Al-Azhar International Medical Journal

Volume 5 | Issue 3 Article 3

2024
Section: Urology

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How to Cite This Article

Ramadan, Ahmed Galal Shaaban; Koritenah, Ayman Kotb Mohammed; AlGammal, Mohamed Ibrahim AlMetwally; and Badran, Yasser Ali Ahmed (2024) "Efficacy of adding sildenafil to dapoxetine in treatment of dapoxetine non-responding mono-symptomatic premature ejaculation," *Al-Azhar International Medical Journal*: Vol. 5: Iss. 3, Article 3.
DOI: https://doi.org/10.58675/2682-339X.2310

ORIGINAL ARTICLE

Efficacy of Adding Sildenafil to Dapoxetine in the Treatment of Dapoxetine Nonresponding Mono-symptomatic Premature Ejaculation

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Abstract

Background: **Primary premature ejaculation (PE) has been treated with selective serotonin reuptake inhibitors; however these medications have a low success rate.**

Aim: **The aim is to evaluate the efficacy and safety of adding sildenafil to dapoxetine for patients with premature, symptomatic ejaculation who did not respond to dapoxetine alone.**

Patients and methods: **This randomized controlled trial was conducted at the urology outpatient centers of Al-Azhar University, Al-Hussein Hospital, and Sayed Galal Hospital. This research included 200 male PE patients placed into two groups. For 8 weeks, 110 patients in group A got sildenafil 50 mg as an additional treatment to dapoxetine 30 mg. Group B consisted of 90 participants who received dapoxetine 30 mg with a placebo for the same duration as group A.**

Results: **The study included 200 PE cases with no erectile dysfunction. Group A showed an increased International Index of Erectile Function (IIEF) score and improved PE diagnostic tool results. Posttreatment intravaginal ejaculatory latency time (IVLT) was significantly changed among groups, with 48 patients in group A having a posttreatment IVLT of more than or equal to 4 min compared to 19 in group B. There were also significant differences in the sex satisfaction scale after treatment, with 27.3% of patients in group A being extremely satisfied compared to 15.6% in group B.**

Conclusion: **Dapoxetine and sildenafil combination treatment for patients with PE without erectile dysfunction appears to lengthen the patient's IVLT, IIEF score, and sex satisfaction score, with improvements in PE diagnostic tool results as compared to dapoxetine alone.**

Keywords: Dapoxetine, Premature ejaculation, Sildenafil

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are used for the treatment of mental illnesses like depression and anxiety. SSRIs inhibit serotonin reuptake into the presynaptic axon terminal by connecting to the serotonin transporter, which leads to raising serotonin synaptic levels; reproductive problems, especially delayed ejaculation, are a well-known side effect of this medicine.[1] SSRIs have been effectively used to treat PE based on this assumption. This kind of medicine is especially advised for those who have persistent PE.[2]

The first chemicals particularly formulated for the management and therapy of PE are dapoxetine (30 mg or 60 mg dosages). It is a short-acting SSRI with a short half-life that is approved in a number of countries throughout the world. It is given orally 1−3 h before intercourse, as needed.[2]

In people with lifelong PE, all features of premature ejaculation (PE) can be treated with dapoxetine.[3] According to Jiann and Huang's[4] research, approximately half of PE patients were dissatisfied with their therapy with dapoxetine.

Phosphodiesterase-5 inhibitors were additionally studied in an attempt to improve the patient's

Accepted 1 December 2023.
Available online 6 May 2024

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https://doi.org/10.58675/2682-339X.2310

impression of ejaculatory control; nevertheless, their use as a pharmaceutical method for PE therapy is still debatable.[5]

In Europe, dapoxetine is the only SSRI licensed for on-demand therapy for PE. Many doctors are reconsidering the use of PDE5-I in PE due to the numerous precautions and bad effects associated with SSRIs.[6]

The purpose of this trial was to evaluate the safety and efficacy of combining sildenafil with dapoxetine in patients with premature, symptomatic ejaculation who did not respond to dapoxetine alone.

2. Patients and methods

A single-blind, placebo-controlled, randomized trial was conducted. The research was conducted in urology departments at Al-Azhar University in Cairo, Egypt.

Starting in October 2022 and continued for year, patients were chosen randomly from people seeking medical assistance at outpatient clinics. Males who did not respond to dapoxetine alone and had primary or acquired mono-symptomatic ejaculation that was premature (PE) for at least 2 months were included in the clinical trial. Individuals were regarded to have pelvic inflammatory disease if they satisfied the criteria outlined by the global organization for sexual medicine in their definition of PE.[7]

2.1. Inclusion criteria

Patients with good erectile functions more than or equal to 22 on International Index of Erectile Function (IIEF) score and having stable, regular intimate relationships for at least 2 months before the trial and being at least 20 years old.

2.2. Exclusion criteria

Patients with cardiac problems and receiving nitrites, men with chronic prostatitis, urinary tract infection, severe renal or hepatic illness, neurological conditions, and central nervous system drugs.

2.3. Procedures

On 200 male patients with PE, a single-blind placebo-randomized controlled trial was performed.

Our participants were divided into two groups (A and B). Patient recruitment was accomplished by a simple randomized procedure (flipping a coin) in which none of the patients knew which group they were assigned to.

Group A: 110 participants received sildenafil 50 mg (1 h before intercourse) as additive therapy to dapoxetine 30 mg (1–3 h before intercourse) for 8 weeks.

Group B: for the same duration as group A, 90 participants received a placebo and 30 mg of dapoxetine.

It was instructed for all patients to have sex at least twice weekly. Utilizing the validated Arabic versions of the IIEF-5 and the preterm ejaculation diagnostic tool, all patients were assessed both before and after treatment. The survey was filled out in person. All patients were told to use a stopwatch to keep track of their intravaginal ejaculatory latency time (IVLT) before and after treatment. The stopwatch was under the control of the female companion.

All patients were asked to rate their sexual pleasure on a scale of 0–5 before and after therapy.

2.4. Ethical consideration

The research was thoroughly discussed with the patients before their participation in the trial. Before enrolling, the patients provided informed written permission. During the study, extreme caution was exercised. It was clear that the participant was free to leave the research at any moment. Informed consent and all study materials were maintained in separate lockers, with only study investigators having access to them.

2.5. Statistical analysis

Utilizing (https://www.calculator.net) to determine the size of the sample, a level of confidence of 95% and a 5% margin of error were used. The significance level was set at 0.05. For statistical analysis, version 24 of the Statistical Package for Social Sciences (SPSS) was used. to express the qualitative data, percentage, and frequency were utilized. Data analysis was conducted using IBM SPSS Statistics version 24.0, developed by IBM Corporation in the United States in 2016. Since the quantitative data were not normally distributed, the interquartile range and median were presented.

3. Results

Comparison of demographic data between studied groups (Table 1). Concerning age, we found a statistically negligible variance ($P = 0.235$) in age among the groups that were studied (group A and group B) (Table 2).

Table 1. Comparison of demographic data between studied groups.

	Group A ($N = 110$)	Group B ($N = 90$)	Statistical test	P value
Age (years)				
Median	42	39	MW = 4467	0.235 NS
Interquartile range	32–47	33–44		
Parity				
Median	2	2	MW = 4570	0.327 NS
Interquartile range	1–3	1–2.25		
BMI (kg/m^2)				
Median	24	24	MW = 4408	0.178 NS
Interquartile range	23–27	23–26		
DM				
No	94 (85.5)	84 (93.3)	$\chi^2 = 3.1$	0.076 NS
Yes	16 (14.5)	6 (6.7)		
HTN				
No	90 (81.8)	76 (84.4)	$\chi^2 = 0.24$	0.623 NS
Yes	20 (18.2)	14 (15.6)		

χ^2, χ^2 test; DM, diabetes mellitus; HTN, hypertension; MW, Mann–Whitney U test.
P value more than 0.05 is considered nonsignificant (NS).

Table 2. Comparison of assessment (before treatment) between studied groups.

Assessment before treatment	Group A ($N = 110$)	Group B ($N = 90$)	Statistical test	P value
Intercourse frequency				
Median	2	2	MW = 4754	0.587 NS
Interquartile range	2–2	2–2		
IIEF score				
Median	22	22	MW = 4668	0.469 NS
Interquartile range	21–23	22–23		
PE diagnostic tool				
Median	14	14	MW = 4233	0.074 NS
Interquartile range	12–15	13–15		
IVLT				
≤1 min	110 (100)	90 (100)	–	–
2–3 min	0	0		
≥4 min	0	0		
Sex Satisfaction Scale				
Extremely unsatisfied	74 (67.3)	48 (53.3)	$\chi^2 = 4.09$	0.129 NS
Moderate unsatisfied	32 (29.1)	38 (42.2)		
Neither satisfied nor unsatisfied	4 (3.6)	4 (4.4)		

IVLT, intravaginal ejaculatory latency time; MW, Mann–Whitney.

Regarding IVLT, PE diagnostic tool, IIEF score, and sex satisfaction scale, we could not find any statistically significant variance between the two groups under study (group A and group B).

Fig. 1 showed that there was an insignificant variance ($P = 0.726$) among the analyzed groups (group A and group B) in terms of dapoxetine duration history. In group A, the median dapoxetine duration was 10 weeks with an IQR of 10–13 weeks, whereas in group B, the median dapoxetine duration was 12 weeks with an IQR of 10–12 weeks, as seen in Fig. 1.

Statistically significant ($P = 0.018$) increased intercourse frequency after treatment when compared with intercourse frequency before treatment in group A. Highly significant statistically ($P < 0.001$) increased IIEF score after treatment when compared with the IIEF score before treatment in group A. Extremely significant statistically ($P < 0.001$) decreased PE diagnostic tool after treatment when compared with PE diagnostic tool before treatment in group A. Extremely significant statistically ($P < 0.001$) between pretreatment and posttreatment IVLT in group A was as follows: IVLT was less than or equal to 1 min in 42 (38.2%) patients after treatment versus 110 (100%) patients before treatment. IVLT was 2–3 min in 20 (18.2%) patients after treatment versus 0 (0%) patients before treatment. IVLT was more than or equal to 4 min in 48 (43.6%) patients after treatment versus 0 (0%) patients before treatment. Highly significant statistically variance ($P < 0.001$) between pretreatment and posttreatment, the sex satisfaction scale in group A was as follows.

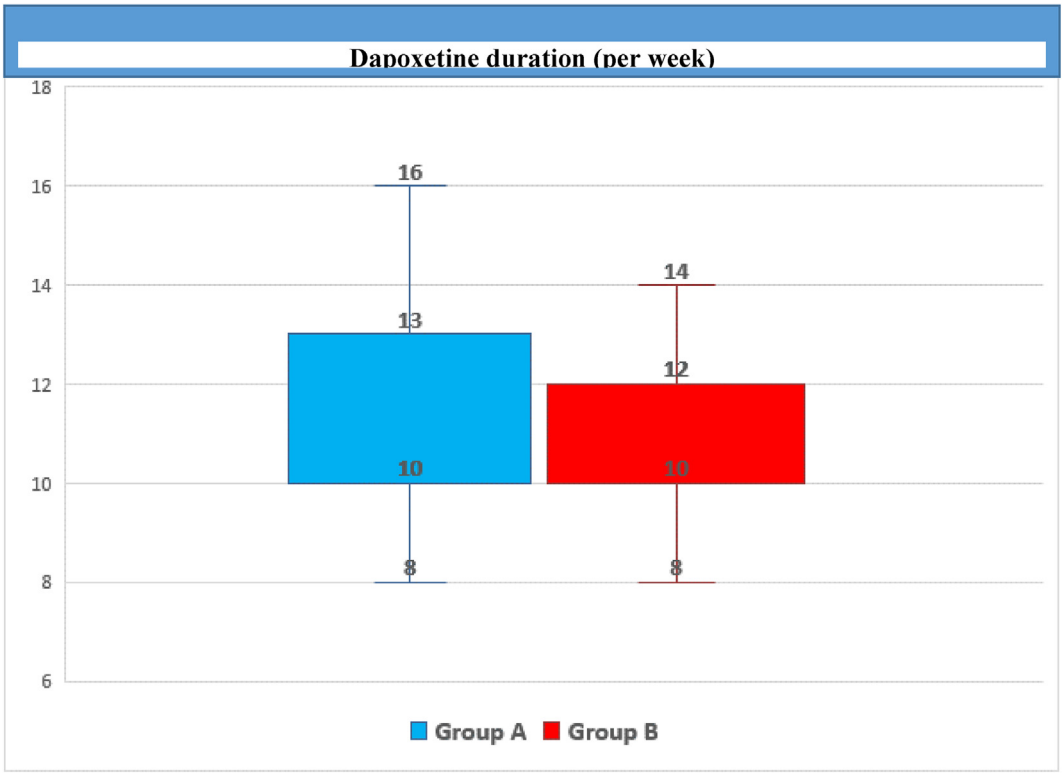

Fig. 1. Comparison of the history of dapoxetine duration between the studied groups.

Table 3. Comparison of assessment (before and after treatment) in group A.

Group A	Before ($N = 110$)	After ($N = 100$)	Statistical test	*P* value
Intercourse frequency				
Median	2	2	MW = 5010	0.018S
Interquartile range	2–2	2–3		
IIEF score				
Median	22	23	MW = 2870	<0.001 HS
Interquartile range	21–23	22–24		
PE diagnostic tool				
Median	14	8	MW = 2178	<0.001 HS
Interquartile range	12–15	5–12		
IVLT				
≤1 min	110 (100)	42 (38.2)	$\chi^2 = 98.4$	<0.001 HS
2–3 min	0	20 (18.2)		
≥4 min	0	48 (43.6)		
Sex satisfaction scale				
Extremely unsatisfied	74 (67.3)	14 (12.7)	$\chi^2 = 116.4$	<0.001 HS
Moderately unsatisfied	32 (29.1)	16 (14.5)		
Neither satisfied nor unsatisfied	4 (3.6)	23 (20.9)		
Moderately satisfied	0	27 (24.5)		
Extremely satisfied	0	30 (27.3)		

IVLT, intravaginal ejaculatory latency time.

There were 30 (27.3%) patients extremely satisfied after treatment versus 0 (0%) patients before treatment, as shown in Table 3.

A highly significant statistically ($P < 0.001$) increased intercourse frequency after treatment when compared with intercourse frequency before treatment in group B. Highly significant statistically ($P < 0.001$) increased IIEF score after treatment when compared with the IIEF score before treatment in group B. Highly statistically significant ($P < 0.001$) decreased PE diagnostic tool after treatment when compared with PE diagnostic tool

before treatment in group B. A highly statistically significant alteration ($P < 0.001$) among pretreatment and posttreatment IVLT in group B was as follows: IVLT was less than or equal to 1 min in 51 (56.7%) patients after treatment versus 90 (100%) patients before treatment. IVLT was 2–3 min in 20 (22.2%) patients after treatment versus 0 (0%) patients before treatment. IVLT was more than or equal to 4 min in 19 (21.1%) patients after treatment versus 0 (0%) patients before treatment. The extremely statistically significant variance ($P < 0.001$) among the pretreatment and posttreatment sex satisfaction scale in group B was as follows: there were 14 (15.6%) patients extremely satisfied after treatment versus 0 (0%) patients before treatment, as shown in Table 4.

In comparison to group B, group A had a statistically significant ($P = 0.005$) higher IIEF score (after treatment). After therapy, group A saw a highly statistically significant ($P < 0.001$) drop in the PE diagnostic tool when compared with group B. There was a statistically variance ($P = 0.003$) in IVLT (after therapy) between the two examined groups, A and B. Posttreatment IVLT was less than or equal to 1 min in 42 (38.2%) patients in group A versus 51 (56.7%) patients in group B. Posttreatment IVLT was 2–3 min in 20 (18.2%) patients in group A versus 20 (22.2%) patients in group B. Posttreatment IVLT was more than or equal to 4 min in 48 (43.6%) patients in group A versus 19 (21.1%) patients in group B. The statistically significant change ($P = 0.008$) between the studied groups (group A and group B) as regards the sex satisfaction scale (after treatment) was as follows: there were 14 (12.7%) patients extremely unsatisfied in group A versus 30 (33.3%) patients in group B. There were 16 (14.5%) patients moderately unsatisfied in group A versus 10 (11.1%) patients in group B. There were 23 (20.9%) patients who were neither satisfied nor unsatisfied in group A versus 14 (15.6%) patients in group B. There were 27 (24.5%) patients moderately satisfied in group A versus 22 (24.4%) patients in group B. There were 30 (27.3%) patients extremely satisfied in group A versus 14 (15.6%) patients in group B, as shown in Table 5.

4. Discussion

This trial included 200 men with PE who were placed into two groups, 110 people in group A received 50 mg of sildenafil in addition to 30 mg of dapoxetine for 8 weeks. Ninety individuals in group B consumed 30 mg of dapoxetine and a placebo for the same duration as those in group A.

There was a statistically insignificant variance in age, parity, BMI, or hypertension between both groups tested. Also was a statistically negligible variance in intercourse rate, IIEF score, PE diagnostic tool, sex satisfaction scale, and IVLT (before therapy) across study groups.

Our findings revealed that there was a statistically insignificant variance ($P = 0.086$) in intercourse frequency (after treatment) between the examined groups. In comparison to group B, there was a statistically significant ($P = 0.005$) rise in the IIEF score (after therapy) in group A.

Table 4. Comparison of assessment (before and after treatment) in group B.

Group B	Before ($N = 90$)	After ($N = 90$)	Statistical test	*P* value
Intercourse frequency				
Median	2	3	MW = 2480	<0.001 HS
Interquartile range	2–2	2–3		
IIEF score				
Median	22	23	MW = 2492	<0.001 HS
Interquartile range	22–23	22–23.25		
PE diagnostic tool				
Median	14	10	MW = 2283	<0.001 HS
Interquartile range	13–15	8–15		
IVLT				
≤1 min	90 (100)	51 (56.7)	$\chi^2 = 49.8$	<0.001 HS
2–3 min	0	20 (22.2)		
≥4 min	0	19 (21.1)		
Sex satisfaction scale				
Extremely unsatisfied	48 (53.3)	30 (33.3)	$\chi^2 = 62.04$	<0.001 HS
Moderately unsatisfied	38 (42.2)	10 (11.1)		
Neither satisfied nor unsatisfied	4 (4.4)	14 (15.6)		
Moderately satisfied	0	22 (24.4)		
Extremely satisfied	0	14 (15.6)		

IVLT, intravaginal ejaculatory latency time.

Table 5. Comparison of assessment (after treatment) between studied groups.

Assessment (after treatment)	Group A ($N = 110$)	Group B ($N = 90$)	Statistical test	P value
Intercourse frequency				
Median	2	3	4302	0.086 NS
Interquartile range	2–3	2–3		
IIEF score				
Median	23	23	3858	0.005S
Interquartile range	22–24	22–23.25		
PE diagnostic tool				
Median	8	10	3386	<0.001 HS
Interquartile range	5–12	8–15		
IVLT				
≤1 min	42 (38.2)	51 (56.7)	$\chi^2 = 11.5$	0.003S
2–3 min	20 (18.2)	20 (22.2)		
≥4 min	48 (43.6)	19 (21.1)		
Sex satisfaction scale				
Extremely unsatisfied	14 (12.7)	30 (33.3)	$\chi^2 = 13.8$	0.008S
Moderately unsatisfied	16 (14.5)	10 (11.1)		
Neither satisfied nor unsatisfied	23 (20.9)	14 (15.6)		
Moderately satisfied	27 (24.5)	22 (24.4)		
Extremely satisfied	30 (27.3)	14 (15.6)		

IVLT, intravaginal ejaculatory latency time.

After therapy, group A showed an extremely significant ($P < 0.001$) decline in the PE diagnostic tool relative to group B, and there was a statistically significant better results between both groups (groups A and B) in the IVLT and sex satisfaction score.

The current study agreed with Abu El-Hamd and Abdelhamed who investigated the safety and therapeutic efficacy of utilizing paroxetine, dapoxetine, sildenafil, and combinations of dapoxetine and sildenafil immediately for the management of patients with preterm ejaculation. They examined 150 PE patients who did not have ED between March 2015 and May 2016. Five distinct groups were randomly assigned to patients. They found that the combined sildenafil with dapoxetine group had significantly higher ILET values, higher satisfaction scores than dapoxetine group, and highly statistically significant ($P < 0.001$) decline PE diagnostic tool than dapoxetine group.[8]

According to Lee *et al.*'s[9] study from 2011, compared to a low dose of dapoxetine alone, a combination of dapoxetine and mirodenafil showed better results in terms of IVLT and the PE profile index (PEP index). These results were consistent with our own research.

Also, the study of Hosseini and Yarmohammadi,[10] found that in potent patients with PE, fluoxetine plus sildenafil appeared to produce considerably better effects than paroxetine alone in terms of ejaculatory latency time, frequency of intercourse, and intercourse satisfaction.

Our study showed a statistically significant ($P = 0.018$) increase in intercourse frequency after therapy when compared to group A's pretreatment intercourse frequency. Additionally, there was a statistically significant ($P < 0.001$) increase in the IIEF score and a decrease in the PE diagnostic tool when group A's pretreatment and posttreatment data were compared.

The study by Abu El-Hamd and Abdelhamed[8] showed that the mean of the PE diagnostic tool[11] was considerably higher in the combined dapoxetine and sildenafil groups after therapy ($P = 0.001$).

We discovered that there was a significant variance ($P < 0.001$) between group A's IVLT and pretreatment and posttreatment sex satisfaction scores.

Additionally, Abu El-Hamd and Abdelhamed[8] discovered that following therapy, the combined dapoxetine and sildenafil group's means of IVLT and satisfaction score were considerably greater ($P = 0.001$).

Our findings demonstrated that, in comparison to pretreatment, highly significant statistically variance ($P < 0.001$) was observed rise in intercourse frequency, a drop in PE diagnosis, and an IIEF score after treatment. Additionally, highly significant statistically variance ($P < 0.001$) was observed in group B's sex satisfaction score and IVLT before and after therapy, which may be due to probability of some psychogenic improvement of our participants in group B.

Our findings corroborated those of Abu El-Hamd and Abdelhamed[8] who discovered that the dapoxetine group's mean PE diagnostic tool was considerably higher following treatment ($P = 0.001$). Additionally, they discovered that the dapoxetine

group's satisfaction score and intravaginal ejaculatory delay time had considerably greater means following therapy ($P = 0.001$).

Also, the study of Hosseini and Yarmohammadi,[10] showed that after 4 months of medication (with just paroxetine), the mean ejaculation latency time and patient satisfaction increased in group B. At baseline, 2 and 4 months after treatment, the mean ejaculation latency times were 0.55, 4.2, and 5.1 min, respectively, and 38 (88.4%) patients in group B were satisfied, while one (2.3%) patient was not satisfied.

4.1. Conclusion

For PE patients without ED, combining dapoxetine and sildenafil medication may lengthen the patients' IVLT, intercourse frequency, IIEF score, and satisfaction score, with improved PE diagnostic tool results as compared to dapoxetine alone.

Conflicts of interest

There are no conflicts of interest.

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