ARTICLE

Bedtime sildenafil oral suspension improves sexual spontaneity and time-concerns compared to on-demand treatment in men with erectile dysfunction: results from a real-life, cross-sectional study

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Phosphodiesterase type 5 inhibitors (PDE5i) are among the first line treatment options in men with erectile dysfunction (ED). On-demand sildenafil has proved to be an effective PDE5i but with lower spontaneity scores compared to daily tadalafil treatment. We aimed to investigate the impact of on-demand sildenafil compared to bedtime use on efficacy and spontaneity scores in men with ED. We retrospectively analysed data from a cohort of men with mild/moderate ED treated for three months with on-demand sildenafil 50 mg oral suspension formulation (OSF) (group 1, $n = 40$), bedtime sildenafil 50 mg OSF (group 2, $n = 40$) and bedtime sildenafil 37.5 mg OSF (group 3, $n = 40$). After three months patients were evaluated with the International Index of Erectile Function-5 items (IIEF-5) and the Psychological and Interpersonal Relationship Scales-Short Form (PAIRS-SF) questionnaires. Propensity score matching was used to adjust for baseline confounders. The IIEF-5 and PAIRS-SF scores were compared between groups at follow-up with the repeated measures ANOVA test. Linear regression analyses tested the associations between study variables and spontaneity scores. After matching, median patient's age and ED duration were 56 (50–61) years and 18 (10–20) months, respectively. Compared to baseline, IIEF-5 scores significantly improved after sildenafil OSF treatment, irrespective of the therapeutic approach (all $p < 0.01$ vs. baseline). The PAIRS-SF spontaneity score was significantly better in group 2 [15 (13–16), $p < 0.01$] and group 3 [14 (14–16), $p < 0.01$] compared to the on-demand use [13 (12–13)]. Fewer time concerns were reported for bedtime use than on-demand sildenafil. Sildenafil OSF bedtime use was found to be an independent predictor for better spontaneity and fewer time concerns scores (all $p < 0.001$). Bedtime sildenafil OSF showed similar efficacy but better spontaneity scores than on-demand use. Bedtime sildenafil is a valuable option for men with ED prioritizing efficacy and sexual spontaneity.

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INTRODUCTION

Erectile dysfunction (ED) is among the most commonly reported sexual problems in men [1]. It can significantly affect men's quality of life, impacting self-esteem, sexual health, and couple's relationships [2]. Furthermore, ED severity has been recognised as a proxy for general men's health, thus encouraging physicians to comprehensively assess patients complaining of sexual dysfunction in the real-life setting [3–5]. There are multiple treatment options for ED, but phosphodiesterase type 5 inhibitors (PDE5i) are usually the first line choice in clinical practice [4].

Several PDE5i are available on the market, each with its own unique pharmacokinetic properties and side effect profile [4]. The choice of PDE5i depends on the frequency of intercourse and the patient's personal experience. Two meta-analyses demonstrated that ED patients who prioritise high efficacy should use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg [6, 7]. Successful treatment of ED, however, may involve more than just improving erectile function, as ED is a complex condition often linked to psychological and relationship issues [8]. The duration of effectiveness, as well as the on-demand use of a PDE5i, may play a crucial role in interpersonal communication and intimacy before sexual intercourse, potentially influencing performance anxiety and pressure [8, 9]. Important sexual outcomes, including sexual self-confidence, spontaneity, and time concerns were found to be significantly improved after treatment with the long-acting PDE5i tadalafil,

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compared with on-demand sildenafil [10, 11]. Similarly, with the use of daily tadalafil patients may feel ready for sex at any time, promoting greater spontaneity in sexual interactions [10]. These are all factors that make tadalafil one of the preferred PDE5i by men with ED [12, 13].

Daily use of sildenafil has been also investigated for the treatment of ED with promising results. In particular, previous studies have shown that nightly (namely, bedtime) sildenafil improved sleep-related erections and erectile-function scores in men with ED [14, 15]. The reported efficacy of daily sildenafil was primary attributed to endothelial function improvement [16]. Since bedtime sildenafil was found to be effective in men with ED and could potentially mitigate the psychological implications related to the on-demand use, it would be of clinical interest to investigate the impact of nightly sildenafil, as compared to on-demand, on sexual spontaneity and time-concerns outcomes.

Thereof, we conducted this real life, cross-sectional study to test the hypothesis that bedtime sildenafil would achieve superior psychosocial outcomes and similar efficacy compared to sildenafil on-demand in men with ED.

MATERIALS AND METHODS

We retrospectively analysed data from a sample of 161 sexually active men consecutively assessed at twelve Italian tertiary-referral academic centres for ED between January 2024 and August 2024. ED was defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [4].

Baseline evaluation

Participant's evaluation was standardized across all centres. A detailed medical and sexual history was collected for each man [17, 18]. Comorbidities were scored with the Charlson Comorbidity Index (CCI) [19], which was categorised as 0 or ≥1. Body mass index (BMI) was calculated for each patient. Smoking status was considered as no smokers (never smoked/ex-smokers) and active smokers, respectively. Similarly, alcohol consumption was categorized as abstainers (no alcohol consumption) and drinkers (any amount per week) [20]. Relationship status was classified as either sporadic/random or stable sexual relationship. Moreover, according to exposure to any PDE5i before the baseline evaluation, patients were subdivided into: PDE5i-naïve and non-PDE5i-naïve patients [21]. Venous blood samples were collected from each patient between 7 AM and 11 AM following an overnight fast. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (tT), and prolactin were measured for each individual.

At baseline, all patients completed the International Index of Erectile Function – 5 items (IIEF-5) questionnaire [22, 23]. ED severity was classified as follows: severe (IIEF-5 score ≤7), moderate (IIEF-5 between 8–11), mild-to-moderate (IIEF-5 between 12–16) and mild (IIEF-5 score 17–21) [22]. Literacy problems as well as other reading and writing problems were excluded in all patients.

Inclusion & exclusion criteria

For this study we considered only participants (18–70 years old) with baseline IIEF-5 scores between 8 and 21 (mild-moderate ED), eligible for PDE5i therapy according to current Guidelines [4], naïve for or not taking any PDE5i since 2 weeks (washout).

We excluded: participants with tT < 3.5 ng/ml ($n = 4$) [24], with known hypersensitivity to sildenafil or its components ($n = 1$); with previous surgical treatment of the penis or pelvic area ($n = 2$); patients with a known history of depression or depressive symptoms, or those taking any antidepressant therapy ($n = 5$); participants who provided incomplete data at follow-up evaluations ($n = 5$). Therefore, a convenience sample of 152 patients was eventually included in the analysis.

Treatment modality

The new sildenafil oral suspension formulation (OSF) was considered for this study [25]. The OSF is a system releasing 0.5 mL of suspension containing 12.5 mg of sildenafil with each pulse. For the specific purpose of this study, three treatment modalities were examined: (i) bedtime (each night before sleeping) sildenafil OSF 50 mg (4 puffs) for three months; (ii) bedtime sildenafil OSF 37.5 mg (3 puffs) for three months; (ii) on-demand sildenafil 50 mg (4 puffs) for three months. For on-demand use, similar to the oral-dispersible formulation, the OSF of sildenafil was recommended 45–60 min before approaching the partner [25, 26]. Patients were encouraged to attempt sexual intercourse using the prescribed drug on at least eight occasions during the period between visits.

Outcomes

To assess the impact of bedtime vs. on-demand sildenafil OSF on erectile function and psychological scores, patients were evaluated after three months of treatment by the treating physician and were asked to complete the IIEF-5 and the Psychological and Interpersonal Relationship Scales-Short Form (PAIRS-SF) questionnaire (Supplementary Material 1) [27]. The PAIRS-SF assesses three key areas: sexual self-confidence, spontaneity, and time-related concerns before and during sexual encounters [27]. These outcomes are significant for both men and their partners, focusing on aspects like spontaneity and the enjoyment of the time leading up to sexual intercourse. All questions of the PAIRS-SF are measured on a scale of 1–4 (1, strongly disagree; 2, disagree; 3, agree; 4, strongly agree). Higher scores reflect greater confidence in the subdomain of self-confidence and more natural sexual behavior in the subdomain of spontaneity; conversely lower scores show less bother in the subdomain of time concern. The occurrence of treatment-related adverse events was also investigated.

Data collection followed the principles outlined in the Declaration of Helsinki. All patients signed an informed consent agreeing to share their own anonymous information for other future studies. The study was approved by the Hospital Ethical Committee (Prot. 060194).

Statistical analyses

The sample size was calculated by using the one-way ANOVA analysis. A previous study showed that sildenafil 50 mg on-demand was able to achieve a mean IIEF-5 improvement of 10 (6) points, compared to baseline, in men with ED [28]. We considered as clinically significant a true difference in means of four points, with a variability of six, between groups [28, 29]. Considering Alpha = 0.05 and Beta = 0.20 (power = 1 - beta = 0.8) we calculated that 40 participants in each group are needed to achieve a power of >80% (Russ-Lenth applet for Windows).

Distribution of data was tested with the Shapiro–Wilk test. Data are presented as medians (interquartile range; IQR) or frequencies (proportions). To control for measurable baseline differences among patients in the three groups, we relied on propensity score matched analyses to adjust for those differences [30]. Propensity scores were computed by modeling logistic regression with the dependent variable as the odds of receiving on-demand treatment and the independent variables as age, serum tT, BMI, and baseline IIEF-5 score. Subsequently, groups were matched using the propensity score (two separate 1:1 nearest neighbor PSM using a caliper width of 0.2 of the standard deviation of the logit of the propensity score).

First, descriptive statistics were used to describe the whole cohort. Second, the Wilcoxon Signed Rank Test assessed potential differences in IIEF-5 scores at 3 months follow-up assessment, compared to baseline. Third, the IIEF-5 and PAIRS-SF scores were compared between groups at 3 months follow-up with the repeated measures ANOVA test.

Finally, univariate and multivariate linear regression analyses tested the associations between study variables and PAIRS-SF spontaneity and time concern scores. Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY, USA). All tests were two sided and statistical significance level was determined at $p < 0.05$.

RESULTS

Table 1 details clinical characteristics of the whole cohort before matching. Patients treated with sildenafil 50 mg OSF bedtime were younger and had higher BMI than those in the other groups (all $p < 0.04$) (Table 1). A higher rate of moderate ED, at baseline, was found in participants treated with sildenafil bedtime 50 mg. After matching, 40 participants were considered in each group and all clinical and psychometric variables were evenly distributed. Overall, median (interquartile range) patient's age and BMI were 56 (50–61) years and 25.1 (23.1–26.9) kg/m^2, respectively. A stable sexual relationship was reported by 71 (59.1%) men and median

Table 1. Demographic characteristics of the whole cohort of patients before matching ($N = 152$).

	Bedtime 50 mg	Bedtime 37.5 mg	On-demand 50 mg	*p*-value*
Number or patients [No. (%)]	52 (34.2)	47 (30.9)	53 (34.9)	
Age (years)				0.04
Median (IQR)	51 (43–55)	56 (46–60)	56 (51–61)	
Range	29–70	29–66	30–70	
BMI (kg/m^2)				0.01
Median (IQR)	26.8 (25.2–29.1)	24.5 (23.0–25.5)	25.7 (23.3–27.9)	
Range	23.8–32.3	22.1–27.5	21.3–30.1	
CCI ≥ 1 [No. (%)]	9 (17.3)	8 (17.0)	8 (15.1)	0.7
Stable sexual relationship [No. (%)]	43 (61.4)	28 (59.5)	31 (58.5)	0.5
Active smokers [No. (%)]	23 (44.2)	22 (46.8)	22 (41.5)	0.2
Current drinkers [No. (%)]	38 (73.1)	36 (76.6)	40 (75.4)	0.1
LH (mUI/mL)				0.5
Median (IQR)	3.8 (2.5–4.2)	3.9 (3.1–4.7)	4.2 (3.2–5.1)	
Range	0.1–61.0	1.2–8.3	1.6–9.8	
FSH (mUI/mL)				0.7
Median (IQR)	5.1 (2.5–8.2)	5.2 (3.1–6.9)	5.4 (3.2–6.9)	
Range	2.1–11.0	2.8–10.5	3.5–12.7	
tT (ng/mL)				0.2
Median (IQR)	4.9 (3.8–7.2)	5.0 (3.9–6.6)	5.1 (3.9–7.6)	
Range	3.5–10.3	3.5–8.2	3.6–10.4	
PRL (ng/mL)				0.4
Median (IQR)	6.8 (4.1–12.7)	7.1 (4.9–8.8)	7.2 (5.0–9.1)	
Range	1.5–18.7	3.1–15.9	2.3–19.2	
Duration of ED (months)				0.1
Median (IQR)	18 (10–21)	18 (10–20)	20 (12–24)	
Range	9–24	24-Jun	24-Oct	
PDE5i naïve [No. (%)]	26 (50.0)	23 (48.9)	27 (50.9)	0.8
Baseline ED severity [No. (%)]				0.02
Mild ED (17–21)	12 (23.1)	14 (29.7)	19 (35.8)	
Mild-to-moderate ED (12–16)	18 (34.6)	24 (51.0)	23 (43.4)	
Moderate ED (8–11)	22 (42.3)	9 (19.3)	11 (20.8)	

BMI body mass index, *CCI* charlson comorbidity index, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, tT total testosterone, *PRL* prolactin, *ED* erectile dysfunction, *PDE5i* phosphodiesterase type 5 inhibitors.
**P* value according to the Kruskal-Wallis test.

serum tT was 5.0 (3.8–6.5) ng/mL. Median ED duration was 18 (10–20) months and baseline ED severity was mild, mild-to-moderate and moderate in 32.5, 44.2 and 23.3% participants, respectively (Fig. 1).

Table 2 shows psychometric scores according to treatment modality. Compared to baseline, IIEF-5 scores significantly improved after sildenafil OSF treatment, irrespective of the therapeutic approach (all $p < 0.01$ vs. baseline). At follow-up, no differences were noted between groups in terms of IIEF-5 scores (Table 2). Fig. 1 depicts rates of ED severity at baseline and 3-months follow-up assessment.

The PAIRS-SF self-confidence scores were similar after sildenafil on-demand and bedtime treatment. Of note, PAIRS-SF spontaneity scores were significantly better after sildenafil OSF bedtime 50 mg [15 (13–16), $p < 0.01$] and 37.5 mg [14 (14–16), $p < 0.01$] compared to the on-demand 50 mg use [13 (12–13)] (Table 2). Similarly, fewer PAIRS-SF time concerns values were reported by the bedtime 50 mg [13 (10–14), $p < 0.01$] and 37.5 mg [13 (12–14), $p < 0.01$] groups than the on-demand [18 (17–19)] one. At follow-up, 19 (15.8%) and 11 (9.1%) participants complained about headache and flushing, respectively. No difference related to adverse events was noted among groups. All side effects were mild in nature and did not cause treatment discontinuation.

Table 3 depicts univariate and multivariate linear regression analysis testing the associations between clinical predictors and PAIRS-SF spontaneity and time concerns scores. Younger age (beta −0.1, $p = 0.03$) and sildenafil bedtime treatment protocol (beta 2.1, $p < 0.001$) were associated with higher spontaneity scores. At multivariable analysis, only bedtime protocol (beta 1.7, $p < 0.01$) emerged as predictor of high spontaneity scores, after accounting for age. Similarly, sildenafil OSF bedtime use (beta −4.4, $p < 0.001$) was found to be an independent predictor for better time concerns scores, after accounting for age (Table 3).

DISCUSSION

In this real-life study we assessed the efficacy of sildenafil OSF on-demand versus bedtime use and the impact of treatment on patients' psychological area of spontaneity and time concerns. Our results showed that both on-demand and bedtime (either 50 mg or 37.5 mg) sildenafil OSF had similar efficacy in improving EF in

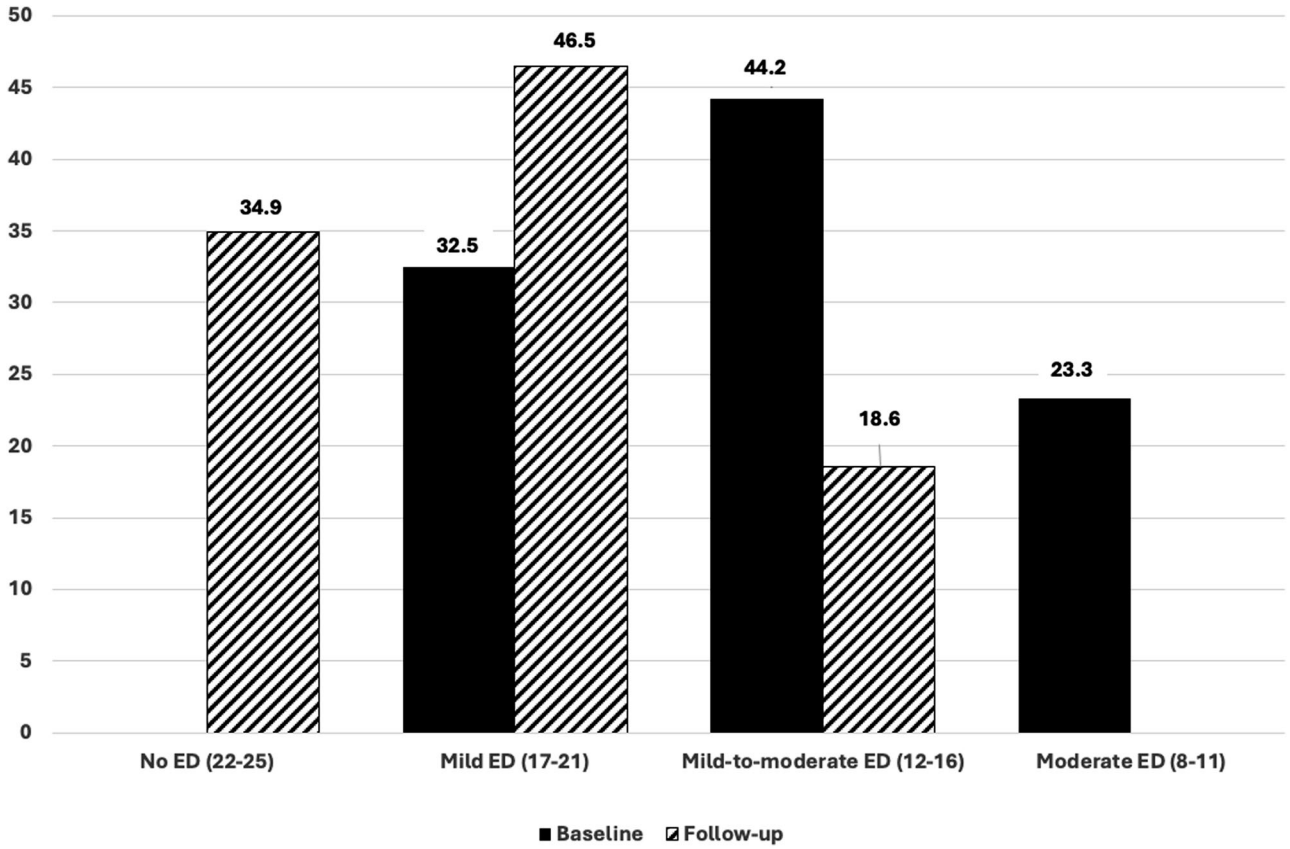

Fig. 1 Rates of erectile dysfunction severity at baseline and 3 moths follow-up.

Table 2. Psychometric scores of the study cohort, after matching, according to treatment received [median (IQR).

	Bedtime 50 mg ($n = 40$	Bedtime 37.5 mg ($n = 40$)	On-demand 50 mg ($n = 40$)	*p*-value*
IIEF-5 questionnaire				
Baseline	15 (12–17)	15 (13–18)	16 (13–17)	0.2
3-months follow-up	22 (19–22)[§]	22 (15–22)[§]	21 (16–21)[§]	0.3
PAIRS-SF questionnaire				
PAIRS-SF – Self confidence				0.6
Median (IQR)	10 (9–12)	9 (9–10)	10 (9–10)	
Range	6–12	9–10	6–11	
PAIRS-SF – Spontaneity				0.001
Median (IQR)	15 (13–16)[†]	14 (14–16)[†]	13 (12–13)	
Range	12–16	14–16	10–13	
PAIRS-SF – Time concern				0.001
Median (IQR)	13 (10–14)[†]	13 (12–14)[†]	18 (17–19)	
Range	9–16	11–14	16–20	

IIEF International Index of Erectile Function, *PAIRS-SF* psychological and interpersonal relationship scales – Short Form.
**P* value according to the repeated measures ANOVA test.
[§]$p < 0.01$ vs. baseline. *P* value according to the Wilcoxon Signed Rank Test.
[†]$p < 0.01$ vs. on-demand group.

men with mild/moderate ED. However, patients treated with bedtime sildenafil reported better spontaneity and fewer time concern scores compared to those who used on-demand sildenafil. Indeed, the bedtime protocol was the only predictor associated with better spontaneity and time concerns scores.

It is known that, despite the demonstrated efficacy of PDE5i [4], patients with ED often report dissatisfaction, since many of them discontinue the prescribed treatment within a year [31]. Therefore, a tailored treatment approach is crucial to improve patient's adherence to the prescribed medication. Treatment efficacy and speed of action are among the most requested characteristics of PDE5i by men with ED [32]. However, ED is a complex issue influenced also by psychological aspects related to the couple's sexual-life [33, 34]; therefore sexual spontaneity and having few

Table 3. Linear regression models predicting PAIRS-SF spontaneity and time concerns (beta; *p* value [95%CI]) in the whole cohort.

	PAIRS-SF – Spontaneity		PAIRS-SF – Time concerns	
	UVA model	**MVA model**	**UVA model**	**MVA model**
Age	−0.1; 0.03	−0.1; 0.4	0.1; <0.01	0.1; 0.2
	[−0.1–−0.01]	[−0.06–0.32]	[0.04–0.25]	[−0.02–0.92]
BMI	0.2; 0.8		0.1; 0.7	
	[−0.22–0.98]		[−0.47–0.54]	
Total Testosterone	0.2; 0.9		0.1; 0.2	
	[−0.9–0.78]		[−0.14–0.48]	
Stable sexual	0.1; 0.9		−1.8; 0.1	
Relationship	[−1.12–1.23]		[−4.21–0.43]	
Baseline IIEF-5	0.3; 0.8		−0.2; 0.8	
	[−0.72–1.13]		[−0.36–0.29]	
Bedtime treatment	2.1; <0.001	1.7; 0.01	−5.3; <0.001	−4.4; <0.001
Vs. on-demand	[1.25–2.95]	[0.74–2.76]	[−6.57–−4.45]	[−6.32–−3.91]

UVA univariate model, *MVA* multivariate model, *BMI* body mass index, *IIEF* international index of erectile function, *PAIRS-SF* psychological and interpersonal relationship scales – Short Form.

time concerns were found to be important details when considering PDE5i for ED [13].

In terms of efficacy, previous meta-analyses have indicated that sildenafil (at doses of 50 mg and 100 mg) is the preferred treatment for men seeking high efficacy along with a favourable safety profile [6, 7]. Our results confirmed that sildenafil 50 mg on demand but also sildenafil bedtime 50 mg and 37.5 mg significantly improved EF in men with mild/moderate ED. This finding is innovative since there is a lack of studies that compared nightly and on-demand sildenafil. Moreover, we showed that sildenafil OSF 37.5 mg bedtime was similar to the on-demand and nightly 50 mg in terms of efficacy. This dosage, unique for the OSF, can have a good clinical applications when balancing treatment effectiveness and the risk of side-effects [25].

The PAIRS-SF self-confidence domain was comparable between the on-demand and bedtime sildenafil, suggesting that improvements in confidence are primarily linked to erection quality, which was similar for both protocols [13]. Of clinical importance, sildenafil bedtime (both 50 and 37.5 mg) was associates with better spontaneity and lower time concerns scores compared to the on-demand use. These findings corroborate previous data showing that daily tadalafil was better than on-demand sildenafil in terms of sexual spontaneity [10, 13]. Our results are innovative since we investigated, for the first time, the impact of nightly sildenafil on spontaneity and time concerns, comparted to sildenafil as needed, in men with ED. Previous studies have shown that nightly sildenafil was able to improve sleep-related erections and overall erectile-function scores in men with ED [14, 15]. Our study demonstrated that bedtime sildenafil OSF 50 and 37.5 mg are good treatment options for men with ED who prioritize efficacy but also sexual spontaneity. In clinical practice, bedtime sildenafil could be used as a first line treatment choice but also in men who are non-reponders or cannot tolerate daily tadalafil due to side effects.

A strength of this study is that we investigated, for the first time, the impact of bedtime (with two dosages) and on-demand sildenafil OSF on patient's sexual function and other psychological areas that are important for couple's well-being. Second, we used the new sildenafil OSF, which was found to be highly appreciated by patients and physicians [25]. This study shows that sildenafil OSF can have a great clinical utility also with bedtime use. Our study is not without its limitations. First, this is not a randomized trial, however, we used propensity score matching to limit baseline differences between groups. Second, we considered a homogenous cohort of white-European men with ED, thus deserving external validation with an independent, larger and more diverse sample. Finally, since at the best of our knowledge, there is no published version of the Italian translation of the PAIRS-SF questionnaires; therefore, we relied on the translation performed by a native English speaker and further validated by an uro-andrologist with international experience.

CONCLUSIONS

On-demand sildenafil OSF 50 mg and bedtime sildenafil OSF (either 50 mg or 37.5 mg) showed similar efficacy in improving sexual functioning in men with mild/moderate ED. Patients treated with bedtime sildenafil had greater spontaneity and fewer time concern compared to those who used on-demand sildenafil. Bedtime sildenafil OSF emerged as a valuable option in men with ED seeking for treatment efficacy and sexual spontaneity.

DATA AVAILABILITY

Data are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

LB wrote the paper, FP, TC, CM, CC, MB, DDT, AP, GP, CP, MM, DA collected data; FP, TC and AP supervised the paper, approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations; all patients signed an informed consent agreeing to share their own anonymous information for other future studies. The study was approved by the Hospital Ethical Committee (Prot. 060194).

ADDITIONAL INFORMATION

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