brought back into balance by this dual action, which raises serotonin levels in the synaptic clefts (8). Therefore, by improving central serotonergic neurotransmission and modifying the ejaculatory reflex, dapoxetine postpones ejaculation. Dapoxetine is a very successful treatment for PE because of its distinct pharmacological mechanism, particularly when a quick start and brief duration of action are needed (3, 8).

On the other hand, PDE-5i raise intracellular *cyclic guanosine monophosphate* (cGMP) levels by activating guanylate cyclase, which in turn improves *nitric oxide* (NO) signaling. The corpus cavernosum, vas deferens, and seminal vesicles' smooth muscles relax as a result of this process, improving erectile function and lowering performance anxiety-two issues that are frequently linked to PE. Compared to SSRIs alone, research indicates that combining PDE-5i with SSRIs, such as dapoxetine, further improves sexual satisfaction and increases IELT. PDE-5i drugs may reduce central sympathetic tone in addition to improving peripheral vascular function, which could lead to better erections and longer ejaculation times (9, 10).

From a clinical perspective, the enhanced efficacy of combination therapy is likely due to its complementary mechanisms. Dapoxetine primarily acts centrally to modulate ejaculatory latency, while PDE-5i address peripheral factors, such as smooth muscle relaxation in the vas deferens and prostate gland, and psychological factors like performance anxiety. This holistic approach makes combination therapy more effective than monotherapy in addressing the multifactorial nature of PE (4, 5).

PDE-5i including sildenafil (50 mg), tadalafil (5 mg or 10 mg), and mirodenafil (50 mg) were employed as adjuncts in the majority of the included trials in this meta-analysis, which used dapoxetine 30 mg as the principal dosage in both the monotherapy and combination therapy groups. Dapoxetine is useful for on-demand use because of its quick absorption and brief half-life, and this standardized dosage represents the approved therapeutic range for the drug (11, 12).

Adverse effects, particularly vasodilatory symptoms such as headaches and flushing, were more frequent in the combination therapy group. For headaches, the pooled RR was 3.00 (95% CI: 1.91-4.71; P < 0.00001), while flushing showed a notable RR of 15.78 (95% CI: 5.48-45.45; P < 0.00001). Additionaly, the increased risk of nasal congestion (RR: 9.00; 95% CI: 1.17-69.01; P = 0.03) observed with combination therapy warrants attention. Nasal congestion is a common side effect of PDE-5i due to their vasodilatory mechanism, which affects the nasal mucosa. However, this adverse effect is typically mild and manageable, making it less concerning in clinical practice. These results are consistent with earlier research showing that groups treated with PDE5i in combination with SSRIs have a higher prevalence of vasodilatory adverse effects. According to *Polat et al. (2015)* (13), using paroxetine and tadalafil together improved IELT considerably, but there were also more side effects, namely headaches and hot flushes. The mechanism of PDE5i, which promotes smooth muscle relaxation and NO-mediated vasodilation, is responsible for these vasodilato-

ry symptoms. Although this technique works well to delay ejaculation and improve erectile performance, it can also cause increased vascular dilatation in locations like the face and cranium, which can result in headaches and flushing (13, 14)

Interestingly, the combination therapy did not significantly increase the risk of nausea (RR: 1.24; 95% CI: 0.91-1.68; P = 0.17), dizziness (RR: 1.06; 95% CI: 0.68-1.68; P = 0.79), fatigue (RR: 1.14; 95% CI: 0.70-1.87; P = 0.60), palpitations (RR: 1.97; 95% CI: 0.69-5.66; P = 0.21), vomiting (RR: 4.00; 95% CI: 0.46-34.78; P = 0.21), sleep disturbance (RR: 2.15; 95% CI: 0.51-9.08; P = 0.30), or constipation (RR: 3.00; 95% CI: 0.13-71.51; P = 0.50), further supporting its tolerability. These results are consistent with previous research showing that dapoxetine is a well-tolerated PE therapy with a better safety profile than other SSRIs (15). Furthermore, some research indicates that dapoxetine may cause moderate side effects such headache, dizziness, and gastrointestinal distress; serious side effects are uncommon, as our analysis demonstrates (16).

Lack of significant clinical interactions between dapoxetine and sildenafil pharmacokinetics supports the safety of combination therapy. Studies have demonstrated that co-administration of 60 mg of dapoxetine with 100 mg of sildenafil does not alter the pharmacokinetics of either drug, thereby preventing the amplification of side effects or compromising the effectiveness of the treatment. Similarly, pharmacokinetic studies with udenafil (200 mg) and dapoxetine (60 mg) reported no clinically significant drugs interactions (16, 17).

The tolerability of dapoxetine in combination therapy is further supported by its unique pharmacokinetic properties, including its rapid absorption and short half-life, which reduce the risk of prolonged exposure to adverse effects. Moreover, compared to other SSRIs, dapoxetine has a superior safety and compliance rate, as evidenced by its well-designed clinical trials and broad licensure. However, it is crucial to remember that further research is needed to determine the long-term consequences of dapoxetine, especially with regard to reproductive health. New information has suggested possible detrimental effects on fertility, underscoring the need for more study to elucidate these conclusions (18, 19). These results emphasize the importance of discussing potential side effects with patients and closely monitoring for tolerability during combination therapy. Although minor adverse effects like headache, flushing, or nasal congestion may occur, the benefits of improved IELT and sexual satisfaction often outweigh these risks.

This systematic review and meta-analysis also have some limitations. First, the included studies exhibited variability in intervention protocols, sample sizes, and durations, which may have contributed to heterogeneity in the results. Second, it may be difficult to completely evaluate the change related to the interventions if post-treatment data are relied upon without regularly taking baseline differences into account. Third, negative impacts were frequently self-reported, which may have resulted in subjective bias or underreporting. Furthermore, the majority of research concentrated on short-term results, underexamining the combo therapy's long-term safety and effectiveness. Future research should address these limitations by standardizing study designs, including diverse populations, and conducting long-term trials to provide more comprehensive insights.

Conclusions

In conclusion, this systematic review and meta-analysis demonstrates that the combination of dapoxetine and PDE-5i significantly improves post-treatment scores of IELT and sexual satisfaction compared to dapoxetine monotherapy, making it an effective treatment option for PE. Despite increased risk of certain side effects, such as headache, flushing, and nasal congestion, the overall tolerability of the combination therapy remains favorable, with no significant increase in adverse effects like nausea, dizziness, fatigue, palpitation, vomiting, sleep disturbance, and constipation.

Declarations

Ethical approval and consent for participate: *Not Applicable. This meta-analysis used only aggregated data from published studies, no individual patient data were collected.*

Availability of data and material: *This study synthesizes data from publicly available sources. The search strategy and list of included studies are provided in Materials and Methods/Supplementary Data. Original trial data can be accessed via Science Direct, Cochrane Library, PubMed, Google Schoolar as well as through the identifiers listed in Figure 1 and Table 1.*

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