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RESEARCH ARTICLE

Efficacy and safety of Sildenafil daily use in HCV positive men with erectile dysfunction

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Abstract

Background: Sildenafil citrate is a specific phosphodiesterase-5 (PDE-5) inhibitor, which has been approved for treatment of erectile dysfunction (ED) in men. Men with liver diseases have higher rate of ED.
Objective: To evaluate the e**fficacy and safety of sildenafil** citrate **daily use** on hepatic functions and ED in normal and chronic hepatitis C patients.
Patients and Methods: The study enrolled 60 males with ED they were divided into 30 patients (HCV negative) and 30 patients (HCV positive). The degree of ED was assessed before and after treatment using International Index of Erectile Function (IIEF-5) questionnaire. They received sildenafil citrate 25 mg daily for 8 weeks. Liver function tests [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), serum total bilirubin (BIL)] were done before start of treatment, 2 weeks after start of treatment and at the end of the study.
Results: Biochemical parameters including ALT, AST, and BIL were significantly higher in hepatitis C positive group before and after sildenafil therapy than the other group. The mean values of ALB were approximately similar in both groups. After treatment with sildenafil, control group had insignificant differences as regard serum ALT, AST, BIL, and ALB. On the other hand, hepatitis group had significant decrease in serum levels of AST and significant increase in serum albumin, whereas, there was insignificant change in serum levels of ALT and BIL. In addition, there was significant increase in IIEF-5 score after treatment with improvement of erectile state.
Conclusion: PDE5-Is can be administered in patients with mild or moderate hepatic impairment, provided that an individual benefit/risk evaluation has been considered prior to their use.

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INTRODUCTION

Hepatitis C virus is a RNA virus that is considered the major cause of acute and chronic hepatitis. It is transmitted chiefly through parenteral exposure to infected materials such as blood transfusions or injections with contaminated needles. Those at highest risk for development of hepatitis C are injection-drug users, people who snort cocaine with shared straws, and health care workers [1].

The HCV prevalence in Egypt is one of the highest in the world, with a reported rate of 14.9%. It is estimated that approximately 100 000–500 000 new infections occur annually, and the annual incidence rate reported by the Ministry of Health is 6.9/1000 persons. A male preponderance has been shown, particularly in rural areas, where there are higher prevalence rates [2,3].

The frequency of sexual transmission of HCV is low (~5%), unlike that of HIV transmission (10%-15%) or HBV transmission (~30%). Based on these data, the Centers for Disease Control and Prevention (CDC) have not recommended barrier precautions (e.g. latex condoms) between stable, monogamous sexual partners when one is HCV positive. Emphasis instead should be placed on avoidance of potential exposure to blood (no sharing of razors, combs, or toothbrushes) [1].

Erectile dysfunction (ED) is the persistent inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance. It can be caused by a variety of psychological and/or pathological factors, including depression, spinal cord injury, testosterone deficiency, ageing, diabetes mellitus and cardiovascular disease [4]. ED incidence increases with age; the largest epidemiologic study available to date has estimated an ED prevalence of 52% in men aged between 40 and 70 years [5].

Several studies have previously reported on the prevalence of sexual dysfunction in patients with chronic liver disease. In particular, ED was found to be prevalent not only in patients with post-alcoholic liver cirrhosis but also in those with chronic HBV and HCV and is associated with a marked reduction in quality of life [6,7]. Chronic liver disease is generally accompanied by clinical signs of hypogonadism such as reduced libido and testicular atrophy, both of which are factors that may be associated with ED [8]. It has also been suggested that chronic HCV infection may result in altered reproductive hormone profiles, which may also affect erectile function [9].

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5). In 1998, the Food and Drug Administration (FDA) approved sildenafil for ED treatment. The discovery of the molecule was a milestone in the pharmaceutical industry and, since its launch; other new substances such as vardenafil and tadalafil have been added to ED management [10]. Numerous clinical trials have been conducted addressing the effectiveness of the drug for ED and its safety regarding the presence or absence of specific comorbidities [11].

In this study, we aimed at investigating the efficacy and safety of sildenafil citrate daily use in treatment of ED in chronic hepatitis C patients.

Patients and Methods

This is a case-control study in men with ED and viral hepatitis (HCV positive). Sixty patients were enrolled from the outpatient clinic of Andrology unite in Dermatology, Andrology and STDs department and department of Tropical Medicine in Mansoura University Hospital from January 2014 to December 2014. This study had adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant before entering the study.

Patients were assigned into two groups: hepatitis group (HCV positive patients with ED) (n =30) and control group: (HCV negative patients with ED) (n =30). Both groups received sildenafil citrate 25 mg daily for 8 weeks. Exclusion criteria were established before commencement of the study. Any men with chronic renal disease, cardiovascular disease, peripheral or autonomic neuropathy, mental illness, history of pelvic trauma and surgery, prostatic disease diabetes mellitus, hypertension, use of drugs or alcohol abuse, patients with chronic liver disease due to other etiologies or patients with liver cirrhosis were excluded from the study. Endocrinal causes of ED were also excluded,

All participants were married with stable relationship. They provided detailed medical histories and had physical examinations (general and local genital) before entry into the trial. All patients were non-responders for on-demand sildenafil therapy. Risks and benefits of the trial, as well as the medications involved, were fully explained and accepted before trial commencement. Portions of an abridged 5-item version of the previously validated International Index of Erectile Function (IIEF-5) (Fig. 1) also known as the Sexual Health Inventory for Men (SHIM), was used to grade ED both before the trial and at its conclusion (8weeks).

International Index of Erectile Function (IIEF-5) is a multidimensional questionnaire consists of 5 questions for assessing ED. The erectile function score represents the sum of questions one through five of the IIEF‑5 questionnaire, with a maximum score of 25; a score ≤ 21 indicates ED. The five questions assess erectile confidence, erection firmness, maintenance ability, maintenance frequency, and satisfaction. The severity of ED is classified into five categories as severe (score 5–7), moderate (score 8–11), mild to moderate (score 12–16), mild (score 17–21), and no (score 22–25) ED [12]. We asked participants to estimate how long they remembered having ED and subsequently calculated the baseline IIEF-5 scores.

The IIEF-5 Questionnaire, the Sexual Health Inventory for Men (SHIM)

Please encircle the response that best describes you for the following five questions:

Over the past 6 months					
1. How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
	1	**2**	**3**	**4**	**5**
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	A few times	Sometimes	Most times	Almost always or always
	1	**2**	**3**	**4**	**5**
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never or never	A few times	Sometimes	Most times	Almost always
	1	**2**	**3**	**4**	**5**
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly	Not difficult
	1	**2**	**3**	**4**	**5**
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	A few times	Sometimes	Most times	Almost always or always
	1	**2**	**3**	**4**	**5**

Figure (1): IIEF-5 total Score: (Rosen etal.,2002)[12]

1-7: Severe ED, 8-11: Moderate ED, 12-16: Mild-moderate ED, 17-21: Mild ED and 22-25: No ED

A total of 30 married, drug naïve patients with chronic hepatitis C were recruited for the study. The diagnosis of HCV-induced chronic liver disease were done in Tropical Medicine Department for naïve patients with chronic active hepatitis C seeking medical care for Pegylated Interferon based combined therapy. Liver disease in each case was made on the basis of serological and virology consisting of anti-HCV positivity, HCV RNA PCR, abnormal serum alanine aminotransferase (ALT) levels. Moreover liver biopsy were done for each patient as a prerequisite for Interferon based therapy and all patients had non cirrhotic liver with Metavir fibrosis score ranging between F1 and F3 in all studied liver biopsy

Several biochemical parameters were also assessed in this study for both groups. These parameters included serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum total bilirubin (BIL), and serum albumin (ALB). Biochemical data were obtained from the tests on the day of the interview. Because of the high prevalence of hypogonadism in hepatic patients, baseline testosterone and prolactin levels were drawn and abnormal levels were excluded from the study.

The anthropometric measurements were performed by trained personnel using a standardized protocol. Body weight was taken by electronic weighing machine and height was measured by stadiometer with the subject barefoot fully erect, with the head in the Frankfurt plane; the back of the head, thoracic spine, buttocks, and both heels together with touching the vertical axis of the stadiometer. The body mass index (BMI) was then calculated formula given by Adolphe Quetelet as weight (in kilograms)/height^2 (in meters).

Instructions regarding properties and correct administration of the study treatment were based on the Summaries of Product Characteristics (SPCs) and the European Association of Urology guidelines on male sexual dysfunction. Patients received sildenafil citrate 25 mg daily for 8 weeks on empty stomach (before dinner). During the 8-weeks treatment period, study visits were scheduled at 2, and 8 weeks; unscheduled visits occurred in case of efficacy or tolerability issues. Biochemical parameters were also assessed in these visits.

Statistical analysis:

Data are expressed as mean value ± standard deviation (SD). All the data were edited and processed using the SSPS version16. Comparison of continuous data was performed using independent-samples t test and the paired-samples t test. Comparison of the rate of response was performed by the use of χ^2 test while the correlation of the

degree of improvement by sildenafil was performed using Pearson correlation. P value of <0.05 was considered statistically significant.

Results

The study included sixty patients, divided into two groups. All the patients completed the entire course of the study. Both groups were well matched as regard number of the patients, age of the patients, duration of marriage and duration of ED.

Hepatitis C group consisted of 30 participants. Their ages range from 29-53 years (44.83 ±6.35). Twenty three patients (76.7%) aged between 40 and 60 years and 7 patients (23.3%) aged between 20 and 40 years. The mean value of BMI (Kg/m^2) was 27.76±2.45. The duration of marriage ranged from 1 to 22 years (14.15± 6.53). The duration of ED ranged from 6-60 months with mean 25.9±15.8 months. HCV viremia was 1610185±40816) IU/ml. Four patients (13.3%) had mild ED, 18 patients (60%) had moderate ED and 8 patients (26%) had severe ED according to IIEF-5 score (Table 1).

The control group had a younger age with mean age 42.86±6.14 years; however, this difference was not statistically significant (P >05). Also, there were no significant differences between the average duration of marriage (14.15±6.53 vs. 15.13±7.69 years) and duration of ED (25.9±15.8 vs. 26.9±31.69 months) between both groups. The mean value of BMI was 27.187±2.6. Before treatment, 13 patients (43.3%) had mild ED, 7 patients (23.3%) had mild-moderate ED, 8 patients (26.7%) had moderate ED, and 2 patients (6.7%) had severe ED which was significantly less affected than that of chronic hepatitis C group (Table 1).

Table (1): Baseline demographics and clinical characteristics.

Clinical character	Hepatitis group (n=30)	Control group (n=30)	Test
Age (years) Mean±SD Range	 44.83±6.35 29-53	 42.86±6.14 29-55	t:1.22 P>0.05
Age group: 20-40 years 40-60 years	 7 (23.3%) 23 (76.7%)	 11(36.7%) 19(63.3%)	χ2:0.71 P>0.05
Duration of marriage (years) Mean±SD Range	 14.15± 6.53 1- 22	 15.13± 7.69 1- 30	t:0.53 P>0.05
ED duration (months) Mean±SD Range	 25.9±15.8 6-60	 26.9±31.69 6-120	t:0.16 P>0.05
BMI (kg/m^2) Mean±SD Range	 27.76±2.45 (24-32)	 27.19±2.6 (23-32)	t:0.87 P>0.05
IIEF-5 score before therapy: Mild ED(21-17) Mild-moderate ED(12-16) Moderate ED(11-8) Severe ED(1-7) No ED(22-25)	 4(13.3%) 0 18(60%) 8 (26.7%) 0	 13(43.3%) 7(23.3%) 8(26.7%) 2(6.7%) 0	χ2:19.21 *P<0.001
IIEF-5 score after therapy: Mild ED(21-17) Mild-moderate ED(12-16) Moderate ED(11-8) Severe ED(1-7) No ED(22-25)	 9(30%) 0 0 0 21(70%)	 8(26.7%) 0 0 0 22(73.3%)	χ2:0.01 P>0.05

P significant if <0.001

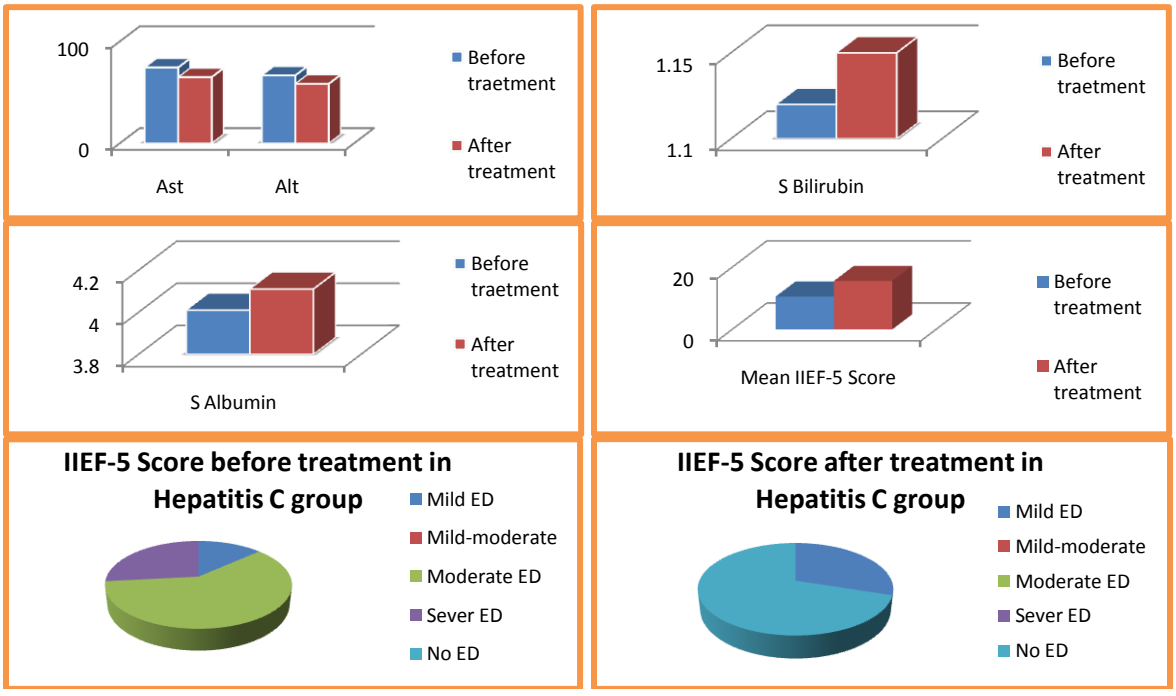
Biochemical parameters including serum ALT, AST, and BIL were significantly higher in hepatitis patients than control before and after sildenafil therapy and higher than their normal ranges also before and after sildenafil therapy. The mean values of ALB were approximately similar in both groups (Table 2). After treatment, control group had insignificant differences as regard serum ALT, AST, BIL, and ALB while hepatitis group had significant decrease in serum levels of AST and significant increase in ALB, whereas, there was insignificant change in serum levels of ALT and BIL (Figure 2)

Table (2): Comparison between both groups as regard biochemical parameters

Group		Mean±SD	Minimum-Max	T
AST (IU/L) before treatment	Control	29.3±5.68	21-41	8.301
	Hepatitis c	74.52±35.13	33-155	**P<0.001
AST (IU/L) after treatment	Control	29.07±5.5	20-40	9.127
	Hepatitis c	65±24.92	34-124	**P<0.001
ALT(IU/L) before treatment	Control	31.1±7.93	18-48	6.306
	Hepatitis c	66.74±36.7	35-169	**P<0.001
ALT after treatment	Control	30.87±8.04	20-46	8.042
	Hepatitis c	58.53±21.43	38-112	**P<0.001
Bilirubin (mg/dL) before treatment	Control	0.86±0.05	0.8-0.9	3.600
	Hepatitis c	1.12±0.48	0.69-2.26	**P<0.001
Bilirubin (mg/dL) after treatment	Control	0.86±0.05	0.8-0.9	4.888
	Hepatitis c	1.15±0.38	0.7-2	**P<0.001
Albumin (g/L) before treatment	Control	4.01±0.08	3.8-4.1	.590
	Hepatitis c	4.01±0.3	2.9-4.1	*P<0.05
Albumin (g/dL) after treatment	Control	4.02±0.68	3.9-4.2	.978
	Hepatitis c	4.11±0.36	2.8-4.3	P>0.05

SD: standard deviation ****P significant if <0.05*** *****P significant if <0.001***

Figure (2): Biochemical parameters and IIEF-5 score before and after treatment in Hepatitis C group.



In hepatitis group, approximately (70%) of patients improved and get IIEF-5 score **> 21** after treatment. In addition, there was significant increase in IIEF‑5 score after therapy with improvement of erectile state of the patients. Furthermore, IIEF score before treatment had significant negative correlations with the age of the patients and duration of ED and significant positive correlation with IIEF score after treatment. Also IIEF score after treatment had significant negative correlation with the duration of ED and age of patients had significant positive correlation with duration of ED **(Table-3)**. No significant correlation was observed in hepatitis C group between IIEF score and level of HCV viremia or Metavir fibrosis score in liver biopsies

Table (3): Some important correlations in the present study

		Duration ED	IIEF score before treatment	IIEF score after treatment
Age	R	0.667**	-.440*	-0.156
	P	0.0001	0.015	0.410
Duration of ED	R	1	-.418*	-.468**
	P		0.022	0.009
IIEF score before treatment	R	-.418*	1	0.696**
	P	0.022		0.0001

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Discussion

Chronic hepatitis C virus (HCV) infection is a major public health problem. Acute infection leads to chronicity in 75% of cases. The important complications of HCV include cirrhosis, liver failure and hepatocellular carcinoma (HCC). Although chronic infection with HCV is usually asymptomatic, patients may report non-specific symptoms, in particular fatigue, anorexia or arthralgia even in the absence of significant liver disease [13]. **Kim [14]** reported that chronic liver disease tends to be naturally asymptomatic because the liver can compensate even when only 10% of total liver function is maintained.

The aim of our study is to evaluate the effect of daily use of 25 mg sildenafil citrate for 8 weeks on hepatic functions and erectile dysfunction in chronic hepatitis C patients who were non-responders for on-demand sildenafil treatment. In the present study, we demonstrated that chronic hepatitis C patients aged from 29-53 years old with mean age 44.83 ±6.35 years with 23 patients (76.7%) aged between 40 and 60 years. **Osella et al. [15]** found that HCV infection is prevalent among persons older than 40 years but is uncommon in those younger than 20 years. This cohort effect suggests a time-restricted exposure, which in many instances appears to have been related to medical procedures (e.g., vaccinations, blood transfusion, and parenteral drug treatment).

Before treatment, this study showed 4 patients (13.3%) had mild ED, 18 patients (60%) had moderate ED and 8 patients (26%) had severe ED in hepatitis C group according to IIEF-5 score., in relation to 13 patients (43.3%)

had mild ED, 7 patients (23.3%) had mild-moderate ED, 8 patients (26.7%) had moderate ED, and 2 patients (6.7%) had severe ED in control group which was significantly less affected than that of chronic hepatitis C group

Although various hypotheses have been formulated to explain the prevalence of ED in patients with liver disease, the mechanism behind this association remains to be fully elucidated. In non-cirrhotic patients, several complex mechanisms of HCV and other viral hepatitis mediators leading to inflammation, increased oxidative stress, insulin resistance and apoptosis is involved [8].Within this context, HCV non-structural proteins may be key mediators in inducing oxidative stress and inflammation through the stimulation of mitochondrial-reactive oxygen species production. Chronic systemic inflammation accompanied by increased C-reactive protein levels has been shown to decrease nitric oxide (NO) synthesis in endothelial cells, ultimately leading to the endothelial dysfunction that may account for the association between ED and hepatitis-related liver disease [16].

In the present study, we demonstrated that biochemical parameters including serum ALT, AST, and BIL were significantly higher in chronic hepatitis C than control patients before and after sildenafil therapy. The mean values of ALB were approximately similar in both groups. After treatment with sildenafil citrate 25 mg daily for 8 weeks, control group had insignificant differences as regard serum ALT, AST, BIL, and ALB. On the other hand, hepatitis group had significant decrease in serum levels of AST and significant increase in serum albumin, whereas, there was insignificant change in serum levels of ALT and bilirubin.

Ji et al. [17] evaluated effects of sildenafil citrate on hepatic function and regeneration in normal and alcohol-fed rats. Sildenafil citrate did not induce significant changes in hepatic function and regenerative activity after partial hepatectomy in normal and alcohol-fed rats, except at concentration of 5 mg/kg sildenafil citrate significantly inhibits hepatic regeneration in normal rats.

Said et al. [18] found that the administration of sildenafil (10 mg/kg body mass for 6 weeks in rat) successfully improved the impaired hepatic functions observed with Thioacetamide-induced liver cirrhosis in rats. It reduced liver: body mass indices, reduced elevated serum ALT, AST, total and direct bilirubin, and ALP levels, serum albumin levels increased, and serum TGF ß1 levels declined. The observed improvement of the serum biochemical parameters was paralleled with significant reduction in hepatic hydroxyproline and collagen content. The association between the improvement in serum biochemical parameters and the reduction in hepatic collagen content was further proven by histopathological examination of the liver specimens and the retraction of fibrosis with sildenafil treatment.

Our study demonstrated that IIEF‑5 score is strongly significantly correlated with IIEF-5 score after sildenafil therapy in both groups. IIEF‑5 score after therapy in chronic hepatitis C patients had statistically significant negative correlation with the duration of ED and negative correlation with age of patients and duration of marriage. Approximately (70%) of patients in both groups improved and get IIEF-5 score **> 21** after treatment.

Leoni et al. [11] reported that the introduction of sildenafil enabled different groups of patients to have their erectile function restored. Among them, the elderly, diabetics, individuals who suffered from incomplete spinal cord injury, patients with Parkinson's disease, or users of serotonin reuptake inhibitors patients with cardiovascular disorders, patients with obstructive sleep apnea, patients with renal disorders, post-prostatectomy patients or post-radiotherapy of prostate cancer. Sildenafil is safe, an effective and well-controlled treatment for ED in patients, both in the absence and in the presence of comorbidities.

Sorrell and Brown [19] conducted a study in patients with end stage liver disease and candidate to liver transplantation indicated that only 5% of the men with ED were prescribed sildenafil the only PDE5-I available at the time of the study. **Fusco et al. [16]** stated that tadalafil of a 10-mg/ dose in patients with mild and moderate hepatic impairment (Child--Pugh Class A and B) is comparable to exposure in healthy subjects.

Rhoden et al. [20] observed a high rate of severe degree and a decrease in frequency of mild degree of ED with aging. **Ponholzer et al. [21]** concluded that age was an important risk factor for ED. Severe ED (IIEF-5 score 5-7) increased from 0.4% (20-30 years) to 0.5% (41-50 years), 1.3% (51-60 years) and to 9.6% in those who were aged 71-80 years.

The success rate of sildenafil in ED treatment was variable in previous studies depending on many factors such as the methods used for assessment of treatment efficacy, underlying etiology of ED, and the diversity of patient's population [22]**. Elhanbly et al. [23]** reported that simple clinical parameters namely a short ED duration (≤2.5 years) plus a higher IIEF-5 score (≥14), could reflect a less severe form of ED and such cases are more likely to respond to sildenafil treatment.

Conclusion

Finally, we can conclude that PDE-5Is can be administered in patients with mild or moderate hepatic impairment, provided that an individual benefit/risk evaluation has been considered prior to their use.

Future recommendation

Larger series of patients are still needed. There is little or no evidence on PDE-5Is effects in patients with severe hepatic impairment. The impact of IFN and other new directly acting antiviral therapy and associated comorbidities on sexual dysfunction should be appropriately evaluated in prospective clinical trials.

Although hepatotoxicity is not included among the reported adverse reactions in the use of any of the available PDE-5Is, inhibitors of CYP 3A4 (i.e., the main metabolic pathway of PDE-5Is) may reduce PDE-5Is clearance, and inducers of these isoenzymes may increase their clearance. Therefore, potential drug—drug interactions should be taken into account, before considering the use of PDE-5Is in hepatic patients.

Conflicts of interest

We declare that no benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. We also declare that we have no conflicts of interest in connection with this paper.

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