

## ERECTILE DYSFUNCTION

**EDEUS, a Real-Life Study on the Users of Phosphodiesterase Type 5 Inhibitors: Prevalence, Perceptions, and Health Care-Seeking Behavior Among European Men With a Focus on 2nd-Generation Avanafil**Giovanni Corona, MD, PhD,<sup>1,2</sup> Mario Maggi, MD, PhD,<sup>2</sup> and Emmanuele A. Jannini, MD<sup>3</sup>

## ABSTRACT

**Introduction:** Erectile dysfunction (ED) is a multidimensional disorder with an estimated prevalence of 1% to 10% in men younger than 40 years and up to 100% in men in their 70s and 80s.

**Aim:** To evaluate the real-life characteristics and unmet needs of men with ED, its impact on well-being, and treatment rates across Europe.

**Methods:** Adult men in Belgium, France, Germany, Italy, Poland, Portugal, and Spain were invited to participate in the survey. Men who did not use at least a drug for sexual health in the past 3 months, had cancer or spinal cord injuries, and/or underwent non-nerve-sparing radical prostatectomy were excluded.

**Main Outcome Measures:** The 15-item International Index of Erectile Function (IIEF-15) with study-specific, self-constructed questions was used.

**Results:** Overall, 940 subjects (age =  $46.2 \pm 13.4$  years) were considered. Subjects ( $n = 778$ ) using on-demand phosphodiesterase type 5 inhibitors (PDE5is) were designated “performers” (60%) without a formal ED diagnosis or “patients” with a medical diagnosis. Patients were older than performers, with more self-reported comorbidities; patients used a higher PDE5i dosage and purchased it from official pharmacies more often than performers did. Of avanafil users ( $n = 39$ ), no differences in total IIEF or subdomain scores were observed after adjusting for confounders. However, avanafil users less often declared its use without an ED diagnosis and a physician prescription. Overall, the latter condition was associated with higher PDE5i-related satisfaction.

**Conclusion:** The survey shows 2 different attitudes toward ED and PDE5i use: for recreational use and without a medical prescription or with a formal diagnosis and medical prescription. Avanafil, a 2nd-generation PDE5i with a good balance between efficacy and tolerability profile, is more frequently prescribed by doctors than self-prescribed compared with other PDE5is. Because the major challenge is to decrease the high dropout of 1st-generation PDE5is, further studies will be needed to clarify this topic. **Corona G, Maggi M, Jannini EA. EDEUS, a Real-Life Study on the Users of Phosphodiesterase Type 5 Inhibitors: Prevalence, Perceptions, and Health Care-Seeking Behavior Among European Men With a Focus on 2nd-Generation Avanafil. Sex Med 2018;6:15–23.**

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**Key Words:** Avanafil; Erectile Dysfunction; Survey; Phosphodiesterase Inhibitors

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## INTRODUCTION

Erectile dysfunction (ED) is a multidimensional disorder with an estimated prevalence ranging from 1% to 10% in men younger than 40 years and up to 100% in men in their 70s and 80s, with higher rates in the United States and Southeast Asia than in Europe.<sup>1</sup> ED is a potential predictor of cardiovascular diseases, especially in younger and less complicated individuals<sup>2–6</sup>; it negatively affects quality of life and fitness of the couple, thus further worsening ED-associated cardiovascular risk.<sup>7–10</sup> However, ED remains under-recognized, underdiagnosed, and

undertreated. In Italy in 2001, a large free-call information service on ED with more than 16,000 phone contacts showed that up to 41% of men with severe ED for more than 3 years had never sought medical help for their problems or discussed it with their general physician.<sup>11</sup>

Since 1998, when sildenafil was 1st approved by the European Medicine Agency (EMA), phosphodiesterase type 5 inhibitors (PDE5is) have revolutionized the evaluation and treatment of ED and improved awareness of the problem in the social and scientific communities.<sup>12–15</sup> 1st-generation PDE5is—sildenafil, tadalafil, and vardenafil—were effective in more than 80% of unselected patients with ED.<sup>12</sup> However, most men with ED do not consider the problem serious or are too embarrassed to consult physicians.<sup>16</sup> A large web survey of more than 5,000 subjects showed that approximately 50% of men with ED did not discuss their condition with general physicians.<sup>16</sup> Even when properly diagnosed, ED treatment and follow-up are challenging. Despite the high efficacy and easy administration of 1st-generation PDE5is, the discontinuation rate and dissatisfaction are very high. A recent meta-analysis indicated a mean discontinuation rate of 4% per month for 1st-generation PDE5is.<sup>17</sup> Furthermore, almost 50% of men stopped their treatment with sildenafil, tadalafil, or vardenafil within 1 year.<sup>17</sup> In recent years, PDE5is became popular among men without ED as a recreational drug to improve sexual performance.<sup>18</sup> This behavior could lead to serious unexpected adverse effects, especially when PDE5is are used in combination with alcohol, illicit drugs, and psychotropic medication or in the presence of concomitant medical conditions.<sup>18</sup>

Approved by the EMA in 2013, avanafil is a 2nd-generation PDE5i with similar efficacy but significantly fewer side effects compared with 1st-generation compounds.<sup>14,15</sup> A meta-analysis of randomized studies showed that avanafil was up to 3-fold superior to placebo in achieving successful sexual intercourse.<sup>14</sup> However, few data on avanafil efficacy and safety in the real-world setting are available.

This study evaluated real-life characteristics and unmet needs of men with ED, its impact on men's well-being, and rates of ED treatment per age and European country. Health care resource attitudes among men with ED were investigated.

## METHODS

### Sample and Recruitment

From November to December 2016, the Erectile Dysfunction European Users Survey (EDEUS) was conducted with the Computer Assisted Web Interviewing method in Belgium, France, Germany, Italy, Poland, Portugal, and Spain. The survey involved adults who belonged to an online market research proprietary panel on “Men's Health Condition” (<https://it.toluna.com/>). Eligible participants had to be men, older than 18 years, sexually active, and to have used drugs for sexual male health during the past 3 months. Men who had cancer, had spinal cord injuries, or underwent non-nerve-sparing radical prostatectomy were excluded.

Informed consent was obtained from each subject registered to the panel. Because of the non-interventional design of the online survey, ethical approval was not mandatory.

### Material

The 15-item International Index of Erectile Function-15 (IIEF-15)<sup>19</sup> and a set of study-specific, self-constructed questions were used to assess general health status, type and dosing of PDE5i prescribed, and treatment expectations and further needs. Questions were related to the previous 3 months. The questionnaire is available as [Supplementary File 1](#).

### Statistical Analysis

Normally distributed data were reported as mean and SD, and non-normally distributed data were expressed as median and interquartile range. According to data distribution, 1-way analysis of variance or Kruskal-Wallis test was applied to detect differences; Spearman or Pearson methods were used to estimate correlations; and unpaired 2-sided Student t-test and Mann-Whitney U-test were applied to compare groups. Multivariate analyses were performed using stepwise multiple linear or logistic regression models whenever appropriate. All statistical analysis was performed with SPSS 21.1 for Windows (SPSS, Inc, Chicago, IL, USA).

## RESULTS

### Demographic Characteristics

From an initial panel of 359,160 subjects who were mailed the survey, 30,905 started the survey. Of these, 3,315 (10.72%) did not complete it and 26,650 (86.23%) did not meet the inclusion criteria. Thus, a final population of 940 subjects was considered for this analysis ([eFigure 1](#)).

The mean age was 46.2 years (SD = 13.4), with a higher prevalence of men 35 to 54 years old ([Table 1](#)). Most subjects had mild-to-moderate or mild ED; based on IIEF results, more than 15% did not self-report ED, although they stated they were interested in ED treatment or erectile function improvement ([Table 1](#)). Dyslipidemia and hypertension were the most common associated comorbidities. Among psychological symptoms, anxiety and depression were reported by more than 20% ([Table 1](#)). Heterosexual men were the clear majority, but more than 10% were bisexual or homosexual ([Table 1](#)). Overall, 778 men (82.8%) reported the use of on-demand PDE5is. Sildenafil was the most common PDE5i used, followed by tadalafil, vardenafil, and avanafil ([Table 1](#)). To make the results more comparable, analysis was based only on subjects who reported on-demand use of PDE5i (n = 778).

### Medical Diagnosis

Of subjects who declared on-demand use of PDE5i, 40% stated they had a medical diagnosis of ED (hereafter referred to “patients”) and the remainder did not receive any formal medical

**Table 1.** Characteristics of entire sample

Total sample, N	940
On-demand PDE5i, n	778
Countries, n	
Italy	250
Germany	250
Portugal	40
France	150
Belgium	50
Spain	150
Poland	50
Age (y), mean $\pm$ SD	46.2 $\pm$ 13.4
Age groups (y), n (%)	
18–34	216 (23)
35–54	461 (50)
$\geq$ 55	254 (27)
ED categories (according to IIEF), n (%)	
Severe	77 (8.2)
Moderate	165 (17.6)
Mild to moderate	299 (31.8)
Mild	257 (27.3)
No ED	142 (15.1)
Associated comorbidities ( $>$ 1 can be present in the same patient), n (%)	
Diabetes	171 (18.2)
Increased cholesterol	280 (29.8)
Increased blood pressure	256 (27.2)
Previous diagnosis of cardiac disease	82 (8.7)
Depression	196 (20.9)
Anxiety symptoms	233 (24.8)
Renal diseases	36 (3.8)
Hepatic diseases	32 (3.4)
Sexual orientation, n (%)	
Heterosexual	818 (87)
Bisexual	66 (7)
Homosexual	47 (5)
Not answer	9 (1)
PDE5i used most often in past month (single answer), n (%)	
Sildenafil	404 (43)
Tadalafil on demand	244 (26)
Tadalafil once daily	141 (15)
Vardenafil	103 (11)
Avanafil	38 (4)
Other	10 (1)

ED = erectile dysfunction; IIEF = International Index of Erectile Function; PDE5i = phosphodiesterase type 5 inhibitor.

ED diagnosis (hereafter referred to “performers”): 49% of these subjects had self-diagnosed ED and 11% did not consider themselves affected by ED (Table 2). Patients were older than other men ( $49.2 \pm 13.7$  vs  $46.3 \pm 13.4$  years;  $P = .004$ ), whereas no differences were observed between subjects with a self-diagnosis or without ED diagnosis (not shown). A higher prevalence of diabetes mellitus was reported by patients ( $n = 73$

of 309) than by performers ( $n = 81$  of 469; 23.6% vs 17.3%;  $P = .03$ ). This association was confirmed after adjusting for age (hazard ratio = 1.51, 95% CI = 1.06–2.16,  $P = .024$ ). No statistically significant differences were reported for other comorbidities (data not shown).

Patients rarely declared on-demand use of PDE5i at the lowest dosing compared with performers; they used the PDE5i as prescribed by physicians or other qualified health care practitioners and more frequently purchased drugs in an official pharmacy (Table 2). Performers mainly used the PDE5i as a recreational drug and rarely to improve erection quality or to gratify their partner; they reported self-prescription of drugs and purchased them in official pharmacies less frequently than patients (Table 2). Subjects who received a PDE5i prescription from physicians or other qualified health care practitioners were more often satisfied or highly satisfied with treatment (66.7 vs 58.3%;  $P = .027$ ).

The main differences between patients and performers were confirmed in a multivariate model after adjusting for age and diabetes (Figure 1A). Similar results were observed when countries were introduced to the model as possible confounders (not shown).

### Drug Dosage Use

Standard recommended dosages of PDE5i were used by 55% of men ( $n = 430$ ), the lowest dosage was used by 25% ( $n = 191$ ), and the highest dosage was used by 20% ( $n = 157$ ; Table 3). Subjects who used the highest dosage were older ( $52.1 \pm 14.0$  vs  $46.3 \pm 13.3$  years;  $P = .003$ ) and with a longer duration of ED and PDE5i use ( $5.4 \pm 4.7$  vs  $4.2 \pm 4.5$  years,  $P = .008$ ;  $4.1 \pm 3.1$  vs  $3.2 \pm 3.0$  years,  $P < .0001$ , respectively). The prevalence of comorbidities was similar among groups (not shown).

Concerning the reason for the use of PDE5i, subjects who used the standard recommended dosage felt more relaxed during sexual intercourse, whereas subjects who used the highest dosage more often wanted to gratify their partner (Table 3). A larger percentage of subjects using the lowest PDE5i dosage reported recreational use of drugs, without statistical differences among groups (Table 3).

Subjects who used the highest dosage more often reported having a medical prescription and purchasing them in an official pharmacy (Table 3), whereas those using the lowest dosage more often reported a self-prescription and a PDE5i purchase from online pharmacies (Table 3).

In a multivariate analysis, after adjusting for age, use of the PDE5i at the highest dosage was still associated with a medical prescription and with a purchase from official pharmacies (Figure 1B). Similar results were observed when countries were introduced to the model as possible further confounders (not shown).

**Table 2.** Analysis for drug dosage, reason for taking PDE5i, advice to take PDE5i, and place used to buy PDE5i by diagnosis groups\*

Question	Category	Diagnosis groups (N = 778), n (%)		
		No (n = 88)	No, but I have some problems (n = 381)	Yes (n = 309)
Age (y), mean ± SD		46.9 ± 14.4	46.2 ± 13.2	49.2 ± 13.7
Drug dosage	Low	26 (29.5) <sup>†</sup>	115 (30.2) <sup>§</sup>	50 (16.2)
	Standard	45 (51.1)	207 (54.3)	178 (57.6)
	High	17 (19.3)	59 (15.5) <sup>‡</sup>	81 (26.2)
Reason for taking PDE5i	To improve strength and hardness of erection	35 (39.8) <sup>§</sup>	210 (55.1) <sup>‡,  </sup>	202 (65.4)
	To be more sure of myself	34 (38.6) <sup>†</sup>	200 (52.5) <sup>  </sup>	156 (50.5)
	To gratify my partner	27 (30.7) <sup>‡</sup>	165 (43.3) <sup>‡,  </sup>	165 (53.4)
	To feel more relaxed with my performance	33 (37.5)	144 (37.8)	125 (40.5)
	To prevent performance anxiety	17 (19.3) <sup>†</sup>	130 (34.1) <sup>  </sup>	94 (30.4)
	From curiosity; to try	9 (10.2) <sup>†</sup>	36 (9.4) <sup>‡</sup>	9 (2.9)
Who decided to take or advised taking PDE5i	Physician	37 (42.0) <sup>§</sup>	204 (53.5) <sup>§</sup>	278 (90.0)
	Myself	35 (39.8) <sup>§</sup>	112 (29.4) <sup>§</sup>	17 (5.5)
	Pharmacist	8 (9.1) <sup>†</sup>	38 (10.0) <sup>§</sup>	7 (2.3)
	Partner	5 (5.7)	24 (6.3) <sup>†</sup>	7 (2.3)
Place usually used to buy PDE5i	Pharmacy	65 (73.9) <sup>‡</sup>	289 (75.9) <sup>§</sup>	274 (88.7)
	Online pharmacy headquartered in my country	13 (14.8)	67 (17.6) <sup>†</sup>	34 (11.0)
	Online pharmacy headquartered abroad	9 (10.2)	36 (9.4)	19 (6.1)
	Other (sex shop, disco, etc)	2 (2.3)	8 (2.1)	2 (0.6)

PDE5i = phosphodiesterase type 5 inhibitor.

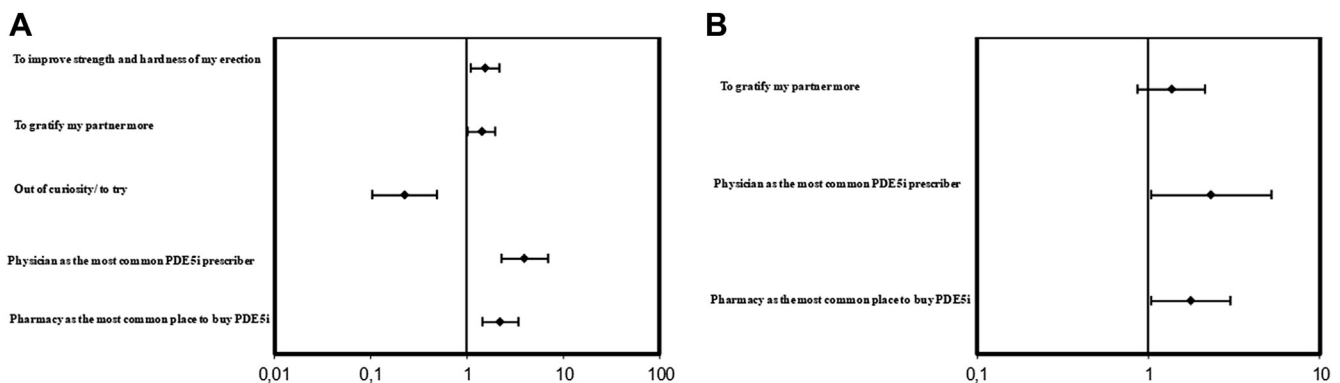
\*1-way analysis of variance or Kruskal-Wallis test was applied to detect differences.

<sup>†</sup> $P < .05$ ; <sup>‡</sup> $P < .0005$ ; <sup>§</sup> $P < .0001$  vs yes; <sup>||</sup> $P < .05$  vs no.

### 1st- and 2nd-Generation PDE5i Users

Of subjects reporting on-demand use of PDE5is, 39 declared using avanafil. Individuals using avanafil were similar to those who used the 1st-generation drugs in age, ED duration, and prevalence of comorbidities (Table 4). No difference between avanafil and other PDE5i users were observed when considering drug dosage group or reason for taking PDE5i (Table 4). Subjects using avanafil rarely declared its use without an ED problem and more often had a prescription from physicians (Table 4).

The overall IIEF-15 score was similar in subjects who used avanafil or other PDE5is ( $63.4 \pm 17.0$  vs  $79.9 \pm 9.7$ ;  $P = .45$ ). Avanafil was more frequently prescribed to subjects with severe ED than other PDE5is (30.8% vs 7.0%;  $P < .0001$ ). Subjects using avanafil reported a lower IIEF-EF score ( $16.0 \pm 7.2$  vs  $19.8 \pm 5.8$ ;  $P < .0001$ ). This difference was not confirmed when subjects with severe ED were excluded (IIEF-EF score =  $20.0 \pm 4.4$  vs  $20.7 \pm 4.6$ ;  $P =$  not significant; Figure 2). No differences in other IIEF subdomains between subjects who used avanafil or other PDE5is were observed (Figure 2).



**Figure 1.** Panel A shows age- and self-reported diabetes-adjusted associations between subjects who received a formal medical diagnosis of erectile dysfunction vs the rest of the sample. Panel B shows age-adjusted associations between subjects using the highest PDE5i recommended dosage vs those using the lowest recommended dosage. PDE5i = phosphodiesterase type 5 inhibitor.

**Table 3.** Analysis for reason for taking PDE5i, advice to take PDE5i, and place used to buy PDE5i by drug dosage groups\*

Question	Category	Drug dosage groups (N = 778), n (%)		
		High (n = 157)	Standard (n = 430)	Low (n = 191)
Age (y), mean ± SD		52.1 ± 14.0	47.1 ± 12.9	44.5 ± 13.9
Reason for taking PDE5i	To improve strength and hardness of erection	97 (61.8)	248 (57.7)	102 (53.4)
	To be more sure of myself	80 (51.0)	225 (52.3)	85 (44.5)
	To gratify my partner	82 (52.2) <sup>†</sup>	200 (46.5)	75 (39.3)
	To feel more relaxed with my performance	51 (32.5)	186 (43.3) <sup>†,  </sup>	65 (34.0)
	To prevent performance anxiety	49 (31.2)	139 (32.3)	53 (27.7)
Who decided to take or advised taking PDE5i	From curiosity, to try	6 (3.8)	31 (7.2)	17 (8.9)
	Physician	118 (75.2) <sup>§</sup>	300 (69.8) <sup>§</sup>	101 (52.9)
	Myself	26 (16.6) <sup>‡</sup>	76 (17.7) <sup>§</sup>	62 (32.5)
	Pharmacist	6 (3.8) <sup>‡</sup>	29 (6.7)	18 (9.4)
	Partner	5 (3.2)	22 (5.1)	9 (4.7)
Place usually used to buy PDE5i	Pharmacy	129 (82.2) <sup>‡</sup>	364 (84.7) <sup>§</sup>	135 (70.7)
	Online pharmacy headquartered in my country	22 (14.0)	53 (12.3) <sup>‡</sup>	39 (20.4)
	Online pharmacy headquartered abroad	16 (10.2)	30 (7.0)	18 (9.4)
	Other (sex shop, disco, etc)	3 (1.9)	5 (1.2)	4 (2.1)

PDE5i = phosphodiesterase type 5 inhibitor.

\*1-way analysis of variance or Kruskal-Wallis test was applied to detect differences.

<sup>†</sup>*P* < .05; <sup>‡</sup>*P* < .0005; <sup>§</sup>*P* < .0001 vs low; <sup>||</sup>*P* < .05 vs high.

Of avanafil users, 20 (51.3%) stated they were satisfied or highly satisfied; this percentage was similar to that reported by subjects using the 1st-generation PDE5is (67.5%; *P* = .93). Data were not adequately powered to compare the prevalence of satisfied patients between avanafil users who did and did not receive a medical prescription.

## DISCUSSION

This real-life internet-based study described the perception of ED as a medical symptom, the ability to discuss the problem with physicians, and the aims in using these drugs in European users. We distinguished 2 subgroups of PDE5i users: subjects seeking a medical diagnosis (patients) and a large percentage of users who did not receive a diagnosis or did not consider themselves affected by ED (performers). The profile of each subgroup is peculiar. Patients were older, with more self-reported organic comorbidities or etiologies, and they were more likely to purchase drugs in official pharmacies than performers. Patients used these drugs mainly to improve erections and their partner's sexual life, whereas performers tried PDE5is for recreational use and often purchased them online.

Since the National Institutes of Health Consensus Conference on Impotence in 1992,<sup>20</sup> the inadequate public and professional understanding of ED started being addressed. However, although numerous patient-oriented campaigns during the past 20 years have stressed the importance of considering ED a

medical symptom,<sup>11,21,22</sup> a relatively large percentage of subjects with an erectile concern (ie, performers) have not been interested in seeking a medical and/or psycho-sexological diagnosis and a medical prescription for these drugs. A survey involving 750 Mexican men with ED showed that only approximately half of them sought treatment for this problem, which was more frequently an alternative treatment than a pharmacologic approach,<sup>23</sup> although alternative treatments were surely less effective than PDE5is.<sup>24</sup> A study of 1,481 Dutch men indicated that 67.3% were bothered by ED, 68.7% did not acknowledge ED, and 85.3% sought help for ED. However, only 10.4% of men with ED received medical care.<sup>25</sup> Of 5,184 European men who self-reported ED, more than 50% did not discuss their condition with physicians, regardless of age.<sup>16</sup> Therefore, high barriers to discuss ED, erectile failures, or simply erectile concerns are still present in a large part of the male population.

As we previously observed in another setting,<sup>16</sup> we found that patients were significantly older than performers, thus suggesting that younger men are culturally less prone than older men to acknowledge ED or an erectile concern as a medical symptom. Main reasons for a delayed or null consultation included embarrassment,<sup>26</sup> social stigma,<sup>27</sup> and, very likely, dissatisfaction with the relationship with physicians and their ability to deal with sexual health.<sup>16</sup> Alexithymia could be considered another possible factor explaining the latter point.<sup>28</sup>

Performers bought these drugs less frequently in official pharmacies than patients, with a high risk of buying fake PDE5is.

**Table 4.** Analysis for diagnosis, drug dosage, reason for taking PDE5i, advice to take PDE5i, and place used to buy PDE5i by avanafil users\*

		Avanafil user groups (N = 778), n (%)	
		No (n = 739)	Yes (n = 39)
Age (y), mean ± SD		47.4 ± 13.6	49.2 ± 14
ED duration (y)			
Associated morbidities, %			
Diabetes		19.2	30.8
Elevated cholesterol		25.6	32.2
Elevated blood pressure		29.8	28.2
Previous diagnosis of cardiac diseases		8.7	17.9
Depression		22.3	28.2
Anxiety symptoms		27.6	25.6
Renal diseases		3.7	0.0
Hepatic diseases		3.4	2.6
Question	Category		
Diagnosis	No	86 (11.6)	2 (5.1)
	No, but I have some problems	371 (50.2) <sup>†</sup>	10 (25.6)
	Yes	282 (38.2) <sup>‡</sup>	27 (69.2)
Drug dosage	Low	179 (24.2)	12 (30.8)
	Standard	413 (55.9)	17 (43.6)
	High	147 (19.9)	10 (25.6)
Reason for taking PDE5i	To improve strength and hardness of erection	423 (57.2)	24 (61.5)
	To be more sure of myself	370 (50.1)	20 (51.3)
	To gratify my partner	341 (46.1)	16 (41.0)
	To feel more relaxed with my performance	286 (38.7)	16 (41.0)
	To prevent performance anxiety	229 (31.0)	12 (30.8)
	From curiosity, to try	52 (7.0)	2 (5.1)
Who decided to take or advised taking PDE5i	Physician	485 (65.6) <sup>†</sup>	34 (87.2)
	Myself	160 (21.7)	4 (10.3)
	Pharmacist	52 (7.0)	1 (2.6)
	Partner	36 (4.9)	0 (0.0)
Place usually used to buy PDE5i	Pharmacy	594 (80.4)	34 (87.2)
	Online pharmacy headquartered in my country	109 (14.7)	5 (12.8)
	Online pharmacy headquartered abroad	62 (8.4)	2 (5.1)
	Other (sex shop, disco, etc)	12 (1.6)	0 (0.0)

ED = erectile dysfunction; PDE5i = phosphodiesterase type 5 inhibitor.

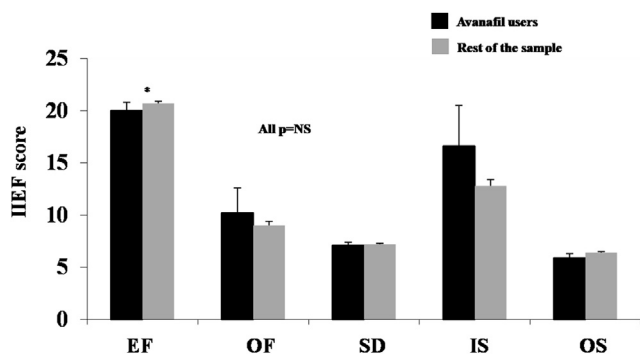
\*1-way analysis of variance or Kruskal-Wallis test was applied to detect differences.

<sup>†</sup> $P < .05$ ; <sup>‡</sup> $P < .0001$  vs rest of sample.

Driven by embarrassment or the desire for cheaper alternatives, performers are often unaware they might be using fake products, thus taking unnecessary health risks.<sup>29</sup> Subjects who bypass doctors often lose the opportunity to have not only ED but also other comorbidities diagnosed; therefore, in this view, impotent patients are paradoxically “lucky” for the unique chance to face the ED-associated comorbidities.<sup>30</sup> Our results are in line with a European survey estimating that in Europe approximately 6 million men bypass the health care system to obtain a PDE5i.<sup>31</sup> It is crucial to discriminate how many performers have a subclinical form of ED and how many truly sexually healthy subjects use PDE5is recreationally to increase sexual performance.<sup>32,33</sup>

Real-life experience seems to contradict the previous assumption that PDE5is cannot improve erectile performance in subjects with normal erection.<sup>34</sup> Several studies have reported on the use of PDE5i in young healthy men (mostly college students) without any medical indication.<sup>18,35</sup> Our European data confirm the observation recently reported in Saudi Arabia, where 61.9% of 370 PDE5i users were recreational performers and 31.8% were patients with ED.<sup>36</sup>

Another interesting finding in our survey is that the highest doses of on-demand PDE5i (avanafil 200 mg, sildenafil 100 mg, tadalafil and vardenafil 20 mg) are much more frequently



**Figure 2.** Differences in International Index of Erectile Dysfunction subdomain scores between avanafil users and non-users. \*After excluding subjects with severe erectile dysfunction. EF = erectile function; IS = intercourse satisfaction; OF = orgasmic function; OS = overall satisfaction; SD = sexual desire.

prescribed by physicians and obtained from an official pharmacy. This can be explained by our additional evidence that the patients were not only older but also had more comorbidities than performers. Furthermore, physicians are more aware of the risks and side effects of PDE5i than users and usually try to minimize the risk of PDE5i failure from underdosing with consequent depression. The expectation is that PDE5is might produce negative effects on men's mood after treatment failure at lower doses. When patients are not satisfied because treatment did not work, the distress is particularly severe.<sup>37</sup> In the clinical setting, this situation induces physicians to start treatment at the highest available doses and then eventually to down-titrate the prescription; in this way, bona fide, psychological, relational, and social consequences of PDE5i failure from underdosing are limited. When the highest doses are prescribed, the first choice should favor the drug with the best ratio of efficacy to side effects.

The last point raised by our data concerns the subgroup of subjects using avanafil, the unique 2nd-generation PDE5i approved in Europe.<sup>38</sup> This drug, characterized by a good balance between efficacy and tolerability profile,<sup>39</sup> is much more frequently prescribed by doctors than self-prescribed compared with other PDE5is. This could suggest that there is still much less awareness of the “users” on the availability of avanafil,<sup>14</sup> likely because avanafil is the most recently marketed PDE5i. Its “personality” as a “no worry drug” (no worry about efficacy,<sup>40,41</sup> no worry about time of onset,<sup>42</sup> no worry about safety<sup>14</sup>) is still unknown to most people compared with the famous “blue pill” (sildenafil) or the “weekend pill” (tadalafil). In the survey, patients using avanafil had significantly more severe ED than patients using other PDE5is; this could explain why the avanafil group reported a significantly lower IIEF-EF score compared with other subjects.

The overall satisfaction with PDE5is was not high (~50%). Very interestingly, this percentage was similar among the 4 PDE5is. This reflects the high discontinuation rate of this class of drug,<sup>17,43</sup> demonstrating that there is still a need for a new taxonomy and a renewed multidisciplinary approach to ED and subclinical ED and

the psychological need of a pharmacologic sexual aid (the “users”), which deserve social and medical attention.<sup>44</sup> Accordingly, the PDE5i-related satisfaction was higher when drugs were prescribed by a physician. Previous studies have clearly documented that a specific tailored therapy and adequate counseling can convert 30% to 50% of the initial PDE5i non-responders to responders<sup>43–46</sup> when offering a holistic, systemic approach to the dysfunction.<sup>47</sup>

The study has some limitations. In the analysis, we considered only subjects who had on-demand use of PDE5i to make the results more comparable and provide a picture of real-life attitudes toward ED among European men; thus, we might have lost important information from subjects who had long-term use and were potentially more likely followed by physicians. Only 5% of participants declared using a 2nd-generation PDE5i; further larger studies are required to confirm our preliminary findings. Although the initial survey was started by more than 30,905 subjects, only a limited number satisfied the inclusion criteria. Hence, selection bias might have influenced our results and they cannot be immediately extended to the general population. Further, the arbitrary division of subjects using PDE5i as patients and performers cannot be generalized because there might have been some overlap between these groups.

## CONCLUSION

The present survey indicates that there are 2 different attitudes toward ED and PDE5i use: the performers' use of PDE5is mainly for recreational use and without a medical prescription and the patients' use is with a formal ED diagnosis and a medical prescription. No differences in efficacy were observed when the 1st generation of PDE5is was compared with the 2nd generation. Avanafil represents a 2nd generation of PDE5i with the highest tolerability profile; in this study, avanafil users were much more frequently prescribed by doctors than self-prescribed. Overall, PDE5i satisfaction was higher in patients who were prescribed by a physician. Further studies would be advisable to better clarify whether the 2nd generation of PDE5is could decrease the high discontinuation rate reported with the 1st generation of PDE5is.

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## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.esxm.2017.10.003>.