ORIGINAL PAPER

Erectile dysfunction treatment with Phosphodiesterase-5 Inhibitors: Google trends analysis of last 10 years and COVID-19 pandemic

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Summary
Objectives: We aimed to analyze the trend change of the most popular Phosphodiesterase-5 Inhibitors (PDE5i) over time and geography by using Google Trends (GT) data in 10 years period and COVID-19 pandemic.
Materials and methods: GT is able to generate a "line-graph", showing how interest has increased or decreased over a period within specific territories. The search values for specific terms are indexed as relative search volume (RSV), which is presented on a scale from 0-100. Avarage annual percentage change (AAPC) and RSV were analyzed to evaluate gain or loss of interest in trends. Search terms were generated for Food and Drug Administration (FDA)-approved PDE5i; tadalafil, sildenafil, vardenafil, avanafil, and their most-used brand names. The data was within "worldwide" from 1 January 2010, to 31 December 2020, using the "global" query category.
Results: The overall interest in PDE5i has doubled. Sildenafil has become the most trend PDE5i of today with a regular increase (AAPC: 0.016, p < 0.01). Although the search trend of tadalafil remained almost constant until 2014, the rate of increase in the last 6 years raised and tadalafil has become the 2nd most popular PDE5i recently (AAPC: 0.007, p < 0.01). For vardenafil there has been a decreased interest (AAPC: -0.009, p < 0.01). There is no significant change in avanafil trend (AAPC: 0.000, p: 0.5). All PDE5i interest on GT decreased notably from February to June 2020. But after June, search trends reached the level before the COVID-19 period in a month.
Conclusions: These findings show us, with its increasing prevalence, erectile dysfunction (ED) has become a major public health problem. People from different geographies search the internet for ED treatment options. Patients should be informed that ED may be the first sign of many comorbid diseases, and patients with ED should be referred to a health institution for diagnosis and treatment.

KEY WORDS: Google trends; Erectile dysfunction; Phosphodiesterase type-5 inhibitors; Health behaviors; Real-world evidence.

INTRODUCTION

Erectile dysfunction (ED) is the recurrent or persistent inability of men to achieve and/or maintain adequate penile erections for satisfactory sexual performance (1). It is pre-dicted that 322 million men around the world will have ED by 2025 (2). The increasing prevalence of ED leads to a more significant economic burden. At this point, oral phosphodiesterase-5 inhibitors (PDE5i) are the first choice of treatment for ED because they are safe, efficient, cost-effective and non-invasive (3). PDE5i which were approved by the *Food and Drug Administration* (FDA) for ED and other diseases are shown on the timeline (4, 5) (Figure 1).

Considering sexual disorders, patients may not feel comfortable to share their problems with the doctors. Then they can try to find out how to treat their sexual problems by themselves on the web (6). A survey from *The National Men's Health Week* showed that 44% of men who developed symptoms of ED, would hesitate to look for a treatment, and 11% of them would not visit a doctor if they decide they might need a medical treatment like PDE5i (7). *Google trends* (GT) is one of these search tools which provides worldwide data about the popularity of searched items during a period. Thus, GT has been continuously used more by marketing specialists for gathering information about potential client interest, as well as differences in that interest by geographic location and time. In the medical area, GT has been used to specify patient interest in surgical procedures and medical treatments (8).
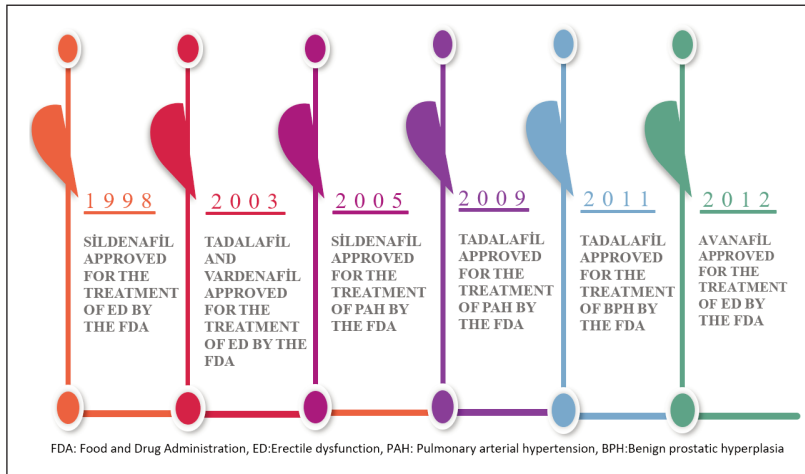
Therefore, we aimed to analyze the trend change of the most popular PDE5i over time including COVID-19 pandemic and geography by using GT data. We also aimed to reveal the possible reasons for the trend changes of PDE5i in terms of time and geography.

MATERIALS AND METHODS

GT produces worldwide search volume info since 2004, offering time-period and category patterns according to a specific term. GT is able to generate a "*line-graph*", showing how interest has increased or decreased over a period within specific territories. The search values for specific terms are indexed as *relative search volume* (RSV), which is presented on a scale from 0-100. A value of RSV 100 indicates the highest search trends, while 50 represents half of the searches. However, 0 demonstrates that no sufficient data were found for the term.

By using the estimated *annual RSV* (ARSV) *annual percentage*

No conflict of interest declared.

Figure 1.
Milestones in the development of phosphodiesterase type 5 inhibitors.

1998	2003	2005	2009	2011	2012
SİLDENAFİL APPROVED FOR THE TREATMENT OF ED BY THE FDA	TADALAFİL AND VARDENAFİL APPROVED FOR THE TREATMENT OF ED BY THE FDA	SİLDENAFİL APPROVED FOR THE TREATMENT OF PAH BY THE FDA	TADALAFİL APPROVED FOR THE TREATMENT OF PAH BY THE FDA	TADALAFİL APPROVED FOR THE TREATMENT OF BPH BY THE FDA	AVANAFİL APPROVED FOR THE TREATMENT OF ED BY THE FDA

FDA: Food and Drug Administration, ED:Erectile dysfunction, PAH: Pulmonary arterial hypertension, BPH:Benign prostatic hyperplasia

The *Kendall Trend Tau Test* was applied to compare data which is collected over time for trends decreasing or increasing consistently.

Search terms were generated for FDA-approved PDE5i; tadalafil, sildenafil, vardenafil, avanafil, and their most-used brand names. The data was within "*worldwide*" from 1 January 2010, to 31 December 2020, using the "global" query category. Data obtained from search terms were plotted in polynomial trend lines. Moreover, international trends for each PDE5i individually were searched and shown in a separate figure. All trend and statistical analyses were performed using Microsoft Excel v.16.0 (*Redmond, Wash*) and SPSS v.24.0 (*SPSS Inc., Chicago, IL, USA*).

change (APC), linear trends in RSV were shown. To measure variations in ARSV between 2 join points, APC was evaluated. Estimated *average APC* (AAPC) and respective *confidence of intervals* (CIs) were used to determine linear trends of ARSV during the whole period. AAPC analysis in rate during a period is provided by a natural log-linear model ($[\ln(y)=xb]$). A negative value of AAPC shows a decreasing RSV and a positive rate refers to increased interest. A log $(x+1)$ transformation was used to the whole dataset if a dependent variable was zero. To assess any inflection points with a significant difference in the trend's slope, a permutation test was used. When slopes were identified or not the trends were called non-constant or constant, respectively.

RESULTS

Trends in geographic locations
Interest in sildenafil was mostly high in South America and Europe, interest in vardenafil was highest in the Eastern European and Asian countries. Interest in tadalafil was not superior especially in a specific region. The highest interest in avanafil was in Mediterranean countries (Figure 2) (Table 1).

Trends in interest over time
The overall interest in PDE5i has doubled in the last 10 years. The leading trend was vardenafil from 2010 to

Figure 2.
International trends in phosphodiesterase- 5 inhibitors.The world map shows the countries with the highest Google Trends search volumes for each search term. The darker regions indicate the places where the search terms are more likely to be searched. If a region on the map isn't highlighted, it doesn't mean the term is not used in that region, however, it is less popular than other regions.
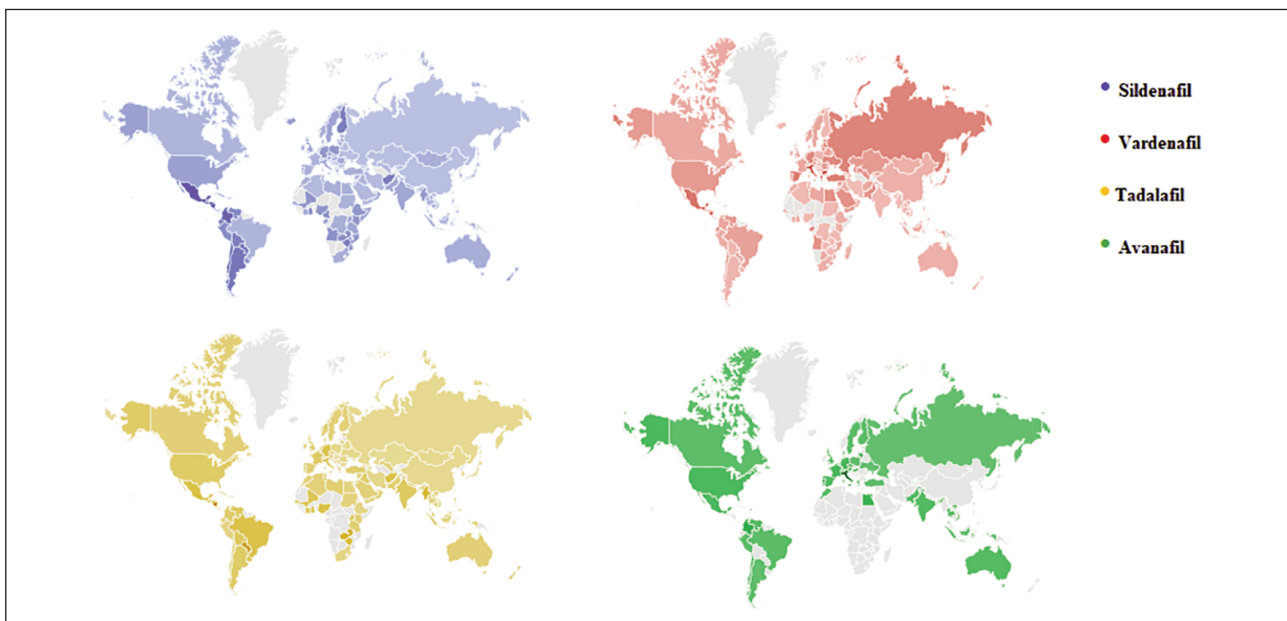
Figure 3.
Google Trends relative search volume for phosphodiesterase-5 inhibitors by month, January 2010 to December 2020.
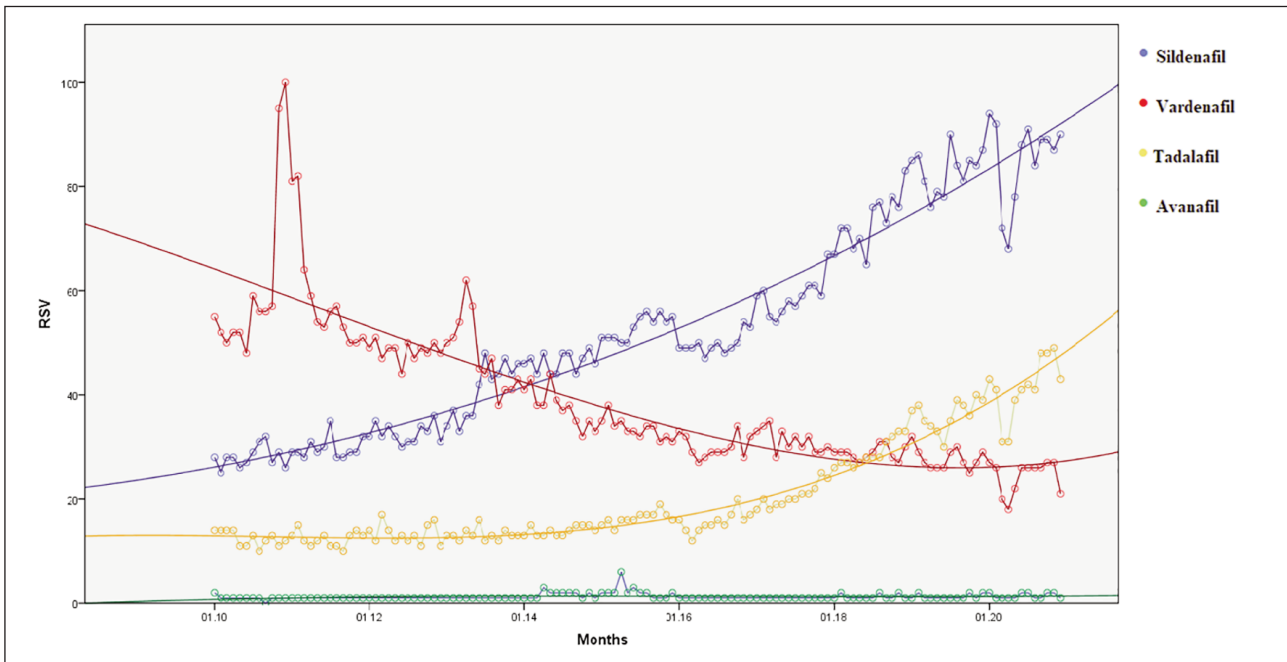

Table 1.
Most trend five countries for each PDE5i.

Sildenafil	Vardenafil	Tadalafil	Avanafil
Finland	Japan	Brazil	Italy
Chile	Russia	Vietnam	Portugal
Colombia	Ukraine	France	Egypt
Argentina	Bulgaria	India	France
Peru	Israel	United Arab Emirates	China

Table 2.
AAPC results of PDE5i queries from 2010 until 2020.

PDE5i	Lower endpoint	Upper endpoint	AAPC	Lower CI	Upper CI	Test statistic	*p-value
Sildenafil	2010	2020	0.016	0.015	0.017	0.874	< 0.01
Vardenafil	2010	2020	-0.009	-0.0010	-0.0010	-0.806	< 0.01
Tadalafil	2010	2020	0.007	0.006	0.008	0.791	< 0.01
Avanafil	2010	2020	0.000	0.000	0.000	0.192	0.5

CI: Confidence interval; AAPC: Avarage annual percentage change; PDE5i: Phosphodiestarese-5 inhibitors.
* The Kendall Trend Tau Test was applied to define p value.

2013, but it has been decreasing over time (AAPC: -0.009, p < 0.01). Sildenafil has become the most trend PDE5i of today with a regular increase (AAPC:0.016, p < 0.01). Although the search trend of tadalafil remained almost constant until 2014, the rate of increase in the last 6 years raised geometrically like sildenafil, and tadalafil has become the 2nd most popular PDE5i recently (AAPC: 0.007, p < 0.01). Avanafil has not become widespread and its trend has shown slight movement in the last 1 year, but it has not been a competitor in general (AAPC: 0.000, p: 0.5) (Figure 3) (Table 2).
The global interest in the term "*erectile dysfunction*" on GT has been substantially lower than the interest in all PDE5i. There was no relationship between the PDE5i interest and the interest in global erectile dysfunction issue.

Trends in interest in COVID-19 period
All PDE5i interest on *Google Trend* decreased notably from February to June 2020. But after June, search trends reached the level before the COVID-19 period in a month. Then the increase-decrease routine continued as before (Figure 3).

DISCUSSION
With the aging population and the increase of comorbid diseases, ED has become more prevalent. Accordingly, the demand for ED treatments is increasing (9, 10). Because PDE5i are both non-invasive and more cost-effective treatments of ED compared to other methods (3, 11), we can see a rising interest in them over the world in the last 10 years in our results.
Jena et al. found a strong correlation between web searches for *Human Immunodeficiency Virus* (HIV) terms and HIV regional incidence rates in the *United States* (US) (12). Tijerina et al. found also a correlation between breast surgery procedures search terms and annual case volumes of breast procedures performed in the US (13). Similarly, in our study, there was a correlation between the trend rate and the amount of PDE5i sales in Europe (14). We demonstrated that people initially search for treatment options for ED on the web, then they buy the most suitable one for themselves. On this point, there is a risk that can endanger patients' health. Countrefeit PDE5i have been an important problem in both well-developed and developing countries. They are cheaper and easy to obtain

through the web (15). Considering the side effects of the drugs and their interactions with other drugs, the patient may be harmed. Moreover, clinical examination is necessary because ED can be the first symptom of cardiovascular diseases, also multiple risk factors and comorbidities are generally associated with ED (16). Both to prevent the use of counterfeit medicines and ensure the correct use of FDA-approved PDE5i, patients' awareness should be raised to see a doctor when they have ED.

When the trends of PDE5i are interpreted separately, it is seen that sildenafil has a clear superiority in recent years. According to the "CONSER" survey conducted by the *Italian Society of Andrology*, the speed of action is the most important factor for both physicians and patients when choosing a PDE5i. On this point, a new oro-soluble form of sildenafil offers advantages (17). Comparing the total numbers of PDE5i prescriptions in Europe, sildenafil is superior to tadalafil and vardenafil in the literature similar to our results of search trends (14). Being the first product in the market, brand name recognition, high efficacy and patient satisfaction are the main factors that maintain the popularity of sildenafil. Another important point is the lower cost of sildenafil compared to other PDE5i. *Hansen et al.* showed that ED treatment with sildenafil was a cost-effective alternative compared to vardenafil and tadalafil (18). Moreover, sildenafil searches seem to be prominent, especially in Latin American countries. Successful results in ED treatment with sildenafil in Latin America may have made sildenafil popular in this region (19). On the other hand, higher prescription rates of tadalafil in a prospective study in Latin America show that trends in the region may change in times advancing (20).

Our study shows that the trend of tadalafil has increased significantly and tadalafil has become popular in many countries from different continents recently. This popularity in different geographies can be interpreted with the high satisfaction of patients. The long duration of action of tadalafil gives the freedom to have unplanned sexual intercourse. This takes away timing concerns and provides sexual self-confidence, especially for the young men with mild sexual dysfunction (21). No interaction with fatty food is another advantage of tadalafil (22). Other important developments that increased the use of tadalafil were the approval for BPH and suggestions for the early use after radical prostatectomy (23, 24). Additionally, the increase in vardenafil trend in 2011 can be explained with the international study conducted with a large patient group in this period (25). This study may have increased the interest in vardenafil on web searches. However, the interest in vardenafil in the later period appears to be less than sildenafil and tadalafil. In addition to this, there is no significant peak of avanafil trend in the last 10 years. Less generic drugs of avanafil and vardenafil compared to sildenafil and tadalafil may also have made this difference in trends (15). On the other hand, high trends of avanafil in Mediterranean countries and vardenafil in the Eastern European and Asian countries can be investigated with further studies in these regions.

Mulhall et al. indicated that patients who were previously prescribed sildenafil were more likely tended to continue with the same medication compared with patients who have previously prescribed tadalafil or vardenafil

(26). On the other hand, there are contradictory results that show that patients are more likely to prefer tadalafil after experiencing sildenafil (27). A study from Canada showed that most patients and physicians preferred tadalafil instead of sildenafil (28). Thus, additional prospective studies are necessary to provide advanced insights into this issue.

In February 2020, when the COVID-19 pandemic started, a trend decreases up to 20% was observed in all PDE5i. Higher interest in COVID-19 related searches can be a reason of this decrease. Moreover, sexual behaviors seem to be negatively affected by the pandemic because of quarantine rules, multiple contact restrictions and fear of contamination (29). *Karagöz et al.* found that the frequency of sexual intercourse decreased in both sexes during the pandemic period compared to the pre-pandemic period (30). However interestingly 3 months later the trend of PDE5i came back to old levels and then started to rise again. Considering that stress and anxiety increase the frequency of ED, as well as the need of PDE5i. So, the pandemic affected the PDE5i trend both badly and well.

To the best of our knowledge, this is the first study that focuses on the differences of PDE5i on Google searches from the aspect of time and geography. Our study has some limitations. Firstly, GT data are anonymous and do not give the possibility for analyzing sub-population groups. Besides, we only had access to RSV and access to raw data was not possible. Furthermore, because the internet is more popular among the young population there may be inadequate data for older men. Lastly, search terms except English languages are not considered. However, we believe that our results reveal the current PDE5i search trends on the web.

CONCLUSIONS

In conclusion, people from different geographies search the internet for ED treatment options. Patients should be informed that ED may be the first sign of many comorbid diseases, and patients with ED should be referred to a health institution for diagnosis and treatment. In recent years apart from the first months of the COVID-19 pandemic, interest and search volume for PDE5i has increased continuously. These findings show us that ED has become a major public health problem with its increasing prevalence. Studies with broad participation are needed to examine different geographical trends in detail.

REFERENCES

1. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol. 2010; 57:804-814.

2. Aytaç IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. 1999; 84:50-56.

3. Rezaee ME, Ward CE, Brandes ER, et al. A Review of economic evaluations of erectile dysfunction therapies. Sex Med Rev. 2020; 8:497-503.

4. Chen L, Staubli SEL, Schneider MP, et al. Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off network meta-analysis. Eur Urol. 2015; 68:674-80.

5. Tzoumas N, Farrah TE, Dhaun N, et al. Established and emerging therapeutic uses of phosphodiesterase type 5 inhibitors in cardiovascular disease . Br J Pharmacol. 2020; 177:5467-5488

6. Cacciamani GE, Bassi S, Sebben M, et al. Consulting "Dr. Google" for prostate cancer treatment options: a contemporary worldwide trend analysis. Eur Urol Oncol. 2019; 1:1-8.

7. National study shows U.S. men avoid the doctor. Available at: http://edition.cnn.com/HEALTH/men/9906/14/mens.health/ Accessed January 6, 2021.

8. Nuti SV, Wayda B, Ranasinghe I, et al. The use of google trends in health care research: A systematic review. PLoS One. 2014; 9:e109583.

9. Wessells H, Joyce GF, Wise M, Wilt TJ. Erectile dysfunction. J Urol. 2007; 177:1675-1681.

10. Shabsigh R. Socioeconomic considerations in erectile dysfunction treatment. Urol Clin North Am. 2001; 28:417-422.

11. Tan HL. Economic cost of male erectile dysfunction using a decision analytic model: For a hypothetical managed-care plan of 100 000 members. Pharmacoeconomics. 2000; 17:77-107.

12. Jena AB, Karaca-Mandic P, Weaver L, Seabury SA. Predicting new diagnoses of HIV infection using internet search engine data. Clin Infect Dis. 2013; 56:1352-1353.

13. Tijerina JD, Morrison SD, Vail DG, et al. The utility of Google trends data for analyzing public interest in breast procedures. Ann Plast Surg. 2019; 82(5S Suppl 4):S325-S331.

14. Causanilles A, Rojas Cantillano D, Emke E, et al. Comparison of phosphodiesterase type V inhibitors use in eight European cities through analysis of urban wastewater. Environ Int. 2018; 115:279-284.

15. Chiang J, Yafi FA, Dorsey PJ, Hellstrom WJG. The dangers of sexual enhancement supplements and counterfeit drugs to "treat" erectile dysfunction. Transl Androl Urol. 2017; 6:12-19.

16. Corona G, Rastrelli G, Isidori AM, et al. Erectile dysfunction and cardiovascular risk: a review of current findings. Expert Rev Cardiovasc Ther. 2020; 18:155-164.

17. Palmieri A, Silvani M, Giammusso B, et al. A "real life" investigation on the prescriptive habits among Italian andrologists: The "CONSER" survey from Italian Society of Andrology (SIA) on Sildenafil oral film. Arch Ital Urol Androl. 2019; 91:115-118.

18. Hansen SA, Aas E, Solli O. A cost-utility analysis of phosphodiesterase type 5 inhibitors in the treatment of erectile dysfunction. Eur J Heal Econ. 2020; 21:73-84.

19. Muneer A, Ralph DJ, Minhas S. Sildenafil citrate (Viagra™). J Drug Eval. 2003; 1:225-246.

20. Rubio-Aurioles E, Reyes LA, Borregales L, et al. A 6 month, prospective, observational study of PDE5 inhibitor treatment persistence and adherence in Latin American men with erectile dysfunction. Curr Med Res Opin. 2013; 29:695-706.

21. Raheem AA, Kell P. Patient preference and satisfaction in erectile dysfunction therapy: A comparison of the three phosphodiesterase-5 inhibitors sildenafil, vardenafil and tadalafil. Patient Prefer Adherence. 2009; 3:99-104.

22. Wright PJ. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. Int J Clin Pract. 2006; 60:967-975.

23. Cantrell MA, Baye J, Vouri SM. Tadalafil: A Phosphodiesterase-5 inhibitor for benign prostatic hyperplasia. Pharmacotherapy. 2013; 33:639-649.

24. Montorsi F, Brock G, Stolzenburg JU, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: A randomised placebo-controlled study (REACTT). Eur Urol. 2014; 65:587-596.

25. van Ahlen H, Zumbé J, Stauch K, Hanisch JU. The real-life safety and efficacy of Vardenafil (REALISE) study: results in men from Europe and Overseas with erectile dysfunction and cardiovascular or metabolic conditions. J Sex Med. 2010; 7:3161-3169.

26. Mulhall JP, McLaughlin TP, Harnett JP, et al. Medication utilization behavior in patients receiving phosphodiesterase type 5 inhibitors for erectile dysfunction. J Sex Med. 2005; 2:848-855.

27. Eardley I, Mirone V, Montorsi F, et al. An open-label, multicentre, randomized, crossover study comparing sildenafil citrate and tadalafil for treating erectile dysfunction in men naïve to phosphodiesterase 5 inhibitor therapy. BJU Int. 2005; 96:1323-1332.

28. Lee J, Pommerville P, Brock G, et al. Physician-rated patient preference and patient- and partner-rated preference for tadalafil or sildenafil citrate: Results from the Canadian "Treatment of Erectile Dysfunction" observational study. BJU Int. 2006; 98:623-629.

29. Maretti C, Privitera S, Arcaniolo D, et al. COVID-19 pandemic and its implications on sexual life: Recommendations from the Italian society of andrology. Arch Ital Urol Androl. 2020; 92:73-77.

30. Karagöz MA, Gül A, Borg C, et al. Influence of COVID-19 pandemic on sexuality: a cross-sectional study among couples in Turkey. Int J Impot Res. 2020 Dec 16:1-9. doi: 10.1038/s41443-020-00378-4. Epub ahead of print.

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