ERECTILE DYSFUNCTION

Influence of Alcohol on Phosphodiesterase 5 inhibitors Use in Middle- to Old-Aged Men: A Comparative Study of Adverse Events

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ABSTRACT

Introduction: Some previous studies reported recreational use of phosphodiesterase type 5 (PDE-5) inhibitors by ingesting the medicine with alcohol in patients with erectile dysfunction, but the rate of misuse in general population has never been researched.

Aim: To investigate the frequency of concomitant alcohol consumption with PDE-5 inhibitors in the general male population. We secondarily analyzed the influence of alcohol on PDE-5 inhibitor.

Methods: 325 men with erectile dysfunction (age 34−78) who received PDE-5 inhibitors at a single medical institution from January 2016−February 2018 were included in the study. All patients fulfilled a survey questionnaire assessing (i) average alcohol consumption amount, (ii) previous use of PDE-5 inhibitors with alcohol and purpose of concomitant alcohol use, (iii) and background knowledge about PDE-5 inhibitors' side effects.

Main Outcomes Measures: The main outcome measure was frequency of concomitant alcohol consumption with PDE-5 inhibitors in the general male population.

Results: Overall 148 patients committed concomitant alcohol use (group 1), and 177 patients did not (group 2). No significant differences were observed between 2 groups regarding types of PDE-5 inhibitors used and underlying disease. Group 2 had significantly more patients with the correct knowledge concerning concomitant alcohol use than group 1 (24.9% vs 13.5%). Group 1 had more patients with average alcohol consumption >15 drinks/week (64.8% vs 14.1%). The reasons for concomitant alcohol use were curiosity (35.1%), enhancing sexual desire (27%) and recommendation from friends (16.9%). Group 1 showed significantly greater complications, including headache (23.6% vs 7.3%) and facial flushing (69.6% vs 12.4%), than group 2. 1 patient in group 1 experienced severe chest discomfort and underwent coronary artery angiography, but no severe obstructive lesion was observed.

Conclusion: 45.5% of middle- to old-age men committed concomitant use of PDE-5 inhibitor with alcohol because of recreational purpose, and this alcohol abuse might lead to severe complications, including chest discomfort and dizziness. **Kim JN, Oh JJ, Park DS, et al. Influence of Alcohol on Phosphodiesterase 5 inhibitors Use in Middle- to Old-Aged Men: A Comparative Study of Adverse Events. Sex Med 2019;7:425−432.**

Key Words: Erectile Dysfunction; Phosphodiesterase Inhibitors; Alcohol

INTRODUCTION

Erectile dysfunction (ED) is a highly prevalent clinical condition affecting approximately 20−40% of men 60−70 years of age, although the rate is variable depending on how ED is defined.[1] Since the introduction of the first oral phosphodiesterase type 5 (PDE-5) enzyme inhibitor, sildenafil citrate in 1997, many analogues of the agent have been developed, and currently, 7 PDE-5 enzyme inhibitors are available for treatment of ED, including sildenafil, tadalafil, vardenafil, avanafil,

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udenafil, mirodenafil, and lodenafil.[2–4] Recently, the use of PDE-5 inhibitors has become common among some men with ED or even men with normal erectile function to enhance their sexual desire and satisfaction.[5–7] Moreover, administration of PDE-5 inhibitors with alcohol for recreational purposes has been continuously reported worldwide.[8,9]Alcohol intake decreases blood pressure (BP) by causing vasodilation as it increases the production of nitric oxide from the endothelium, which results in a subsequent decrease in vascular smooth muscle tone.[10,11] Although PDE-5 is predominantly found in the penile corpora cavernosa and lungs, it still can be expressed in the major systemic vessels. Furthermore, the inhibition of PDE-5 results in smooth muscle relaxation in the corpora cavernosa, as well as in the systemic vasculature, inducing subsequent vasodilation and decrease in BP.[12–14] Thus, concomitant administration of PDE-5 inhibitor and alcohol may possibly induce clinically significant hemodynamic complications by further decreasing BP.[13,15] Although some previous studies have evaluated the impact of PDE-5 inhibitor intake in combination with alcohol,[15–17] there are no studies on the evaluation of the rate of concomitant use of alcohol and PDE-5 inhibitors among the general population. Therefore, this study primarily investigated the frequency of alcohol consumption concomitant with PDE-5 inhibitors in middle- to old-aged men. This study additionally analyzed the influence of alcohol on PDE-5 inhibitors by comparing patients who showed a combined use of alcohol and PDE-5 inhibitor with those who did not.

MATERIAL AND METHODS

This study was a single-center retrospective survey based comparative study of ED patients who underwent PDE-5 inhibitor therapy for the treatment of mild to moderate grade ED from January 2016—February 2018. After obtaining approval of the study from the Institutional Review Board (2019-01-15), written informed consent concerning permission to use of the medical records was obtained from all patients included in the study. All study procedures, including clinical data collection and management, were performed in accordance with the relevant guidelines and regulations. The cohorts included in the study were 325 male subjects with ED (age 34—78) who received PDE-5 inhibitors at the urology outpatient clinic of a single medical institution. The patients who received low-dose PDE-5 inhibitors, such as tadalafil 5 mg, for the purpose of treating urinary symptoms or other systemic symptoms were not included in the study. The clinical records of the patients were reviewed and their underlying medical conditions including age, previous disease history, BMI, and types of PDE-5 inhibitors used were evaluated. All patients filled out a survey questionnaire with open and multiple-choice questions during their visit to the outpatient clinic. The questionnaire consisted of 6 domains, assessing (i) individual medical history, (ii) previous use of PDE-5 inhibitors, (iii) average alcohol consumption per week, (iv) previous use of PDE-5 inhibitors with alcohol and purpose of concomitant alcohol use/types of adverse events experienced when PDE-5 inhibitors were taken simultaneously with alcohol, (v) background knowledge about PDE-5 inhibitors' side effects and previous warning from urologists concerning usage and adverse events of PDE-5 inhibitors, and (vi) experience of PDE-5 inhibitor overdose according to patient's own will. The simplified International Index of Erectile Function (IIEF-5) was also used for evaluating patient's potency and the cohorts with IIEF-5 scores $\leq$21 were categorized as ED patients. This study defined concomitant use of alcohol with PDE-5 inhibitors as simultaneous ingestion of PDE-5 inhibitors with alcohol for certain purposes.

For statistical evaluation, the patients were classified into 2 groups depending on the concomitant use of alcohol with PDE-5 inhibitors. Means and SDs were incorporated for reporting continuous variables, and proportions were used for categorical variables. Moreover, a 1:1 propensity score matching analysis using nearest neighbor matching method with a maximum caliber of 0.02 was undertaken to increase the validity of statistical analysis by minimizing the effects of lacking randomization. The propensity score was derived from clinical factors including age, BMI, IIEF-5 scores, and underlying disease of the patients. All statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL, USA), and $P \leq .05$ were considered statistically significant. The Student *t*-test and the Mann-Whitney tests were performed to compare the clinical factors (continuous variables) of the 2 study groups.

RESULTS

A total of 325 patients were included in the study as all of the patients completely filled all questions listed in the questionnaire. Among them, 148 patients (45.5%) committed concomitant use of alcohol with PDE-5 inhibitors, whereas the other 177 patients (54.5%) did not undergo concomitant alcohol use. Moreover, no patient in both groups ever used other types of ED treatment medications, such as intracavernous alprostadil injection. Table 1 presents the basic characteristics of the patients. Before propensity matching, the mean age of the overall study cohort was 56.2 years and the concomitant alcohol use group had 54.3 years, which was slightly younger than 57.7 years of the non-alcohol use group ($P = .038$). In terms of types of PDE-5 inhibitors used and the prevalence of underlying disease, no significant differences were observed between the 2 groups. The non-alcohol use group had a significantly higher mean total IIEF-5 score than the concomitant alcohol use group (19.71 vs. 15.93, $P = .036$). Among the alcohol use group, only 20 (13.5%) patients were correctly aware of the hazards of concomitant alcohol use with PDE-5 inhibitors, whereas 44 (24.9%) patients correctly knew the side effects in the non-alcohol use group ($P < .001$). However, both groups had high percentage of the patients, who were lack of the knowledge

Table 1. Baseline characteristics

	Before adjustment			After adjustment		
	Group1 (Concomitant use of alcohol)	Group 2 (No concomitant use of alcohol)	*P* value	Group1 (Concomitant use of alcohol)	Group 2 (No concomitant use of alcohol)	*P* value
No. of patients	148	177		90	90	
Age (y), mean ± SD (range)	54.3 ± 10.1 (34–77)	57.7 ± 8.4 (40–78)	.038	56.8 ± 9.5 (37–77)	57.2 ± 9.3 (40–76)	.089
BMI (kg/m^2), mean ± SD	25.2 ± 3.1	24.9 ± 3.7	.054	25.3 ± 2.9	25.0 ± 3.5	.075
IIEF-5 questionnaire						
Total mean IIEF-5 score, mean ± SD	15.93 ± 2.60	19.71 ± 1.54	.036	16.80 ± 3.46	17.13 ± 1.83	.060
Maintenance ability	3.34 ± 0.59	4.35 ± 0.22		3.58 ± 0.61	3.85 ± 0.26	
Maintenance frequency	3.40 ± 0.33	4.28 ± 0.25		3.39 ± 0.45	3.11 ± 0.32	
Erection confidence	3.81 ± 1.01	3.64 ± 0.31		3.55 ± 1.13	3.49 ± 0.30	
Erection firmness	2.23 ± 0.27	3.70 ± 0.39		3.42 ± 0.51	3.17 ± 0.44	
Intercourse satisfaction	2.15 ± 0.40	3.74 ± 0.37		2.86 ± 0.76	3.51 ± 0.51	
Types of PDE-5 inhibitor used, n (%)			.937			.843
Sildenafil 100 mg	65 (43.9)	76 (42.9)		38 (42.2)	38 (42.2)	
Tadalafil 20 mg	56 (37.8)	67 (37.9)		33 (36.7)	31 (34.4)	
Udenafil 100 mg	12 (8.1)	15 (8.5)		8 (8.9)	10 (11.1)	
Mirodenafil 50 mg	15 (10.1)	19 (10.7)		11 (12.2)	11 (12.2)	
Underlying disease, n (%)	79 (53.4)	98 (55.3)	.152	47 (52.2)	49 (54.4)	.716
Hypertension	45 (30.4)	57 (32.2)		22 (24.4)	22 (24.4)	
DM	55 (37.2)	60 (33.9)		31 (34.4)	32 (35.6)	
CAOD	15 (10.1)	21 (11.9)		10 (11.1)	11 (12.2)	
Stroke	18 (12.2)	19 (10.7)		10 (11.1)	10 (11.1)	
Hyperlipidemia	38 (25.7)	46 (26.0)		23 (25.6)	22 (24.4)	
Intake of nitrates	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Intake of SSRI	4 (2.7)	5 (2.8)		2 (2.2)	3 (3.3)	
Prostatectomy	25 (16.9)	30 (16.9)		15 (16.7)	15 (16.7)	
Active cancer	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
BPH	48 (32.4)	59 (33.3)		0 (0.0)	0 (0.0)	
TUR-P	28 (18.9)	34 (19.2)		17 (18.9)	18 (20.0)	
Medications for underlying disease, n (%)			.528			.890
Irbesartan	21 (14.2)	31 (17.5)		14 (15.6)	16 (17.8)	
Valsartan	23 (15.5)	33 (18.6)		15 (16.7)	17 (18.9)	
Amlodipine	5 (3.4)	4 (8.8)		3 (3.3)	3 (3.3)	
Metformin	55 (37.2)	60 (33.9)		29 (32.2)	31 (34.4)	
Sitagliptin	32 (21.6)	37 (20.9)		16 (17.8)	18 (20.0)	
Glimepiride	2 (1.4)	5 (1.7)		2 (2.2)	3 (3.3)	
Diltiazem	6 (4.1)	9 (5.1)		3 (3.3)	4 (4.4)	
Aspirin	33 (22.3)	41 (23.2)		19 (21.1)	19 (21.1)	

(continued)

Table 1. Continued

	Before adjustment			After adjustment		
	Group1 (Concomitant use of alcohol)	Group 2 (No concomitant use of alcohol)	*P* value	Group1 (Concomitant use of alcohol)	Group 2 (No concomitant use of alcohol)	*P* value
Clopidogrel	16 (10.8)	20 (11.3)		8 (8.90	10 (11.1)	
Escitalopram	1 (0.7)	1 (0.6)		1 (1.1)	1 (1.1)	
Tamsulosin	19 (12.8)	20 (11.3)		12 (13.3)	12 (13.3)	
Alfuzosin	20 (13.5)	25 (14.1)		14 (15.6)	15 (15.6)	
Silodosin	6 (4.0)	7 (3.9)		4 (4.4)	5 (5.5)	
Terazosin	3 (2.0)	7 (3.9)		3 (3.3)	3 (3.3)	
Aware of the hazards for concomitant alcohol use			<.001			<.001
Correctly aware	20 (13.5)	44 (24.9)		14 (15.6)	23 (25.6)	
Incorrectly aware	3 (2.0)	19 (10.7)		2 (2.2)	10 (11.1)	
Not aware	125 (84.5)	114 (64.4)		74 (82.2)	57 (63.3)	

BPH = benign prostatic hyperplasia; CAOD = coronary artery obstructive disease; DM = diabetes mellitus; IIEF = International Index of Erectile Function; PDE-5 = phosphodiesterase; SSRI = selective serotonin reuptake inhibitor; TUR-P = transurethral resection of prostate.

regarding the side effects induced by concomitant intake of alcohol and PDE-5 inhibitors (alcohol use group: 82.2%, non-alcohol use group: 63.3%).

Table 2 shows the alcohol and PDE-5 inhibitor consumption patterns of the entire cohort. In terms of average alcohol consumption per week, the concomitant alcohol use group had a higher percentage of patients (64.8%) consuming >15 drinks of alcohol per week, compared with the non-alcohol use group (14.1%). Moreover, 6.8% of the non-alcohol use patients do not consume even a single drink of alcohol per week. Among the concomitant alcohol use group, 10.9% of the patients committed a voluntary overdose of PDE-5 inhibitor according to the patients' own decision, whereas no patient underwent a voluntary overdose in the non-alcohol use group.

The main reasons of consuming alcohol concomitantly with PDE-5 inhibitors are listed in Table 3. Among those reasons, patients' curiosity was the most commonly cited reason (35.1%). Furthermore, 27.0% of the patients committed alcohol abuse for pure recreational purpose, which was to enhance sexual desire. Among the patients using PDE-5 inhibitors incorrectly, 10.9% of them committed concomitant alcohol use with PDE-5 inhibitors nearly every occasion.

Regarding the adverse effects of using PDE-5 inhibitors, the concomitant alcohol use group showed a significantly higher percentage of facial flushing and headaches than the non-alcohol users (facial flushing: 69.6% vs 12.4%; headache: 23.6% vs 7.3%) (Table 4). Furthermore, some patients in the alcohol use group experienced skin rash (0.7%), chest discomfort (2.0%), dizziness (2.0%) and altered vision (3.4%), while no patient in the non-alcohol using group experienced the corresponding adverse events (Table 4). Among the 3 patients who had chest pain after concomitant use of alcohol with PDE-5 inhibitors, 1 patient presented with severe chest pain, which lasted >10 minutes with a significant elevation of ST-segment in electrocardiogram. Consequently, the patient underwent cardioangiography, but no significant narrowing of the coronary vessels was observed. Moreover, the dizziness experienced by patients had a symptomatic duration ≤30 minutes, and 1 of the patients had transient amnesia-like confusion, which only lasted for a brief time (<5 minutes). For the post-propensity matching evaluations, the concomitant alcohol use group showed an overall adverse event rate of 100%, indicating that all concomitant alcohol users experienced ≥1 type of complications after taking PDE-5 inhibitors. In addition, all of these alcohol users, who experienced facial flushing or headache after concomitant ingestion of alcohol and PDE-5 inhibitors, described that the nature of these adverse symptoms was significantly more intense with rapid onset than the side effects produced by drinking alcoholic beverages only. These alcohol users also reported that they occasionally experienced only mild facial flushing and headache, which appeared with slow and gradual onset, when they ingested alcohol. For other PDE-5 inhibitor related adverse

Table 2. Behavioral characteristics of patients

	No. of patients (%)	
	Concomitant alcohol user	Non-concomitant alcohol user
Average alcohol consumption per week		
0	0 (0.0)	12 (6.8)
1–5	13 (8.8)	64 (36.1)
6–10	17 (11.5)	41 (23.2)
10–15	22 (14.9)	35 (19.8)
>15	96 (64.8)	25 (14.1)
Total	148 (100.0)	177 (100.0)
Experience of not following prescription dose (overdose)		
Yes	16 (10.9)	0 (0.0)
No	132 (89.1)	177 (100.0)
Table	148 (100.0)	177 (100.0)

1 drink = 1/2 pint of beer or 1 glass of wine or 1 single spirits.

events, including altered vision and nasal congestion, the patients of the alcohol abusing group described that they had never experienced these types of symptoms when they drank only alcoholic beverages, not with PDE-5 inhibitors.

DISCUSSION

The PDE-5 inhibitors are the first-line oral drugs for treatment of ED. The PDE-5 inhibitors accommodate penile erections by increasing the cyclic guanosine monophosphate level, predominantly within the corpus cavernosum.[18,19] Although the pharmacokinetics of currently market-available PDE-5 inhibitors are similar to one another, the selectivity of PDE-5 isozymes are different between each PDE-5 inhibitor.[19,20] As the rate of ED increases worldwide, urologists and other clinicians are increasingly prescribing PDE-5 inhibitors for the treatment of ED.[20] In accordance with an increase of PDE-5 inhibitors use, some previous studies reported the abuse of PDE-5 inhibitors among young healthy men for the purpose of enhancing their sexual satisfaction.[7] However, few studies have researched the recreational use of PDE-5 inhibitors,[21] and, to our knowledge, no study ever evaluated the rates of alcohol abuse concomitantly with PDE-5 inhibitors. Thus, this study focused on middle- to old-age populations visiting urologic outpatient clinics and compared a population of patients with ED with a broad range of disease severity regarding the concomitant use of alcohol with prescribed PDE-5 inhibitors.

Table 3. Behavioral demography of concomitant alcohol users

	No. of patients (%)
Main reasons for concomitant alcohol use with PDE-5 inhibitors	
Curiosity	52 (35.1)
Reduce refractory time	21 (14.2)
Enhance sexual desire	40 (27.0)
Improve erectile function	0 (0.0)
Recommendation from friends	25 (16.9)
Fear of erectile dysfunction (erection failure)	10 (6.8)
Total	148 (100.0)
Frequency of concomitant alcohol use with PDE-5 inhibitors	
1	12 (8.1)
2–5	52 (35.1)
6–10	68 (45.9)
>10 (nearly every time)	16 (10.9)
Total	148 (100.0)

Behavioral Characteristic

In this study, PDE-5 inhibitors were concomitantly used with alcohol for recreational purpose by 27.0% of the study cohort, which was much higher than the results of a previous study researched by Korkes et al.[2] However, the study by Korkes and colleagues[2] analyzed 167 Brazilian male medical students aged between 17–31 years, whereas this study evaluated middle- to old-aged Korean men with a mean age of 56.2 years. Thus, due to the difference in the characteristics of the study population, we believe our results showed a much higher rate of recreational use of PDE-5 inhibitors than the findings previous studies. According to the medical records reviewed in this study, all patients with ED were warned about the complications associated with the use of PDE-5 inhibitors. However, more than half of the overall study population (239 of 425 patients [73.5%]) was not aware of the complications that can be produced by the concomitant use of PDE-5 inhibitors with alcohol. Specifically, 86.5% of the patients in the concomitant alcohol-use group were either incorrectly aware or not aware of the complications related to PDE-5 inhibitors, which can be produced when PDE-5 inhibitors are ingested with alcohol. This implies that there is a lack of information regarding the complications of PDE-5 inhibitors, which might have acted significantly to increase the number of patients, who consumed PDE-5 inhibitors with alcohol for recreational purposes. Furthermore, the concomitant alcohol use group had a higher percentage of patients (64.8%) with heavy alcohol consumption habits, with consumption of more than 15 drinks per week, compared with non-concomitant alcohol users (14.1%). In addition, 10.9% of the alcohol-using patients also committed overdose of PDE-5 inhibitors to achieve better erectile function. According to the corresponding results, we believe the importance of educating patients with ED about the complications and correct usage of the PDE-5 inhibitors should be more emphasized by clinical urologists. As our results show, a significant proportion of patients believed PDE-5 inhibitors were sexual energy supplements, which may enhance sexual desire and male potency. Thus, the correct pharmacodynamics of the

Table 4. Adverse events after use of PDE-5 inhibitors

	Before adjustment			After adjustment		
Adverse events	Group1 (n = 148) (Concomitant use of alcohol)	Group 2 (n = 177) (No concomitant use of alcohol)	*P* value	Group1 (n = 90) (Concomitant use of alcohol)	Group 2 (n = 90) (No concomitant use of alcohol)	*P* value
Hiccups	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Nausea	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Vomiting	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Dyspepsia	6 (4.0)	5 (2.8)		4 (4.4)	3 (3.3)	
Skin rash	1 (0.7)	0 (0.0)		1 (1.1)	0 (0.0)	
Headache	35 (23.6)	13 (7.3)		21 (23.3)	7 (7.8)	
Facial flushing	103 (69.6)	22 (12.4)		61 (67.8)	11 (12.2)	
Chest discomfort	3 (2.0)	0 (0.0)		2 (2.2)	0 (0.0)	
Palpitation	15 (10.1)	5 (2.8)		9 (10.0)	3 (3.3)	
Dizziness	3 (2.0)	0 (0.0)		2 (2.2)	0 (0.0)	
Altered vision	5 (3.4)	0 (0.0)		3 (3.3)	0 (0.0)	
Nasal congestion	17 (11.5)	14 (7.9)		10 (11.1)	8 (8.9)	
Total	148 (100)	49 (27.7)	<.001	90 (100)	26 (28.9)	<.001

PDE-5 inhibitors also should be educated to the ED patients, especially to the frequent alcohol users, to prevent incorrect usage of the corresponding medication.

Adverse Events After the PDE-5 Inhibitors Use

In this study, the most frequent complication of PDE-5 inhibitors was facial hot flushing in both study groups. More than two-thirds of the alcohol-using group (69.6%) experienced facial flushing, whereas only 12.4% of the non-alcohol-using group experienced this symptom. Facial flushing is a symptom induced by the vasodilation effect of PDE-5 inhibitors, and it occurs in 7% of overall PDE-5 users, according to previous studies.[22,23] Furthermore, a study by Carson et al[24] suggested that the rate of vasodilation symptoms decreases markedly with repetitive use of PDE-5 inhibitors. They showed that the rate of vasodilation symptoms decreased from 7−1% after 16 weeks of treatment with PDE-5 inhibitors.[24] The prevalence of hypertension in this study was 30.4% and 32.2% in the alcohol- and non-alcohol-using groups, respectively. These rates are slightly higher than the results from previous studies, including those of McMahon et al.[25] Moreover, almost one-third of the cohort was undergoing benign prostatic hyperplasia treatment with α blockers. Thus, a relatively higher ingestion rate of vasodilators in this study, including α blockers, might have caused a further increase in vasodilation symptoms, such as facial flushing. Other vasodilators (amlodipine, diltiazem) were prescribed in 11 and 13 patients in the alcohol- and non-alcohol-using groups, respectively. Because the rate of using these vasodilators was similar between the 2 groups, the influence of those medications on alcohol and PDE-5 inhibitors induced vasodilation symptoms may be insignificant, but further evaluations are required to clarify the related pharmacodynamics. In addition, the alcohol-using group also presented higher rates of other vasodilation symptoms, including headache and nasal congestion, compared with the non-alcohol users. Although alcohol itself can result in some degree of vasodilation symptoms, such as facial flushing or headache, the alcohol-abusing patients described the characteristics of PDE-5 inhibitor−related vasodilation symptoms were quite different with the symptoms induced by alcoholic beverage ingestion alone. Our study results showed that facial flushing or headache, which appeared after concomitant ingestion of alcohol with PDE-5 inhibitors, showed a higher intensity with more rapid onset compared with the vasodilation symptoms induced solely by alcohol ingestion. Thus, we reckon concomitant use of PDE-5 inhibitors with alcohol exacerbates vasodilation symptoms, but the definite pharmacodynamic mechanism of these symptoms should be further researched.

Previous studies demonstrated that a small portion of PDE-5 inhibitor using patients (0.1−11%) experience mild transient visual symptoms, including a change in color perception and increased light sensitivity.[26] Moreover, critical ocular complications such as cilio-retinal artery occlusion or non-arteritic anterior ischemic optic neuropathy might also occur in PDE-5 inhibitor users, although the incidence rate is significantly lower than other PDE-5 inhibitor−related complications.[27] Our results showed that only the alcohol-using group experienced temporary altered vision, which resolved spontaneously without any specific intervention. However, the effects of the concomitant use of alcohol and PDE-5 inhibitors on ocular complications should be further researched.

In this study, a patient in the alcohol-using group underwent coronary angiography due to severe chest pain with significant ST-segment elevation in electrocardiogram. Previous studies, including Hellstrom et al,[28] demonstrated the association between the PDE-5 inhibitors and cardiovascular disease, because ED is recognized as a type of vascular disease. Manfroi

et al[29] suggested that PDE-5 inhibitors might cause a redistribution of arterial blood within the patients having atherosclerotic disease, which would exacerbate insufficient coronary perfusion by diverting arterial blood stream away from the coronary vessels. This consecutive process of blood diversion is called *coronary steal phenomenon*, and it might result in myocardial infarction. The single patient with severe chest pain after concomitant ingestion of alcohol and PDE-5 inhibitor underwent no specific coronary interventions, such as coronary-stent insertion, and an attending cardiologist diagnosed the chest pain as temporary coronary steal phenomenon, which resolved spontaneously. Although the rate of cardiac symptoms in the cohort was low, we believe the risk of alcohol consumption with PDE-5 inhibitors might be significant enough to induce coronary disease or systemic hemodynamic instability. Thus, alcohol use in ED patients receiving PDE-5 inhibitors should be repeatedly warned by clinicians prescribing the corresponding medications.

This study contains a few limitations. First, the relatively small cohort size may not allow any certain conclusion applicable to general male population regarding the complications induced by the simultaneous consumption of alcohol and PDE-5 inhibitors. Second, the pathophysiological approaches were not performed for each type of PDE-5 inhibitor—related complication, because the current study was based on patient surveys and a review of their medical records. Thus, the degree of contribution from concomitant alcohol consumption to each complication was not analyzed pharmacodynamically. In addition, the prevalence of a point mutation in the aldehyde dehydrogenase-2 (ALDH2) gene was not evaluated in this study. Because ALDH2, a key enzyme in alcohol metabolism, is commonly polymorphic in East Asian populations, including Koreans,[30] the difference in ALDH2 prevalence might have affected the study results, especially within the alcohol-using group. Despite some limitations, this is the first study evaluating the behavioral pattern of ED patients, in terms of concomitant alcohol consumption with PDE-5 inhibitors, among the middle- to old-age male population. This study also demonstrated that simultaneous ingestion of PDE-5 inhibitors and alcohol possibly increased the PDE-5 inhibitor—related complications.

CONCLUSION

We found that 45.5% (148 of 325 patients) of middle- to old-aged men committed concomitant use of PDE-5 inhibitor with alcohol for recreational or other non-medical purposes. Among the alcohol users, most (84.5%) were not aware of the hazards related to concomitant alcohol use. Concomitant ingestion of alcohol and PDE-5 inhibitors increased the risk of PDE-5 associated complications, including vasodilation symptoms, but life-threatening complications were seldom observed. Therefore, the correct information concerning PDE-5 inhibitors should be thoroughly explained to the patients with ED, especially to the frequent alcohol users.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.esxm.2019.07.004.