ORIGINAL ARTICLE

Comparative efficacy of on-demand Sildenafil, Tadalafil and daily Tadalafil for treatment of erectile dysfunction: A 12-week randomized controlled study

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ABSTRACT

Background: Comparison of available first line agents for treating Erectile Dysfunction (ED) with each other regarding efficacy in Indian context remains scant. Sexual and mental health disorders frequently overlap and it is prudent to explore the potential of these medications to improve common comorbid psychiatric symptoms.
Aim: To compare the efficacy of on-demand Sildenafil, on-demand Tadalafil and daily Tadalafil for ED, as well as their impact on premature ejaculation (PME) and mental health.
Methods: Seventy-five individuals diagnosed with ED (ICD-11) were randomly assigned to one of the three treatment groups with 25 participants in each group: Group A (Sildenafil 50–100 mg SOS), Group B (Tadalafil 10–20 mg SOS), and Group C (Tadalafil 5 mg daily). Severity of sexual functioning was evaluated using the International Index of Erectile Function (IIEF), Sexual Encounter Profile question 2 and 3 (SEP2/3), Premature Ejaculation Diagnostic Tool (PEDT). Depression, Anxiety, and Stress Scale (DASS-21) assessed mental health status. Assessments were repeated at 2 weeks intervals till 12 weeks. Blood investigations were carried out at baseline and at the end of study period.
Results: *Daily* Tadalafil was superior to *on-demand* Sildenafil or Tadalafil in improving erectile function ($P < 0.05$), particularly in penetration (SEP 2/3) and was equally effective as *on-demand* Tadalafil on IIEF, while outperforming Sildenafil. It also significantly reduced depression and anxiety symptoms at 12 weeks ($P < 0.05$). *On-demand* Tadalafil was most effective for managing associated PME, which was comorbid with ED in 66.7% of cases.
Conclusion: *Daily Tadalafil* was more effective than *on-demand* Tadalafil or Sildenafil for treating ED, especially in patients with mood symptoms. PME was found to be quite common with ED and responded best to on demand Tadalafil. Tadalafil was superior to Sildenafil in all domains.

Key words: Depression, erectile dysfunction, impotence, premature ejaculation, Sildenafil, Tadalafil

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INTRODUCTION

Erectile Dysfunction (ED) prevails as a major sexual concern for men.[1] Worldwide prevalence varies from 37.5% to 52%.[1,2] In Indian context, it has been reported that one in five males suffers from at least one sexual disorder with reported prevalence for ED of about 15.7%.[3]

ED stems from a complex interplay of psychological, social, and physiological factors. Studies show men with depression have a higher risk of ED, with reported frequencies ranging from 5% to 15%.[4] Men with ED were found to experience depression at a rate 1.8 times higher than those without ED.[5] Even when ED's primary pathology is organic, psychological stressors can exacerbate it.[6]

Various treatment options for ED are available and tailored based on underlying causes, patient profile, and preference. These include psychotherapy, oral pharmacotherapy (regular or on-demand), intraurethral and topical medications, penile injections, vacuum erection devices, penile prosthesis implantation, and revascularization surgeries.[2] Oral phosphodiesterase 5 (*PDE5*) inhibitors remain the first-line treatment choice for all types of ED (psychological, physiological, or mixed) due to their excellent safety profile and effectiveness.[7] In India, the most widely available and commonly used oral *PDE5* inhibitors are Sildenafil and Tadalafil.

Sildenafil is typically used as on-demand for ED treatment, whereas Tadalafil's longer half-life of approximately 17.5 hours permits daily dosing.[8] Tadalafil can be taken as on-demand or daily, with its prolonged action lasting up to 36 hours, offering flexibility in timing relative to sexual activity.[9] Unlike Sildenafil, Tadalafil shows no significant interactions with food or alcohol.[10]

Few RCTs directly compare Tadalafil on-demand to daily Tadalafil. Two such existing trials have revealed that daily Tadalafil was more efficacious than on-demand Tadalafil based on IIEF score.[11,12]

While there is literature available on western population comparing PDE5 inhibitors in different dosing regimens, head-to-head comparison between Sildenafil and Tadalafil in the Indian context are currently lacking. The relationship between ED, PME, and mood symptoms is also yet to be thoroughly investigated. By addressing these gaps, the study aims to provide valuable insights and potentially guide therapeutic strategies.

Primary Objective: To assess and compare the efficacy of sildenafil and tadalafil in persons with erectile dysfunction

Secondary Objective: To assess changes in PME and depressive-anxiety symptoms with treatment of erectile dysfunction

METHODS

Study design and setting

A randomized controlled study was conducted at Marital and Sex Clinic (MSC) run by the Department of Psychiatry of a tertiary care hospital located in North India. The study protocol was approved by the institutional ethics committee prior to start of recruitment. The trial protocol was prospectively registered in the Clinical Trials Registry-India database on January 12, 2023(CTRI/2023/01/048951).

Sample size

Sample size was calculated taking the confidence interval of 95% and power of the study to be 80%. A non-inferiority limit of 6 units difference in ED severity (i.e., mean IIEF scores) between the three groups yielded a sample size of 21 subjects in each arm.[13] Considering a 20% attrition rate, 25 participants were recruited for each treatment arm, resulting in a total study sample size of 75 participants.

Formula used for sample size calculation is as follows:

$$n = \frac{f\ (\alpha, \beta) \times 2 \text{ x } \sigma^2}{d^2}$$

and

$$f(\alpha, \beta) = [\phi^{-1}(\alpha) + \phi^{-1}(\beta)]^2$$

where n is the required sample size,

d is the difference in effect of interventions

σ is the standard deviation (estimated),

ϕ-1 is the cumulative distribution function of a standardized normal deviate

Recruitment of study participants

Initially, patients with ED, defined as per ICD-11 as "an inability or marked reduction in ability in men to attain or sustain a penile erection of sufficient duration or rigidity to allow sexual activity."[14] seeking treatment at the MSC were screened as per the study inclusion and exclusion criteria. Inclusion criteria had participants aged 18–50 years, who had adequate literacy to complete the evaluation questionnaires, were staying with their spouse for a minimum period of last 6 months, anticipated having the same adult female sexual partner throughout the study duration, and had not received either sildenafil or tadalafil in the past month.

Key exclusion criteria were participants who were taking organic nitrates for any reason, had a history of unstable angina, cardiac stents, or life-threatening arrhythmias. Additionally, individuals with a history of primary hypoactive

sexual desire disorder or erectile dysfunction due to spinal cord injury were excluded. Those with any clinical history of undergoing prostate surgery (e.g., radical prostatectomy), treated or untreated hypogonadism with below normal serum testosterone levels, or major co-morbid mental illnesses such as schizophrenia and bipolar disorder were also excluded.

Furthermore, participants with a history of hypersensitivity or allergy to either sildenafil or tadalafil were not eligible for inclusion in the study. Eligible patients ($n = 77$) were enrolled in the study after taking an informed written consent.

Procedure

These 77 participants were assessed at baseline for socio-demographic and relevant clinical details using a standardized patient intake proforma designed by the authors for this study. Blood parameters including Complete Blood Count (CBC), Serum electrolytes and Renal Function Test (SERFT), Liver Function Test (LFT), Thyroid Stimulating Hormone (TSH), Lipid profile, Serum Testosterone, Serum Vitamin B12 were ordered as part of the routine clinical practice. Baseline ECG monitoring was also done. Baseline sexual functioning was assessed using the following validated tools:

International Index of Erectile Function (IIEF-15)

IIEF-15[16] is a widely used questionnaire designed to assess the severity of ED and monitoring treatment outcomes. It comprises 15 questions that cover five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The total score ranges from 5 to 75, with higher scores indicating better erectile function. It has been translated into numerous languages and validated in diverse populations, making it applicable across different cultures and settings. Hindi and English version were used for the purpose of study.

Sexual Encounter Profile question 2 and 3 (SEP2/3)

SEP[15-17] is a clinician administered questionnaire used in clinical trials and research to assess the outcomes of sexual encounters. It consists of several questions designed to capture various aspects of sexual performance and satisfaction. Researchers often choose questions 2 and 3 of the SEP because they focus on key aspects of sexual function and satisfaction. Question 2 asks about the *ability to achieve* an erection sufficient for intercourse. Question 3 enquires about the *maintenance* of an erection during intercourse. It helps understand not only the initial success of achieving an erection but also its sustainability throughout the sexual encounter, which is vital for satisfactory sexual performance and overall sexual satisfaction.

Premature Ejaculation Diagnostic Tool (PEDT)

PEDT[18] is a brief questionnaire to aid in the diagnosis of Premature Ejaculation (PME). It consists of five questions that assess various aspects of ejaculatory control and sexual satisfaction. Respondents rate their experiences on a scale from 0 to 4, with higher scores indicating more significant difficulties with premature ejaculation.

The mental health status of participants was assessed using the Depression, Anxiety and Stress Scale (DASS-21)[19]

DASS-21 is a widely used self-report questionnaire designed to assess the severity of symptoms related to depression, anxiety, and stress. It consists of three subscales, each comprising seven items: depression, anxiety, and stress. Scores for each subscale are calculated by summing the ratings for the relevant items, with higher scores indicating greater symptom severity. The DASS-21 has been translated into numerous languages and validated in various populations, demonstrating good reliability and validity. Hindi and English version were used for the purpose of study.

Two (2) participants were excluded due to low baseline serum testosterone levels, resulting in a total of 75 participants after baseline assessment. They were randomized into the following three parallel groups in a 1:1:1 ratio using based on computer-generated random number table: Group A (Sildenafil SOS), Group B (Tadalafil SOS), and Group C (Tadalafil daily) as shown in the flow chart. Allocation concealment was performed by sequentially numbered opaque sealed envelopes.

Dosage of respective drugs was kept in the therapeutic range of up to 50–100 mg of Sildenafil on SOS basis, up to 10–20 mg of Tadalafil on SOS basis, and 5 mg fixed dose of Tadalafil on daily basis in the Groups A, B, and C, respectively, as per US FDA recommendation.[9] The initial dose of Sildenafil in Group A was 50 mg on-demand and in Group B was Tadalafil 10 mg on-demand. The attending clinician then up-titrated it to a maximum of 100 mg and 20 mg, respectively, on as required basis depending upon the clinical response. The daily dose of Tadalafil in Group C was fixed at 5 mg/day. Participants were instructed to take Sildenafil SOS empty stomach 1 hour before intercourse, Tadalafil SOS 1 hour before intercourse irrespective of last food intake, and daily dose of Tadalafil at a fixed time each day irrespective of the timing of sexual activity. Participants were instructed to take only one dose of study medication in single day (calendar day). Participants were instructed to bring empty strips of medicine on follow ups to monitor compliance.

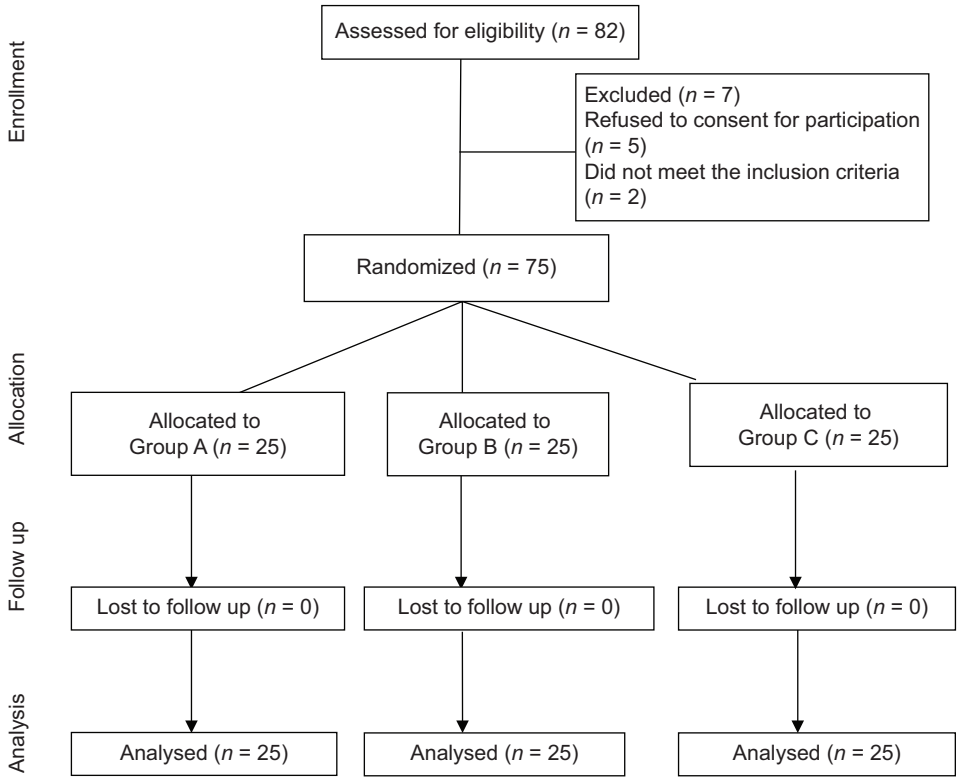
Follow-up assessments using IIEF, SEP2/3, PEDT, DASS-21 were conducted at 2 weeks interval till 12 weeks by the principal investigator. Blood investigations and ECG were repeated at the end of the study period (12-weeks). A telephonic follow-up reminder call by the principal

investigator was made 1 day prior to the scheduled follow-up date to participants.

Participants not willing to continue with the study after enrolment were considered as drop-outs and managed as per the standard treatment protocol. Participants prescribed other medications such as selective serotonin re-uptake inhibitors (SSRIs) or other anti-depressants (e.g., trazodone, dapoxetine, paroxetine etc.) were also included in the study and the same was recorded. The use of oral benzodiazepines (e.g., clonazepam) for control of anxiety, restlessness, and sleep disturbances by the treating clinician were allowed during the study period.

Psycho-education sessions were provided by the principal investigator to all the participants using a semi structured proforma that included a brief description of the anatomy of male reproductive tract, the aetiology of ED, the various treatment options available along with the clarifications of myths and misconceptions about sexual dysfunction. Those requiring or opting for psychotherapy were listed for the same, and sessions were initiated after completion of study period that is, after 12 weeks. Participants were encouraged to attempt sexual activity with the partner preferably at a frequency of at least once per week during the study period.

Flow chart of the study:



Statistical analysis

Descriptive statistics were used to understand and compare the profile of three study groups. Continuous data were presented as mean and standard deviation whereas qualitative data was presented as frequency and percentage. Data was checked for normal distribution using Shapiro-Wilk test and depending on the distribution, appropriate parametric or non-parametric statistics were used. For normally distributed data ANOVA was used, and for skewed distribution, Kruskal Wallis test was conducted. Qualitative data for the three groups was compared by applying Chi-square test and Fisher's Exact test, wherever applicable, was used for comparing the proportion between the three groups. The point of statistical significance was considered as the two-tailed *P* value of less than 0.05 for all tests.

RESULTS

Participants enrolled in the three groups at baseline showed no significant difference.

Table 1 displays that the socio-demographic characteristics of the patients enrolled in all the three groups had no significant difference based on age, occupation, education, socio-economic status, and locality. There is no significant difference in the distribution of substance use and comorbid systemic illnesses among the allocated groups.

Table 2 displays that the clinical characteristics of the patients enrolled in all three groups had no significant difference except for baseline serum sodium values.

Table 3 shows comparison of International Index of Erectile Function (IIEF) scores among the three treatment groups. IIEF scores at baseline (0 weeks) was comparable in all the three groups. The change in score at every 2 weeks was statistically significant in all 3 groups till 12 weeks. In post-hoc analysis, the change in score at every 2 weeks was statistically significant between Group A and Group B as well as Group A and Group C.

Table 4 shows comparison of Sexual Encounter Profile (SEP 2) and (SEP 3) scores among three treatment groups. There was significant improvement in all 3 groups on SEP 2 and SEP 3 from 2nd week onwards till 12 weeks. In post- hoc analysis, the SEP 2 score at 2 weeks and 4 weeks was statistically significant for Group C. SEP 3 score at different time points also favored Group C, over Group A and B.

Figures 1 and 2 display the number of participants suffering from premature ejaculation at the start and end of study

Figure 3 shows the comparison of Depression scores as per DASS-21 among the three treatment groups. There was significant change in scores from baseline to 12 weeks in all 3 groups. The most significant change in score was obtained for Group C.

During the study period, 14 participants (n = 6 Paroxetine; n = 8 Dapoxetine) were prescribed SSRIs and 11 required

Table 1: Socio-demographic variables among the three groups at baseline

Variable		Group A (n=25) (Mean±SD)	Group B (n=25) (Mean±SD)	Group C (n=25) (Mean±SD)	Significance (P)
Age (years)		35.20±10.13	34.08±9.15	35.60±8.42	0.65
Variable		**Frequency (%)**			
Education	School educated	8 (32.0%)	10 (40.0%)	13 (52.0%)	
	College educated	17 (68.0%)	15 (60.0%)	12 (48%)	0.35
Occupation	Employed	19 (76%)	19 (76%)	18 (74.7%)	0.93
	Unemployed	6 (24.0%)	6 (24.0%)	7 (28%)	
Income (INR)	<5000	8 (32.0%)	9 (36.0%)	7 (28%)	
	5001–10000	5 (20.0%)	9 (36.0%)	8 (32%)	0.60
	>10000	12 (48.0%)	7 (28.0%)	10 (40%)	
Locality	Urban	16 (64.0%)	16 (64.0%)	13 (52%)	
	Rural	9 (36.0%)	9 (36.0%)	12 (48%)	0.61
Substance use	Present	14 (56%)	12 (48%)	10 (48%)	0.53
	Absent	11 (44%)	13 (52%)	15 (52%)	
Comorbid systemic illness	Present	7 (28%)	4 (16%)	6 (24%)	0.59
	Absent	18 (72%)	21 (84%)	19 (76%)	

Table 2: Clinical variables across three treatment groups at baseline

Baseline clinical variables	Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	Significance (P)
Body Mass Index (kg/m^2)	24.05±4.11	24.42±2.73	23.66±3.36	0.74
Hemoglobin	13.58±1.23	13.01±0.92	13.23±1.14	0.19
Total Leucocyte Count	7.75±1.94	7.89±2.15	6.79±1.55	0.06
Platelet Count	231.92±76.30	228.68±72.23	237.56±66.77	0.77
Serum sodium	142.12±3.13	139.88±3.61	139.60±3.66	0.02*
Serum Potassium	4.36±0.52	4.44±0.47	4.50±0.50	0.57
Serum Chloride	103.24±3.81	102.48±3.16	101.84±3.69	0.39
Serum Urea	21.40±6.45	26.00±8.57	25.36±10.20	0.18
Serum Creatinine	0.97±0.30	1.14±0.33	1.10±0.39	0.14
Uric acid	4.13±1.67	4.49±1.65	4.50±1.50	0.45
Total Bilirubin	0.83±0.70	0.71±0.30	0.62±0.31	0.29
Alkaline Phosphatase	86.48±23.34	88.24±20.13	89.48±27.73	0.91
SGOT	42.72±20.80	36.08±10.87	33.08±14.90	0.1
SGPT	39.16±24.15	33.04±15.04	34.44±16.04	0.88
Total Cholesterol	163.16±42.59	175.08±49.66	181.76±37.68	0.32
Triglycerides	144.52±47.28	142.88±40.97	130.12±17.83	0.54
HDL	51.20±11.18	48.08±10.32	47.12±13.36	0.44
LDL	125.12±28.77	125.48±26.41	129.24±35.33	0.79
VLDL	34.64±8.51	31.44±6.99	36.48±9.06	0.1
Serum TSH	3.16±1.20	2.70±1.47	2.71±1.29	0.38
Serum Testosterone	357.76±94.73	419.76±170.75	452.20±176.21	0.25
Vitamin B12	425.96±169.39	479.48±166.16	472.32±201.27	0.52
Fasting blood sugar	111.20±30.66	112.80±33.10	114.56±32.76	0.82

*P value is significant

Table 3: Comparison of International Index of Erectile Function (IIEF) scores among the three treatment groups across 12 weeks

	Group A (Sildenafil SOS) (*n*=25)		Group B (Tadalafil SOS) (*n*=25)		Group C (Tadalafil Daily) (*n*=25)		*P*
	Mean±SD	Median (I.Q.R)	Mean±SD	Median (I.Q.R)	Mean±SD	Median (I.Q.R)	
IIEF-15 0 week	14.36±5.41	14.00 (10.50–19.00)	11.72±4.69	12.00 (9.50–14.50)^	12.12±4.76	13.00 (7.50–16.00)#	0.17*
Change in IIEF from 0 to 2 weeks	1.32±1.38	1.00 (1.00–2.00)^#	2.44±1.53	2.00 (2.00–3.00)^	2.80±1.44	3.00 (2.00–4.00)#	<0.01*
Change in IIEF from 2 to 4 weeks	1.00±1.16	1.00 (0.00–2.00)^#	2.36±1.25	2.00 (1.50–3.00)^	3.28±1.57	3.00 (2.00–4.00)#	<0.01*
Change in IIEF from 4 to 6 weeks	1.52±0.92	1.00 (1.00–2.00)^#	2.28±0.89	2.00 (2.00–3.00)^	3.32±1.70	3.00 (2.00–4.00)#	<0.01*
Change in IIEF from 6 to 8 weeks	1.48±2.50	1.00 (0.00–2.00)^#	4.32±9.61	2.00 (1.00–4.00)^	3.84±7.84	2.00 (1.50–3.50)#	<0.01*
Change in IIEF from 8 to 10 weeks	0.80±2.26	1.00 (0.50–2.00)^#	0.20±9.95	2.00 (1.00–2.50)^	−0.52±11.83	2.00 (1.00–3.00)#	0.04*
Change in IIEF from 10 to 12 weeks	0.72±0.94	1.00 (0.00–1.00)^#	1.68±1.31	2.00 (1.00–3.00)^	1.76±1.23	2.00 (1.00–2.00)#	<0.01*
Overall change in IIEF from 0 to 12 weeks	6.84±3.51	7.00 (4.50–9.00)^#	13.28±3.94	14.00 (10.00–15.50)^	14.48±4.49	14.00 (11.50–16.50)#	<0.01*

*Kruskal-Wallis test. ^Group A vs B *P*<0.05 #Group A vs Group C *P*<0.05

Table 4: Comparison of Sexual Encounter Profile (SEP) question 2 and 3 score during the study time among the three treatment groups

	Group A (Sildenafil SOS) (*n*=25)		Group B (Tadalafil SOS) (*n*=25)		Group C (Tadalafil Daily) (*n*=25)		*P*
	Mean±SD	Median (I.Q.R)	Mean±SD	Median (I.Q.R)	Mean±SD	Median (I.Q.R)	
SEP 2 0 week	0.92±1.04	1.00 (0.00–2.00)	1.24±1.09	1.00 (0.00–2.00)	1.36±0.95	1.00 (1.00–2.00)	0.25*
SEP 2 2 week	1.48±1.16	1.00 (0.50–2.00)#	1.72±1.14	2.00 (1.00–3.00)	2.44±1.26	2.00 (2.00–4.00)#	0.02*
SEP 2 4 week	1.88±1.27	2.00 (1.00–3.00)#	2.80±1.08	3.00 (2.00–4.00)	3.12±1.33	3.00 (2.00–4.00)#	<0.01*
SEP 2 6 week	2.48±1.16	3.00 (2.00–3.00)#	3.64±1.04	3.00 (3.00–5.00)@	4.00±1.08	4.00 (3.50–5.00)#@	<0.01*
SEP 2 8 week	3.12±1.05	3.00 (2.00–4.00)#	4.12±0.73	4.00 (4.00–5.00)@	4.40±0.76	5.00 (4.00–5.00)#@	<0.01*
SEP 2 10 week	3.48±1.09	4.00 (3.00–4.00)#	4.52±0.65	5.00 (4.00–5.00)@	4.60±0.71	5.00 (4.00–5.00)#@	<0.01*
SEP 2 12 week	3.48±1.12	4.00 (3.00–4.00)#	4.60±0.58	5.00 (4.00–5.00)@	4.76±0.52	5.00 (5.00–5.00)#@	<0.01*
SEP 3 0 week	1.00+1.12	1.00 (0.00–2.00)	1.40+1.26	1.00 (0.00–3.00)	1.72+1.28	2.00 (1.00–3.00)	0.11*
SEP 3 2 week	1.52+1.23	1.00 (0.50–2.00)#	3.04+4.37	2.00 (1.50–3.00)	2.84+1.38	3.00 (2.00–4.00)#	<0.01*
SEP 3 4 week	1.84+1.18	2.00 (1.00–3.00)#	3.12+1.24	3.00 (2.00–4.00)@	3.40+1.41	4.00 (2.00–5.00)#@	<0.01*
SEP 3 6 week	2.60+1.23	3.00 (2.00–3.50)#	3.80+0.87	4.00 (3.00–5.00)@	3.96+1.06	4.00 (3.00–5.00)#@	<0.01*
SEP 3 8 week	3.16+1.28	3.00 (2.00–4.00)#	4.04+0.84	4.00 (3.00–5.00)	4.56+0.77	5.00 (4.00–5.00)#	<0.01*
SEP 3 10 week	3.28+0.98	3.00 (2.50–4.00)#	4.48+0.65	5.00 (4.00–5.00)@	4.64+0.76	5.00 (4.50–5.00)#@	<0.01*
SEP 3 12 week	3.52+1.09	4.00 (3.00–4.00)#	4.68+0.48	5.00 (4.00–5.00)@	4.76+0.52	5.00 (5.00–5.00)#@	<0.01*

*Kruskal Wallis test. #Group A vs Group C *P*<0.05 @Group B vs C *P*<0.05

benzodiazepines for depressive and anxiety symptoms which did not resolve solely with phosphodiesterase 5 inhibitors. However, majority ($n = 61$, 82%), individuals suffering from co-morbid PME responded solely to treatment with PDE5 inhibitors.

During the study, eight participants experienced mild adverse drug reactions. Of these, seven were from the Sildenafil group and reported symptoms such as headache, facial flushing and dizziness, side effects commonly associated with this medication. One participant in the Tadalafil on-demand group reported mild myalgia, a known but less frequent side effect of Tadalafil. No participant reported any serious adverse drug reaction necessitating discontinuation or change.

DISCUSSION

This study aimed to compare the efficacy of Sildenafil (on demand) and Tadalafil (on demand and daily use) in persons suffering from ED along with other significant correlates over a 12-week period.

Majority of the participants, suffering from ED were aged less than 30 years [Table 1], contrary to the general understanding that ED is commoner in elderly men.[20] This trend could possibly be due to predominance of psychogenic ED among the younger population with marriage significantly influences the decision to seek treatment for sexual dysfunction, as the partner can play a pivotal role in identifying symptoms and supporting the patient in pursuing treatment.

The three groups were comparable among the use of substance (including alcohol, smokeless tobacco, synthetic or natural opioid use) suggesting that the differences among groups were not likely due to the effect of substance use.[21] The three groups were comparable for baseline clinical, hematological, and biochemical parameters [Table 2], supporting the validity of the randomization process.

In a 12-week crossover study involving 367 men with ED, doses of PDE5 inhibitors (25, 50, or 100 mg for Sildenafil and 10 or 20 mg for Tadalafil) were titrated to determine optimal efficacy. While both drugs showed similar results in penetration diaries, variations were observed in successful intercourse as measured by the IIEF and SEP. Interestingly, Tadalafil was preferred by 71% of participants, with only 29% selecting Sildenafil.[22]

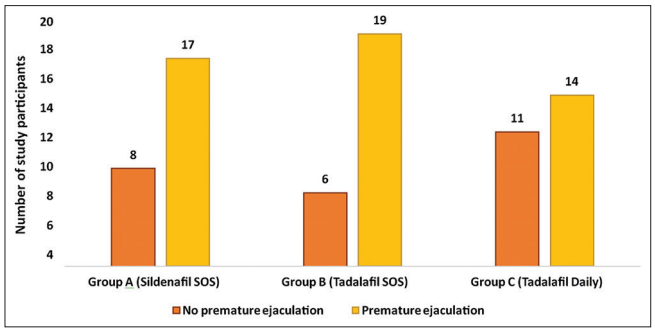


Figure 1: Distribution of Premature Ejaculation (PME) using Premature Ejaculation Diagnostic Tool (PEDT) at baseline among the three treatment groups

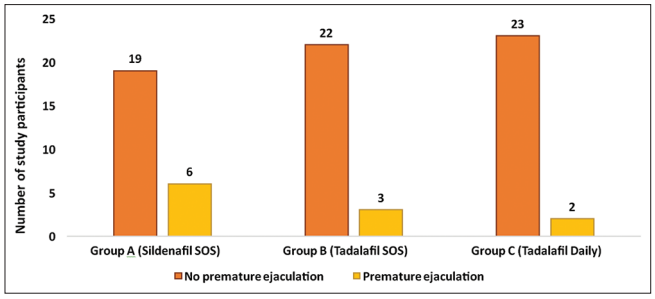


Figure 2: Distribution of Premature Ejaculation (PME) using Premature Ejaculation Diagnostic Tool (PEDT) at the end of 12 weeks among the three treatment groups

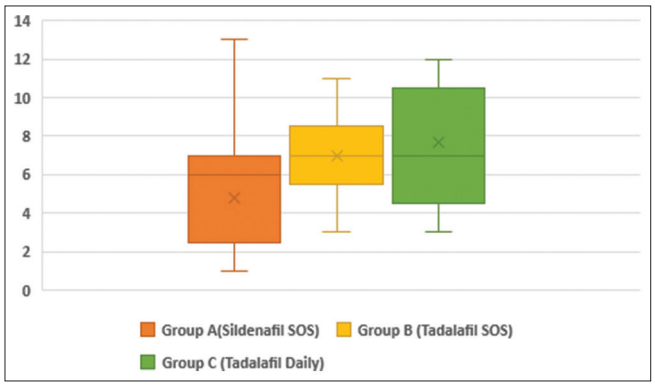


Figure 3: Comparison of change in Depression score on The Depression, Anxiety, and Stress Scale (DASS-21) from 0 to 12 weeks among the three treatment groups

Our primary outcome was that Tadalafil demonstrated significantly superior efficacy to sildenafil in improving erectile dysfunction based on the IIEF scores [Table 3], which also supports the findings of earlier studies.[23,24] Notably, IIEF also demonstrated that daily Tadalafil had a similar efficacy to on demand Tadalafil and which is further substantiated by the available literature.[25] This paves the way for allowing flexibility in dosing regimen that can practically reduce pill count and money spent on treatment.

Interestingly, after baseline [Table 4], SEP Question 2 (hardness) and SEP 3 (penetration) scores were statistically significant progressively from 2nd week onwards till 12 weeks, indicating greater improvement in ED with Tadalafil compared to Sildenafil, particularly the superiority of *daily* Tadalafil use to *on demand* Tadalafil after 12 weeks of treatment.

Another study reported that men with moderate to severe ED, who failed to respond with on-demand Tadalafil, did respond to daily doses of 10 mg or 20 mg Tadalafil over a period of 12 weeks. Daily Tadalafil improved erectile function in significantly a greater number of patients than on-demand Tadalafil treatment.[13]

A pioneering study in Asian men evaluating the efficacy and safety of on-demand Tadalafil for ED by administration of 10 mg Tadalafil, 20 mg Tadalafil, or placebo to participants showed significant improvement in the Erectile Function domain of IIEF with both Tadalafil doses. Tadalafil was well tolerated across a diverse clinical population with varying demographics, ED severity, and comorbidities.[26]

Our study findings correlate to the 2019 study where Tadalafil, particularly daily dose regimen excelled in improving penetration capability and erectile hardness compared to other domains of erectile dysfunction when compared to on demand Tadalafil.[27]

Our secondary outcome was that all PDE5 Inhibitors significantly improved premature ejaculation as measured by reduction in PEDT scores with Tadalafil decreasing the scores in a greater number of participants.

PME was present in 66.67% participants during the initial assessment highlighting a close overlap between the two most common male sexual disorders at least in our sample [Figure 1]. Another study reported that up to 30% of men with ED have comorbid PME, which is also a noteworthy number in itself.[28]

A possible reason for this could be the challenges in distinguishing between PME and ED due to inadequate sex education in our participants. PME may also be a covert condition and patients may not be aware of it unless specifically enquired about ejaculatory timing.[29] Several mechanisms have been described to support a common etiology of ED and PME such as NO/cGMP pathway; peripheral relaxation of smooth muscles of vas, seminal vesicle, prostate; locally induced peripheral analgesia, and so on.[30]

Contrary to traditional belief that Sildenafil is only used for treatment of ED, studies have shown its response in patients with premature ejaculation.[18] In our study, on demand Tadalafil also showed superiority over daily dose regimen of Tadalafil for the treatment of PME [Figure 2]. This finding highlights the need for further research to

delineate the exact mechanism of response to PME with administration of PDE5 inhibitors and common etiological pathways. While individual studies supporting the use of Sildenafil or Tadalafil for PME are available, comparative studies are still lacking.[31,32]

Importantly, none of the participants withdrew from the study, as all side effects were mild and were effectively managed with reassurance and prompt dose adjustments.

Another secondary outcome was that all *PDE5* Inhibitors significantly improved depression and anxiety symptoms as measured by reduction in DASS-21 scores. Fall in scores was maximum for Tadalafil when compared with Sildenafil group [Figure 3].

Assessment of Depression and Anxiety domains from DASS-21 score in the participants clearly demonstrates a fall from moderate depression to its resolution during the study, possibly highlighting the preponderance of secondary depressive symptoms due to ED [Figure 3]. Any significant superiority of daily Tadalafil over on demand Tadalafil could not be established in this domain which suggests that flexible dosing regimen is as good as daily regimen at least in improving depressive symptoms, but a more systematic research in this avenue is warranted to give recommendations with confidence.[5] The link between ED and depression is undeniable, emphasizing the need for regular depression screening among ED patients and routine ED assessment for those with depression.[33]

Our study addresses a visible gap in literature of head-to-head trials on Indian population comparing the efficacy of these two agents and regimens of phosphodiesterase 5 inhibitors in persons with ED. With the longitudinal prospective study design, temporal relationship between variables can be confidently commented upon.

Despite the authors intention to maximize replicability, certain limitations exist. The sexual partner was not interviewed; independent diagnosis of depression or anxiety disorders was not made. Age of onset of ED and PME, the duration of sexual problems and co morbid medication use was not recorded. Blinding could not be conducted in the clinical setting since SOS *PDE5* users needed to be educated about its use and a placebo arm could not be included in the study due to ethical considerations.

CONCLUSION

The study compared the efficacy of Tadalafil and Sildenafil in treating ED and associated conditions. Tadalafil demonstrated superior efficacy over Sildenafil in improving erectile function, though daily versus on-demand use of Tadalafil did not show clear superiority based on IIEF scores. Tadalafil also showed better efficacy than Sildenafil in treating ED with comorbid PME. Daily Tadalafil was found superior in improving penetration ability and erectile hardness (SEP 2/3 scores) compared to on-demand use. Daily Tadalafil was associated with reduced depression symptoms. The authors recommend that though daily Tadalafil has similar efficacy to on-demand Tadalafil for individuals with only erectile dysfunction, it is preferable in individuals having co-morbid depressive symptoms. The study underscores the critical need for expansive research to validate these findings and thoroughly explore the optimal utilization of PDE5 inhibitors not only for treating ED but also for addressing comorbid PME and concurrent mood symptoms.

Ethics approval

The study protocol was approved by the local institutional ethics committee in November 2022, prior to start of recruitment. The trial protocol was prospectively registered in the Clinical Trials Registry-India database on January 12, 2023(CTRI/2023/01/048951).

Data sharing statement

Deidentified individual participant data will not be made available.

Declaration regarding the use of generative AI

Generative AI tool ChatGPT was used solely to enhance the clarity and fluency of English language in this manuscript. All original ideas and interpretations, however, remain the work of authors who assume full responsibility for the entire content of the manuscript, including the parts generated by the AI tool.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Table 5: Distribution of participants requiring add on drugs during the study period

	Group A (Sildenafil SOS) (*n*=25)	Group B (Tadalafil SOS) (*n*=25)	Group C (Tadalafil Daily) (*n*=25)
Paroxetine	3	4	1
Dapoxetine	2	1	3
Clonazepam	7	3	1

Table 5 shows that during the study period, 14 participants were prescribed SSRIs and 11 benzodiazepines while the remainder received treatment solely with phosphodiesterase 5 inhibitors.

Table 6: Association between treatment for SSRI and three treatment groups

Participants requiring Dapoxetine/ Paroxetine	Group A (Sildenafil SOS) (*n*=25)	Group B (Tadalafil SOS) (*n*=25)	Group C (Tadalafil Daily) (*n*=25)	Total
Yes	5 (20.0%)	5 (20.0%)	4 (16.0%)	14 (18.7%)
No	20 (80.0%)	20 (80.0%)	21 (84.0%)	61 (81.3%)
		P: 1.00*		

*Fisher's exact test

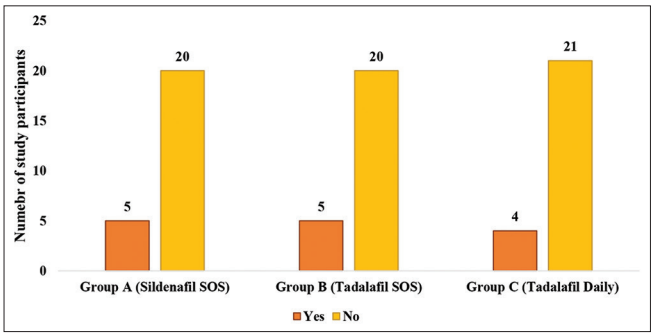

Figure 4: Shows number of participants who required treatment with SSRIs for PME in each of the treatment groups

Distribution of the study participants according to PME treatment in the three groups

Table 6 and Figure 4 shows association between PME treatment and treatment groups among the study participants.

PME treatment was comparable in the three groups (*P*-value 1.00).