The Journal of Sexual Medicine, 2024, 1–5
https://doi.org/10.1093/jsxmed/qdae064
Original Research

Spontaneous erectile function recovery among young men with erectile dysfunction taking tadalafil 5 mg once a day

Edoardo Pozzi, MD[1,2,3], Christian Corsini, MD[1,2], Alessandro Bertini, MD[1,2], Federico Belladelli, MD[1,2], Massimiliano Raffo, MD[1,2], Fausto Negri, MD[1,2], Francesco Cattafi, MD[1,2], Simone Cilio, MD[2,4], Luca Boeri, MD[5], Paolo Capogrosso, MD[6], Alessia d'Arma, MD[2], Ranjith Ramasamy[3], Francesco Montorsi, MD[1,2], Andrea Salonia, MD, PhD[1,2,*]

[1]Department of Urology, University Vita-Salute San Raffaele, Via Olgettina, 58, 20132 Milan, Italy
[2]Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Via Olgettina, 58, 20132 Milan, Italy
[3]Desai Sethi Urology Institute, Miller School of Medicine, University of Miami, Miami, 33136 FL, United States
[4]Urology Unit, Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, 80138 Naples, Italy
[5]Department of Urology, Foundation IRCCS Ca' Granda – Ospedale Maggiore Policlinico, 20122 Milan, Italy
[6]Department of Urology, Circolo & Fondazione Macchi Hospital – ASST Sette Laghi, 21100 Varese, Italy

*Corresponding author: University Vita-Salute San Raffaele, Division of Experimental Oncology/Unit of Urology, URI – Urological Research Institute, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy. Email: salonia.andrea@hsr.it

Abstract

Background: Daily (once a day [OaD]) tadalafil intake is a valuable option for men favoring spontaneous over scheduled sexual intercourse.
Aim: The study sought to assess the rate of and the clinical factors associated with spontaneous, medication-free erectile function (EF) recovery after discontinuation of tadalafil 5 mg OaD in a cohort of young men seeking first medical help for psychogenic erectile dysfunction (ED) as their primary complaint.
Methods: Data from 96 consecutive patients <50 years of age seeking first medical help for ED and prescribed tadalafil 5 mg OaD were analyzed. Patients completed the International Index of Erectile Function (IIEF) and underwent baseline penile color Doppler ultrasound. Follow-up involved clinical assessments or phone interviews. Spontaneous medication-free EF recovery was defined as IIEF EF domain score >22 after tadalafil discontinuation, prompting cessation of follow-up. Descriptive statistics compared tadalafil OaD responders and nonresponders. Cox regression hazard models explored the association between baseline characteristics and EF recovery risk post–drug discontinuation. Kaplan-Meier analyses estimated EF recovery probability over time.
Outcomes: The primary outcome was EF recovery after discontinuation of tadalafil 5 mg OaD.
Results: Overall, median age was 39 (interquartile range [IQR], 32-45) years. Of all, 82 (85.4%) patients achieved EF recovery after tadalafil OaD discontinuation, while 14 (14.6%) patients were identified as nonresponders. Median tadalafil usage time (from beginning to discontinuation) was 3 (IQR, 2-11) months. The most common treatment-emergent adverse event was headache in 9 (9.4%) patients. Nonresponders were older (43 [IQR, 42-45] years vs 38 [IQR, 31-44] years; $P = .03$), had higher body mass index (25.5 [IQR, 23.4-29.9] kg/m^2 vs 23.6 [IQR, 21.8-25.9] kg/m^2; $P = .04$), and reported lower baseline IIEF EF domain scores (12 [IQR, 7-15] vs 15 [IQR, 10-22]; $P = .02$) than responders. Nonresponders and responders did not differ in terms of baseline ED severity, Charlson comorbidity index, smoking, alcohol consumption, regular physical exercise, and color Doppler ultrasound parameters. Upon Cox regression analysis, younger age (hazard ratio, 0.95; 95% confidence interval, 0.92-0.99; $P = .01$) was associated to EF recovery, after adjusting for baseline ED severity, body mass index, smoking, and Charlson comorbidity index ≥1. The Kaplan-Meier analysis displays the probability of EF recovery over time, indicating rates of 43%, 60%, and 72% at 3-, 6-, and 12-month follow-up intervals, respectively.
Clinical Implications: Tadalafil 5 mg OaD is an effective short-term treatment for psychogenic ED, allowing its discontinuation after achieving a normal medication-free EF.
Strengths and Limitations: The main limitations are the limited number of participants and the potential neglect of confounding factors.
Conclusion: Almost 1 out of 2 young men with primary psychogenic ED who were prescribed with tadalafil 5 mg OaD recovered spontaneous medication-free EF after 3 months of treatment. Overall, the younger the patient was, the higher the chance there was of spontaneous EF recovery after drug discontinuation.

Keywords: erectile dysfunction; PDE5 inhibitor; tadalafil; epidemiology.

Introduction

Erectile dysfunction (ED) significantly affects young men, with 1 in 4 men under 40 years of age seeking medical help for ED.[1,2] Despite the common assumption that ED in this demographic is primarily psychogenic,[3,4] many young patients present with severe ED.[1] Lifestyle modifications are often the first step in treatment, followed by the use of phosphodiesterase type 5 (PDE5) inhibitors.[5] Of all, tadalafil stands out due to its extended half-life of 17.5 hours, enabling a more flexible dosing schedule in comparison with other largely available PDE5 inhibitors.[6,7] Tadalafil can be taken on demand before sexual activity or once a day (OaD), regardless of planned sexual activity. The latter regimen provides a consistent effective profile, making it a valuable alternative

Received: December 17, 2023. **Revised:** May 8, 2024. **Accepted:** May 14, 2024

for men preferring nonscheduled sexual intercourse.[8,9] This could be particularly beneficial for younger men with ED, helping them overcome emotional hurdles and re-establish a satisfactory sexual life.[2,10] However, factors that influence EF recovery in young men using OaD tadalafil remain poorly understood. Therefore, we aimed to explore the prevalence and the clinical factors associated with spontaneous medication-free EF recovery after discontinuing tadalafil 5 mg OaD in a cohort of young men seeking first medical help for ED.

Methods

Data from a cohort of 478 heterosexual sexually active men, consecutively seeking first medical help for ED at a tertiary referral center between 2018 and 2022 and prescribed with tadalafil either on-demand or OaD after several suggestions for lifestyle modifications, were analyzed. Of note, all included patients were PDE5 inhibitor naïve at the time of their first clinical assessment. Each patient underwent a detailed medical examination and history taking. Health-significant comorbidities were scored using the Charlson comorbidity index (CCI).[11] A thorough evaluation of sociodemographic characteristics was also conducted, including recreational activities such as smoking history, alcohol usage, and regular physical exercise (defined as a minimum of 2 h/wk). Smoking habits were measured in pack-years and subsequently divided into 2 categories: nonsmokers (those who never smoked) and ex-smokers/current smokers. Alcohol consumption was likewise divided into abstainers (those who did not consume alcohol) and drinkers (those who consumed any amount per week). Body mass index (BMI), defined as weight in kilograms divided by the square of height in meters, was recorded for each patient. All participants completed the International Index of Erectile Function (IIEF) at baseline. ED severity was scored using the Cappelleri's criteria, with severe ED identified as an IIEF erectile function domain (IIEF-EF) score $\leq$11.[12] Furthermore, all patients compiled the Beck Depression Inventory (BDI), with clinical depression defined as a BDI score $\geq$17. All patients were investigated for either primary or secondary concomitant premature ejaculation, as defined according to the widely applied classification criteria suggested by the International Society for Sexual Medicine.[13] Primary psychogenic ED was defined according to the criteria outlined by the current Sexual and Reproductive Health Guidelines of the European Association of Urology.[5]

Each patient had total testosterone levels measured via a direct chemiluminescence immunoassay; venous blood samples were drawn between 7 AM and 11 AM after an overnight fast. Moreover, glycated hemoglobin along with complete blood count was collected for each patient. As for study protocol, blood analyses were performed by the same laboratory. According to our internal protocol, dynamic penile color doppler ultrasound (CDDU) was performed in every patient at baseline. Specifically, CDDU measurements were taken after 20 minutes from intracavernosal injection of alprostadil 20 μg and self-sexual stimulation. Pathological CDDU was defined with an average peak systolic velocity <35 cm/s.[14,15] The average CDDU values between corpora cavernosa have been eventually considered. Patients with pathological veno-occlusive mechanism were excluded (n = 1). The follow-up protocol for our cohort was designed with an initial 3-month assessment. Specifically, all patients who were re-evaluated 3 months after the initial consultation were included in the study in order to assess their response to the treatment and any potential side effects. Following this, the follow-up intervals were extended to every 6 months. To ensure that we captured comprehensive data, phone calls were integrated into the follow-up to account for instances in which in-person visits were not possible. Once the treatment goal was achieved, the decision to discontinue the treatment regimen was made (by the treating physician). Thereafter, participants were asked to fulfill the IIEF after the treatment discontinuation by reporting the actual date of questionnaire completion. From that point forward, if a patient maintained his erectile function (EF) after stopping the treatment at the time of the subsequent follow-up (IIEF >22), they were then considered a responder. This ensured to accurate calculation of the median time from treatment discontinuation to IIEF completion (thus, EF recovery). If such outcome was achieved, follow-up data collection was discontinued (Supplementary Figure 1).

For the specific purpose of this study, we only considered those under 50 years of age, with a baseline normal CDDU and who were prescribed tadalafil 5 mg OaD (n = 125).

Data collection followed the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to provide their own anonymous information for future studies. The study was approved by the Institutional Review Board (Authorization Protocol URI 001-2010, further amended in December 2015 by the Ethic Committee IRCCS Ospedale San Raffaele, Milan, Italy).

Statistical analysis

Statistical analysis consisted of several steps. First, descriptive statistics were used to compare clinical and sociodemographic characteristics between responders and nonresponders. Median and interquartile range (IQR) or frequency and proportion were reported for continuous or categorical variables, respectively. The Mann-Whitney and chi-square tests were used to compare the statistical significance of differences in the distribution of continuous or categorical variables among patients of the 2 groups, respectively. Second, Cox regression hazard models tested the association between patients' baseline characteristics and the risk of EF recovery. Last, Kaplan-Meier analyses estimated the probability of EF recovery over time.

Results

Of 125, 29 (23.2%) patients were lost at follow-up. Consequently, the ultimate analyses were carried out on a group of 96 young ED patients for whom follow-up data were accessible. Table 1 details the descriptive statistics of the whole cohort and responder and nonresponder groups. Median tadalafil length of intake was 3 (IQR, 2-11) months. The median time from treatment discontinuation to IIEF-EF assessment was 1 (IQR, 0.4-2) months. The overall median follow-up was 7 (IQR, 4.4-13) months. The reported treatment-emergent adverse events (TEAEs) during treatment were headache in 9 (9.4%), transient myalgia in 1 (1%), and nasal congestion in 1 (1%) patient, respectively. No patients discontinued treatment because of these TEAEs.

Of all, 82 (85.4%) men exhibited spontaneous medication-free EF recovery after OaD tadalafil discontinuation, while 14 (14.6%) patients were classified as nonresponders. Overall,

Table 1. Sociodemographic-clinical and hormonal characteristics of the whole cohort of patients and those who were tadalafil responders vs nonresponders after discontinuation of tadalafil OaD.

Variable	Whole cohort (n = 96)	Tadalafil nonresponders (n = 14)	Tadalafil responders (n = 82)	*P* value
Age, y	39 (32-45)	43 (42-45)	38 (31-44)	.03
Relationship				.3
Partnered/married	73 (76)	11 (78.6)	62 (75.6)	
Single	23 (2)	4 (28.5)	19 (23.1)	
CCI ≥1	5 (5.2)	1 (7.1)	4 (4.9)	.1
BMI, kg/m^2	23.9 (22.2-26)	25.5 (23.4-29.9)	23.7 (21.8-25.9)	.04
Arterial hypertension, mm Hg	1	11 (11.5)	3 (21.4)	.5
Regular alcohol use (>1 L/wk)	17 (17.7)	2 (14.3)	15 (18.3)	.7
Smoking				.2
Current smokers/ex-smokers	39 (40.6)	6 (42.8)	(40.2)	
Adverse events				.2
Headache	9 (9.4)	1 (7.1)	8 (9.8)	
Transient myalgia	1 (1)	0 (0)	1 (1.2)	
Nasal congestion	1 (1)	0 (0)	1 (1.2)	
Premature ejaculation (primary)	18 (18.8)	2 (14.3)	16 (19.5)	.3
tT, ng/mL	5 (3.5-6)	4.6 (3.5-5.9)	5.1 (3.5-6)	.9
LH, mIU/mL	3.5 (2.7-4.7)	3.5 (3.1-3.7)	3.6 (2.6-4.7)	.9
HbA1c, mmol/mol	5.2 (5-5.4)	5.2 (5.1-5.2)	5.3 (5-5.5)	.7
IIEF total	47 (26-55.5)	42 (24-50.5)	47.5 (26.8-56)	.4
IIEF-IS	8 (4-10.5)	7 (0-8.5)	9 (5-11)	.04
IIEF-OF	9 (6-10)	9 (8-1)	9 (6-10)	.6
IIEF-SD	7.50 (6-9)	7 (5.5-8.5)	8 (6-9)	.3
IIEF-OS	6 (3.5-8)	6 (3.5-6)	5.50 (3.7-8)	.3
IIEF-EF	15 (10-22)	12 (7-15)	15 (10-22)	.02
Severe ED	29 (30.2)	6 (42.9)	23 (28)	.4
BDI	2 (6-13)	10 (5-15)	4.5 (2-13)	.2
Treatment duration, mo	3 (2-11)	6.5 (1.3-22)	3 (2-9.5)	.4
Average PSV, cm/s	49.1 (38.4-59.8)	45.3 (37.6-58.4)	46.7 (37.9-61)	.08
Average RI	1 (1-1)	1 (1-1)	1 (1-1)	1

Values are median (interquartile range) or n (%). Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; CCI, Charlson comorbidity index; ED, erectile dysfunction; EF, erectile function; HbA1c, glycated hemoglobin; IIEF, International Index of Erectile Function; IS, intercourse satisfaction; LH, luteinizing hormone; OaD, once a day; OF, orgasmic function; OS, overall satisfaction; PSV, peak systolic velocity; RI, resistance index; SD, sexual desire; tT, total testosterone.

Table 2. Multivariate Cox regression analysis predicting spontaneous non–drug-assisted erectile function recovery after discontinuation of tadalafil OaD.

Variable	HR (95% CI)	*P* value
Age	0.95 (0.92-0.99)	.01
IIEF-EF <11	0.92 (0.55-1.54)	.7
Smoking	0.87 (0.52-1.47)	.6
BMI	0.96 (0.90-1.02)	.2
CCI ≥1	0.89 (0.64-1.24)	.5

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; IIEF, International Index of Erectile Function erectile function domain; OaD, once a day.

42 (43%), 57 (60%), and 70 (72%) patients achieved spontaneous medication-free EF recovery at 3, 6, and 12 months, respectively. Tadalafil nonresponders were older (*P* = .03), had higher BMI (*P* = .04), had and lower baseline IIEF-EF scores (*P* = .02) as compared with tadalafil responders. No difference was observed between responders and nonresponders in terms of baseline severe ED (IIEF-EF <11), BDI scores, rates of CCI ≥1, smoking, alcohol consumption, serum total testosterone and glycated hemoglobin levels, average peak systolic velocity at CDDU, rates of TEAEs, overall treatment duration, and rates of premature ejaculation (Table 1).

At multivariate Cox regression analysis, younger age (*P* = .01) was associated with spontaneous EF recovery, after adjusting for baseline severe EF, BMI, CCI ≥1, and smoking status (Table 2).

Table 3. Kaplan-Meier estimates of spontaneous non–drug-assisted erectile function recovery after discontinuation of tadalafil OaD.

Month	Kaplan-Meier estimate (95% CI) (%)
3	43 (41-62)
6	60 (49-69)
12	75 (64-83)

Abbreviations: CI, confidence interval; OaD, once a day.

Table 3 shows the Kaplan-Meier estimates pertaining to EF recovery following tadalafil OaD discontinuation. More in detail, the estimates of EF recovery at the 3-, 6-, and 12-month follow-up intervals were 43%, 60%, and 72%, respectively. Figure 1 graphically displays the cumulative probability of EF recovery over time after discontinuation of tadalafil 5 mg OaD.

Discussion

The rate of young men presenting for ED compliant is relevant and significantly growing. Of all, many young men depict criteria suggestive for severe ED, mostly primary psychogenic in nature. Current real-life findings showed that almost half of young ED patients taking tadalafil 5 mg OaD for 3 months achieved medication-free EF recovery after treatment discontinuation. Even more interestingly, the efficacy of this regimen appeared to further improve beyond this initial time frame. Moreover, the younger the patient, the greater the chance

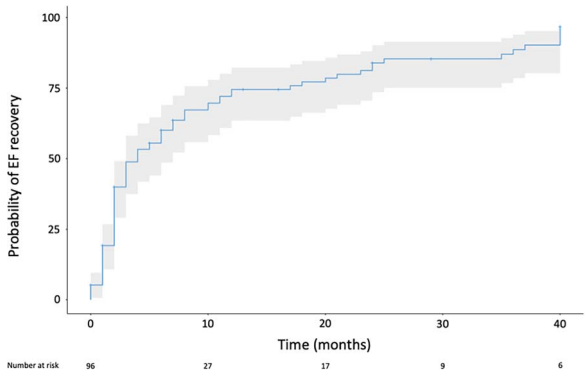

Figure 1. Kaplan-Meier showing the estimated probability of spontaneous erectile function (EF) recovery over time after tadalafil once a day (OaD) discontinuation (cumulative probability).

of effective treatment success, thus demonstrating that age per se eventually plays a significant role in determining the likelihood of success in achieving spontaneous EF recovery after having received tadalafil 5 mg OaD.

The study also revealed that nonresponders were not only older, but also had higher BMI, and reported lower baseline IIEF-EF scores compared with tadalafil responders. This information could be helpful for healthcare professionals in identifying which patients are likely to benefit the most from tadalafil 5 mg OaD with the specific goal of subsequent discontinuation and tailoring treatment plans accordingly.

The scientific literature extensively showed the role of tadalafil in restoring EF across various contexts and situations. In this context, Brock et al[16] conducted a comprehensive meta-analysis aiming to compare the EF response to tadalafil in on-demand and OaD dosing regimens across various clinical subpopulations, using the IIEF questionnaire as a parameter to define treatment outcomes. Their analysis, inclusive of men with common associated conditions, treatments, and risk factors for ED, revealed the effectiveness of tadalafil in both dosing regimens and at different doses.[16] Notably, the study did not conclusively favor on-demand over OaD tadalafil within specific ED patient populations. However, it is important to acknowledge that their comparison involved varied ED etiologies and tadalafil doses, and lacked a detailed analysis of EF improvement over time and, more importantly, after tadalafil discontinuation. Additionally, other studies have explored daily tadalafil for ED treatment, with generally positive outcomes. In this context, in one of the original randomized clinical trials, Porst et al[17] aimed to evaluate the effectiveness and safety of OaD tadalafil, administered at 2.5 mg and 5 mg, in patients presenting varying degrees of ED severity alongside with comorbid conditions. Irrespective of the dosage, their findings indicated that tadalafil OaD regimen was well tolerated and resulted in significant EF improvements. Specifically, individuals with mild ED witnessed improvement rates of 54.3% and 74.8% for the respective doses. Similarly, patients with moderate ED experienced enhancements at rates of 51.3% and 63.1%, respectively, while those with severe ED reported improvement rates of 33.7% and 44.5% for the 2.5 mg and 5 mg doses, respectively.[17] As such, we found similar results at long-term follow-up; in fact, 72% of men achieved spontaneous EF recovery after 12 months of treatment. Similar findings were also reported by Karabakan et al,[18] who investigated the efficacy of tadalafil 5 mg OaD across different domains (ejaculation time, EF, and lower urinary tract symptoms) on 60 patients. The authors found a significant improvement on all domains explored with specific emphasis on EF improvement.[18] Although this holds true, in contrast to prior studies, our analysis reports the results specifically examining the persistence of spontaneous medication-free EF recovery after tadalafil OaD discontinuation. Indeed, we found that almost 85% of relatively young men with primary psychogenic ED maintained spontaneous medication-free adequate EF after tadalafil 5 mg OaD deliberated discontinuation. Thereof, our focus on young men with normal CDDU parameters, while intentionally excluding those with organic ED, stands out as a relatively new investigation in the field of sexual medicine. Indeed, our findings suggest that tadalafil 5 mg OaD in the context of psychogenic ED may be used as a valuable and effective "temporary" therapeutic approach, thus allowing to stop the drug after a limited period of time while having recovered adequate and satisfactory EF. Theoretically, this regimen would aid in "breaking" psychological barriers associated with primarily psychogenic ED, offering an effective solution for the restoration of a normal, medication-free EF.

The study is not without limitations. First, it is important to note that it was limited to a relatively small cohort of heterosexual sexually active men, which may restrict the generalizability of the results. Second, far from preconceptions of noninclusion, we are aware that current findings could be not effectively expandable to the non-White European ethnic groups, as well as to a nonheterosexual or nonbinary population. Third, we lack data on very long-term follow-up, as these patients might have a relapse of their ED even after several months of their treatment discontinuation. As such, the median follow-up time after treatment discontinuation could only be calculated up to the point when patients have been lost to follow-up, but not from the time since when they potentially experienced ED relapse and eventually had resumed treatment (any). This could potentially impact the accuracy of our findings. Fourth, we do not have the overall median follow-up of the cohort because we ceased patient follow-up after assessing their EF upon medication discontinuation. Fifth, although we have clearly followed the European Association of Urology guidelines on this matter,[5] distinguishing between primary psychogenic and organic ED is challenging due to their frequent overlap. To reduce confounding factors, we focused on a younger cohort (under 50 years of age) and those with normal CDDU parameters. Sixth, we neither gathered nor analyzed data concerning the potential influence of psychotherapy on our patient cohort, knowing that this omission could have introduced relevant bias into our results. Last, the relatively small cohort size prevented us from segregating the participants into distinct categories based on the severity of their ED. Likewise, due to the limited sample size, we faced a potential deficiency in statistical power, which could have affected the strength of our exploratory analysis. Hence, while our study offers valuable insights, these limitations need to be taken into consideration upon interpretation of current results. Nonetheless, this is the first study investigating the performance of tadalafil 5 mg OaD in a cohort of young men with ED after treatment discontinuation, showing its efficacy over the management workup of this type of patients in a real-life setting. Specifically, considering that nearly half of the patients achieved medication-free EF recovery after discontinuing the use of tadalafil 5 mg OaD at the 3-month mark, we suggest an average treatment duration of at least 3 months. However,

this recommendation should be interpreted with caution due to the aforementioned limitations. To validate these preliminary findings, further research involving a larger and more heterogeneous cohort is necessary.

Conclusions

This study indicates that approximately half of young patients with psychogenic ED achieved medication-free EF recovery after discontinuing tadalafil 5 mg OaD over a period of 3 months of therapy. These insights are essential for healthcare providers to more accurately identify the patients who are most likely to benefit from a temporary course of tadalafil 5 mg OaD, ultimately enhancing sexual spontaneity and overall patient satisfaction.

Acknowledgments

The authors express their gratitude to Mrs. April Dawn Mann, Director of The Writing Center at the University of Miami, Florida, USA, for her assistance in revising the manuscript's English.

Author contributions

E.P. (Conceptualization [Equal], Data curation [Equal], Formal analysis [Equal], Methodology [Equal], Project administration [Equal], Writing – original draft [Equal]). C.C. (Data curation [Equal]). A.B. (Data curation [Equal]), F.B. (Data curation [Equal]), M.R. (Data curation [Equal]), F.N. (Data curation), F.C. (Data curation [Equal]), S.C. (Data curation), L.B. (Data curation), P.C. (Data curation), A.D.(Data curation), R.R. (Supervision [Equal], Writing – review & editing [Equal]), F.M. (Supervision), A.S. (Conceptualization [Equal], Project administration [Equal], Supervision, Writing – review & editing).

Supplementary material

Supplementary material is available at *The Journal of Sexual Medicine* online.

Funding

None declared.

Conflict of interest

None declared.

References

1. Capogrosso P, Colicchia M, Ventimiglia E, *et al.* One patient out of four with newly diagnosed erectile dysfunction is a young man–worrisome picture from the everyday clinical practice. *J Sex Med*. 2013;**10**(7):1833–1841. https://doi.org/10.1111/jsm.12179
2. Pozzi E, Capogrosso P, Chierigo F, *et al.* Clinical profile of young patients with erectile dysfunction: preliminary findings of a real-life cross-sectional study. *Eur Urol Focus*. 2018;**6**(1):184–189. https://doi.org/10.1016/j.euf.2018.10.003
3. Salonia A, Bettocchi C, Boeri L, *et al.* European Association of Urology guidelines on sexual and reproductive Health-2021 update: male sexual dysfunction. *Eur Urol*. 2021;**80**(3):333–357. https://doi.org/10.1016/j.eururo.2021.06.007
4. Pozzi E, Fallara G, Capogrosso P, *et al.* Primary organic versus primary psychogenic erectile dysfunction: findings from a real-life cross-sectional study. *Andrology*. 2022;**10**(7):1302–1309. https://doi.org/10.1111/andr.13212
5. Salonia A, Bettocchi C, Capogrosso P, *et al. EAU Guidelines on Sexual and Reproductive Health*. EAU Guidelines. Edn. presented at the EAU Annual Congress, Paris; 2023.
6. Curran M, Keating G. Tadalafil. *Drugs*. 2003;**63**(20):2203–2212; discussion 2213-2214. https://doi.org/10.2165/00003495-200363200-00004
7. Ventimiglia E, Capogrosso P, Montorsi F, Salonia A. The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf*. 2016;**15**(2):141–152. https://doi.org/10.1517/14740338.2016.1131818
8. Zhou Z, Chen H, Wu J, *et al.* Meta-analysis of the long-term efficacy and tolerance of tadalafil daily compared with tadalafil on-demand in treating men with erectile dysfunction. *Sex Med*. 2019;**7**(3):282–291. https://doi.org/10.1016/j.esxm.2019.06.006
9. Paduch DA, Bolyakov A, Polzer PK, Watts SD. Effects of 12 weeks of tadalafil treatment on ejaculatory and orgasmic dysfunction and sexual satisfaction in patients with mild to severe erectile dysfunction: integrated analysis of 17 placebo-controlled studies. *BJU Int*. 2013;**111**(2):334–343. https://doi.org/10.1111/j.1464-410X.2012.11656.x
10. Capogrosso P, Ventimiglia E, Boeri L, *et al.* Should we tailor the clinical management of erectile dysfunction according to different ages? *J Sex Med*. 2019;**16**(7):999–1004. https://doi.org/10.1016/j.jsxm.2019.03.405
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;**40**(5):373–383. https://doi.org/10.1016/0021-9681(87)90171-8
12. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the international index of erectile function. *Urology*. 1999;**54**(2):346–351. https://doi.org/10.1016/S0090-4295(99)00099-0
13. McMahon CG, Althof SE, Waldinger MD, *et al.* An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. *J Sex Med*. 2008;**5**(7):1590–1606. https://doi.org/10.1111/j.1743-6109.2008.00901.x
14. Montorsi F, Sarteschi M, Maga T, *et al.* Functional anatomy of cavernous helicine arterioles in potent subjects. *J Urol*. 1998;**159**(3):808–810. https://doi.org/10.1016/S0022-5347(01)63738-8
15. Montorsi F, Guazzoni G, Barbieri L, *et al.* Genital plus audiovisual sexual stimulation following intracavernous vasoactive injection versus re-dosing for erectile dysfunction–results of a prospective study. *J Urol*. 1998;**159**(1):113–115. https://doi.org/10.1016/s0022-5347(01)64029-1
16. Brock G, Ni X, Oelke M, *et al.* Efficacy of continuous dosing of tadalafil once daily vs tadalafil on demand in clinical subgroups of men with erectile dysfunction: a descriptive comparison using the integrated tadalafil databases. *J Sex Med*. 2016;**13**(5):860–875. https://doi.org/10.1016/j.jsxm.2016.02.171
17. Porst H, Giuliano F, Glina S, *et al.* Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol*. 2006;**50**(2):351–359. https://doi.org/10.1016/j.eururo.2006.02.052
18. Karabakan M, Keskin E, Akdemir S, Bozkurt A. Effect of tadalafil 5mg daily treatment on the ejaculatory times, lower urinary tract symptoms and erectile function in patients with erectile dysfunction. *Int Braz J Urol*. 2017;**43**(2):317–324. https://doi.org/10.1590/S1677-5538.IBJU.2016.0376