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Original Article

Sequential, non-arteritic anterior ischemic optic neuropathy in patients taking sildenafil: a report of ten cases

Alberto Galvez-Ruiz, MD, PhD *; Nawal Arishi, MD

Abstract

Aim/purpose: To present a summary of 10 cases of non-arteritic anterior ischemic optic neuropathy (NAION) in patients who received phosphodiesterase type 5 (PDE-5) inhibitors.
Methods: A case series of 10 patients who, after regular intake of Sildenafil, presented with a first episode of NAION in one eye. NAION was diagnosed based on the following criteria: acute, painless, unilateral loss of vision, fundus features consistent with NAION and exclusion of other possible causes.
Results: Despite the initial adverse event (first episode of NAION), all of these patients continued to use the medication and developed a second episode of NAION in the contralateral eye. Only one of the 10 patients presented with bilateral simultaneous NAION.
Conclusion: This largest case series published to date, reinforces the general consensus that PDE-5 inhibitors are contraindicated in patients with a history of unilateral NAION.

Keywords: Non-arteritic anterior ischemic optic neuropathy, Sildenafil, Phosphodiesterase type 5 inhibitors

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Introduction

There are more than 35 million users of Sildenafil (Viagra; Pfizer) worldwide since its introduction in 1998.[1] Over time other drugs belonging to the phosphodiesterase type 5 inhibitors (PDE-5) have been introduced, including Tadalafil (Cialis; Eli Lilly) and Vardenafil (Levitra; Bayer) (see Fig. 1).

Oral intake of these PDE-5 inhibitors has been associated, albeit rarely, in cases of non-arteritic anterior ischemic optic neuropathy (NAION) in patients. However, it was unclear whether these cases of NAION are secondary to PDE-5 inhibitor intake, to the concomitant existence of cardiovascular risk factors or a combination of factors.[2]

We present a series of 10 patients who, after a sustained intake of Sildenafil, presented with their first episode of NAION in one eye. Despite this adverse event, all of the patients continued to use Sildenafil and later suffered a second episode of NAION in the contralateral eye. To the best of our knowledge, this is the largest series to date of sequential NAION in patients who received Sildenafil.

Methods and materials

A retrospective review was performed on 10 male patients with a mean age of 50.7 years (range, 38 years and 70 years) who were regularly ingesting Sildenafil. All of the patients had cardiovascular risk factors, with diabetes being the most frequent risk factor. Data gathering with respect to the exact dose of Sildenafil and the time elapsed between Sildenafil intake and the manifestation of visual symptoms

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Division of Neuro-Ophthalmology, King Khaled Eye Specialist Hospital, Saudi Arabia

* Corresponding author. Address: King Khaled Eye Specialist Hospital, Division of Neuro-ophthalmology, P.O. Box 7191, Riyadh 11462, Saudi Arabia. Tel.: +966 1 482 1234.
e-mail addresses: algarui@yahoo.com, agalvez@kkesh.med.sa (A. Galvez-Ruiz).

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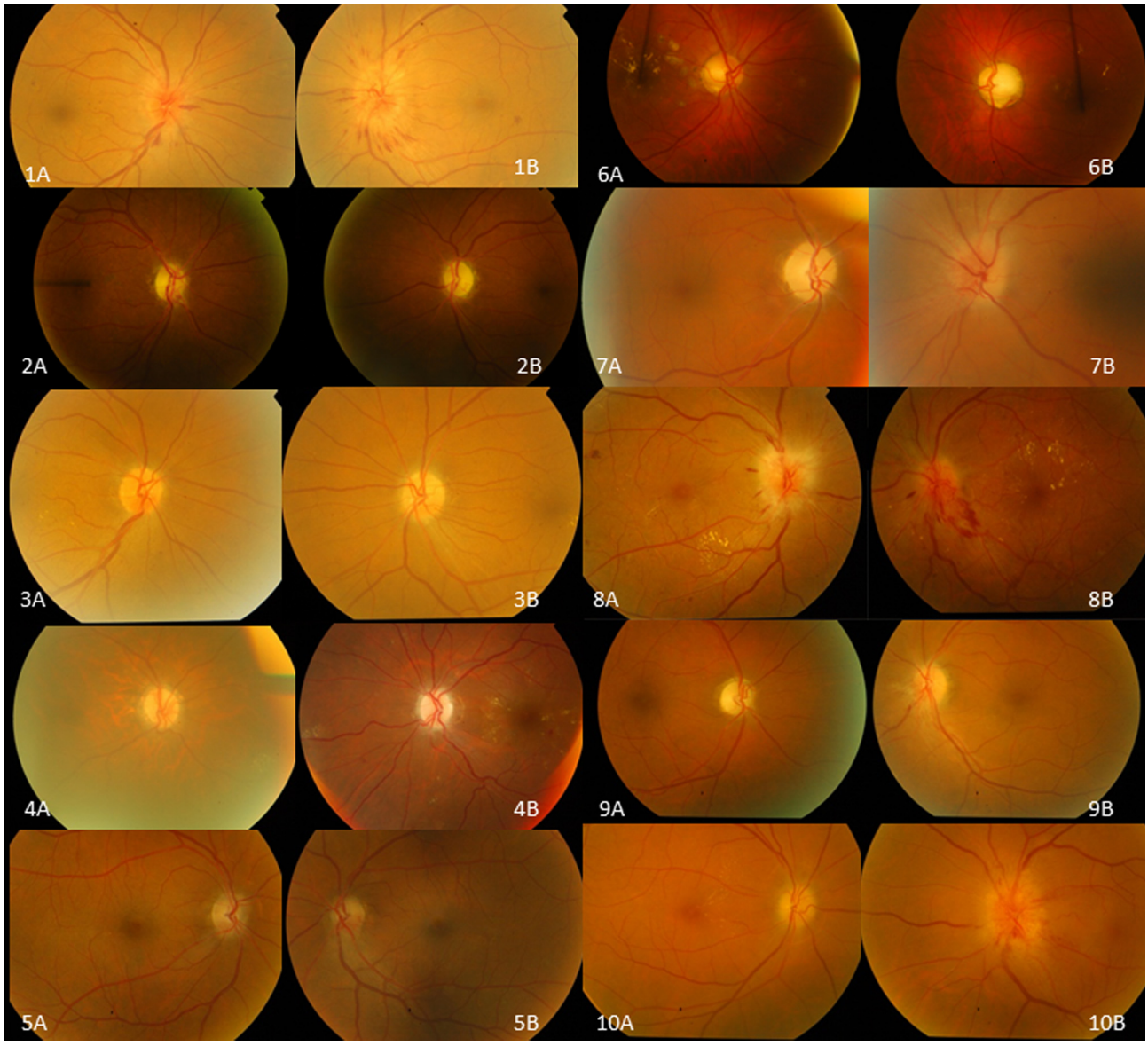

Figure 1. Fundoscopy of 10 patients from the clinical series showing the appearance of the optic nerve OU after episodes of non-arteritic, ischemic optic neuropathy. A. OD. B. OS.

were difficult in the majority of these patients. This difficulty is due in part to the scarce medical resources and the lack of importance attributed to medical treatment in the local population in the remote regions of the country (where this study was performed). However, all of the patients shared the characteristic of regular use of this Sildenafil (>2–3 times per week) during the weeks and months prior to the onset of ocular ischemia. The following criteria were required for the diagnosis of NAION: acute, painless, unilateral loss of vision, presence of fundus features compatible with NAION such as optic disk edema with splinter hemorrhages in the acute setting with contralateral disk-at-risk and exclusion of other possible causes through Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), Anti-nuclear Ab (ANA), Anti-DNA, Treponema pallidum hemagglutination assay (TPHA), Rapid Plasma Reagin (RPR) and cranial and orbital magnetic resonance imaging (MRI) within normal limits (as warranted).

This study was registered with the institutional review board and was approved by the ethics committee of the institution (King Khaled Eye Specialist Hospital).

Results

Case reports

Table 1 summarizes the patient data including demographics, systemic and ophthalmic features, the interval between the two episodes of NAION and Sildenafil dosage.

Discussion

We present a series of 10 patients who used Sildenafil for a prolonged period of time. All of these patients shared a

Table 1. Summarized information of the 10 patients showing age, gender, cardiovascular risks, first and second episode of NAION with fundoscopy and visual field if available, period of time between two attacks and Sildenafil doses.

	Age	Cardiovascular risk factors	First episode NAION VA	Fundoscopy	GVF First episode	Second episode NAION VA	Fundoscopy	GVF Second episode	Period of time between episodes	Sildenafil doses
Patient 1	52 years male	DM	OD	OD optic disk edema with peri-papillary splinter hemorrhages (Fig. 1. 1A)	Non available	OS VA 20/20 20/40	OD: superior sectoral pallor OS: Optic disk edema with peri-papillary splinter hemorrhages (Fig. 1. 1B)	Absolute inferior nasal defect OU (Fig. 2. 2A–B)	1 month	100 mg routinely (>2–3 times per month) for the past year
Patient 2	50 years male	DM Ischemic heart disease	OS	Non available	Non available	OD VA 20/300 20/100	Temporal papillary pallor OU (Fig. 1. 2A–B)	Absolute inferior nasal defect OU with a cecocentral scotoma OS (Fig. 2. 2A–B)	6 months	Routinely used Sildenafil for over a year
Patient 3	52 years male	DM	OS	Non available	Non available	OD VA 20/25 20/30	Superior sectoral pallor OU (Fig. 1. 3A-B)	HVF OD: inferior altitudinal defect OS: Inferior nasal sector defect (Fig. 2. 3A–B)	Several months	He had used Sildenafil regularly for approximately two years (2–3 times per week)
Patient 4	41 years male	DM	OS	Non available	Non available	OD VA 20/100 20/30	Optic disk-at-risk was observed in the fundus of the eye with temporal pallor OU (Fig. 1. 4A–B)	OD: Superior arcuate defect with inferior constriction OS: inferior temporal sector (Fig. 2. 4A–B)	Several months	He had been taking Sildenafil regularly (>2–3 times per week)
Patient 5	45 years male	DM	OS	Non available	Non available	OD VA 20/80 20/30	Superior altitudinal pallor OU, with a small papillary excavation (disk-at-risk) (Fig. 1. 5A–B)	OU: inferior altitudinal defect, although it was more pronounced OD (Fig. 2. 5A-B)	Unknown	Patient had taken Sildenafil regularly (>2–3 times per week) for 6 months
Patient 6	38 years male	DM dyslipidemia	Simultaneous OU VA 20/30 20/40	OD: superior altitudinal pallor OS: temporal pallor (Fig. 1. 6A-B)	HVF: OD superior sector defect with superior paracentral scotoma OS: inferior altitudinal defect and a superior arcuate defect (Fig. 2. 6A-B)	–	–	–	Simultaneous	Just before the event, the patient stated having taking Sildenafil daily
Patient 7	56 years male	Hypertension Hypercholes-terolemia	OD	Non available	No available	OS VA Hand motion Finger count	Global pallor of the optic disk, bilaterally, without excavation (Fig. 1. 7A–B)	OD residual central and temporal islet OS isopter concentric reduction with a nasal inferior defect (Fig. 2. 7A–B)	3 weeks	He had been taking Sildenafil regularly (>2–3 times per week) for 6–8 months prior
Patient 8	51 years male	DM dyslipidemia	OD	OD: disk edema with peri-papillary splinter hemorrhages OS: normal coloration	Non available	OS VA 20/25 20/40	OD: temporal pallor OS optic disk edema with peri-papillary splinter hemorrhages with predominance in the	OD global sensibility decrease OS: an inferior nasal defect (Fig. 2. 8A–B)	Few months	Sildenafil intake in the days prior to the vision loss OU

(continued on next page)

Table 1 (*continued*)

	Age	Cardiovascular risk factors	First episode NAION VA	Fundoscopy	GVF First episode	Second episode NAION VA	Fundoscopy	GVF Second episode	Period of time between episodes	Sildenafil doses
				without excavation (Fig. 1. 8A)			inferior pole OS (Fig. 1. 8B)			
Patient 9	52 years male	DM Hypertension	OD	Non available	Non available	OS VA 20/60 20/50	OD: pallor, with predominance in the superior pole OS: elevation of the optic disk with peri-papillary splinter hemorrhages in the inferior pole (Fig. 1. 9A-B)	OD concentric reduction in the visual field with the presence of a nasal and central islet. OS: an inferior nasal defect (Fig. 2. 9A–B)	1 year	Routine use of Sildenafil (>2–3 times per week for over 1 year)
Patient 10	70 years male	DM dyslipidemia	OD	OD: optic disk edema with peri-papillary splinter hemorrhages	Non available	OS VA 1/200 1/200	OD: residual edema with temporal pallor. OS: global elevation with hyperemia and peri-papillary splinter hemorrhages (Fig. 1. 10A-B)	Concentric reduction in the visual field with a relative inferior altitudinal defect OU, which was predominant OS (Fig. 2. 10A–B)	2 months	He was taking Sildenafil regularly for several months (>2–3 months)

common characteristic: regular intake of Sildenafil despite an episode of NAION.

There is no general consensus regarding the possible cause-and-effect relationship between the use of PDE-5 medications and the onset of NAION. Some investigators such as Gorkin et al.[2] are reluctant to admit this relationship between Viagra and NAION. However, others, such as Hayreh[3] suggest that Viagra and other PDE-5 inhibitors can clearly result in the development of NAION. Until 2011, this possible relationship had been reported in 49 patients, mainly through case reports with varying levels of evidence.[4]

McGwin et al.[5] published one of the most important studies to clarify this possible relationship. McGwin et al.[5] conducted a retrospective, matched, case-control study in which 38 male patients with a diagnosis of NAION and 38 controls without NAION were included. Their[5] results indicated a positive association between the intake of Viagra and/or Cialis and the risk of developing NAION (the odds ratio suggested an approximate increase of 75–80%). However, this association was not statistically significant. Sobel et al.[6] questioned the validity of McGwin et al's[5] study by indicating numerous biases.

Studies similar to Gorkin et al's[2] propose that cases of NAION in patients on PDE-5 are purely related due to chance. These authors[2] argue that individuals who suffer from erectile dysfunction and use PDE-5 medications have cardiovascular risk factors with a greater frequency including diabetes, hypertension, dyslipidemia and tobacco use. Given that these cardiovascular risk factors increase the risk of developing NAION, it is not surprising to find a greater frequency of spontaneous NAION in individuals with erectile dysfunction.[2]

Gorkin et al.,[2] analyzed data from the Global Clinical Trials and the European Observational Studies and estimated the incidence of NAION after exposure to Sildenafil to be 2.8 cases per 100,000 patients per year. Gorkin et al.[2] compared this incidence to two studies of the incidence of NAION in the general population.[7,8] Using these comparisons, Gorkin et al.[2] concluded that the incidence of NAION cases in patients who take Sildenafil is similar to that of the general population, ruling out a possible causal association or increased occurrence of NAION related to PDE-5. The validity of Gorkin et al's. study was questioned by others[3] as Dr. Gorkin was working for Pfizer, the manufacturer of Viagra, indicating a serious conflict of interest.

A key component to the relationship between NAION and PDE-5 is establishing the mechanism of action of the medication through which this complication occurs. Several studies have hypothesized that PDE-5 produce an alteration or negative influence in the auto-regulation of blood flow of the optic nerve.[4,5,9]

In light of these studies, it is difficult to establish a cause-effect relationship between PDE-5 use and the development of NAION.[10] However Hayreh[3] proposes that ''all the available evidence suggest a cause-and-effect relationship between the ingestion of erectile dysfunction drugs and the development of NAION''. These authors proved that nocturnal arterial hypotension is the precipitating risk factor for NAION and Viagra can increase this nocturnal hypotension. Additionally Hayreh[3] showed that Viagra can be associated with an increase of norepinephrine levels that can produce vasoconstriction and ischemia in the optic nerve head. Hayreh[3] concluded that the chances of NAION after taking

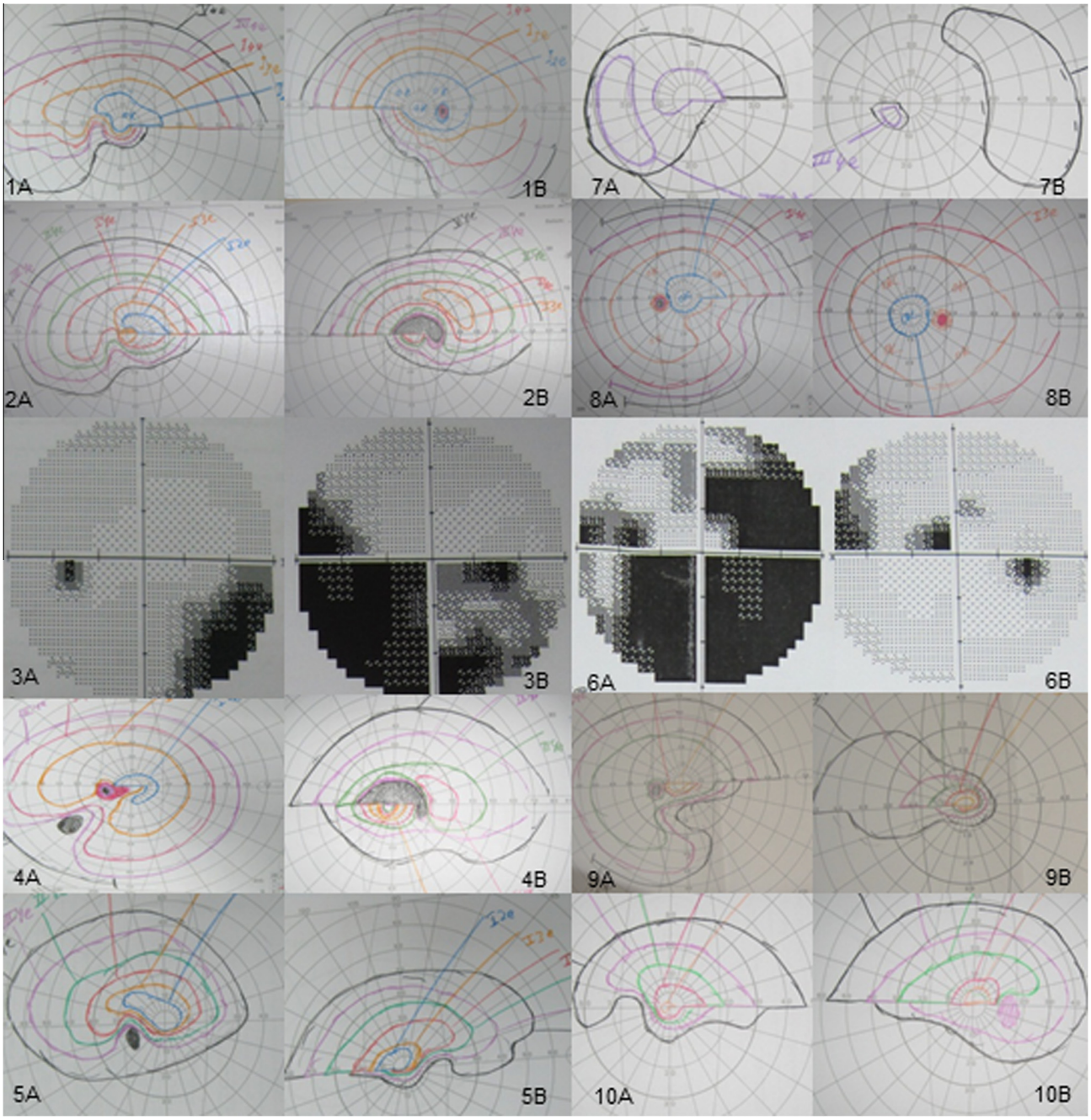

Figure 2. Visual campimetry OU in 10 patients, presented after episodes of non-arteritic, anterior, ischemic optic neuropathy. A. OD. B. OS.

Viagra intake depend on the number of predisposing risk factors for the development of NAION and how much nocturnal hypotension develops after Viagra intake.

In our case series 9 of 10 patients were diabetic and some of them had other cardiovascular risk factors (hypertension, hyperlipidemia and coronary stent). In view of the presence of these risk factors we conclude that our patients were at a much greater risk of developing NAION following the use of Sildenafil compared to normal healthy individuals.[11]

Evaluation of the literature on this topic indicates that there is no contraindication of PDE-5 use in patients with a past history of monocular NAION.[1,4,5,9,12–15] However, there is a statement by the FDA and a Statement of European Supplementary protection certificate class labeling.[1,4,5,9,12–15]

Fraunfelder et al.,[15] reported episodes of NAION after a single dose (at a single point in time) and after multiple doses. Our series presents a group of patients who suffered from consecutive episodes of NAION. All of these patients reported the continued use (multiple doses >3–4 times per month) of Sildenafil before and after the first episode of NAION. All of these patients also continued to use Sildenafil after the first episode of NAION until the development of NAION in the contralateral eye.

There are some limitations in this study. For example, the incomplete data on the exact dose of Sildenafil taken and the time interval between intake and the development of visual symptoms. However these data are difficult to collect due to the limited importance given to medicine by individuals

in the region of the country where this study was performed. Additionally medical resources are also scarce as this a remote region. However, routine exposure to Sildenafil (>2–3 times per week) was confirmed in all of the patients during the weeks and months prior to the ocular ischemia. (see Fig. 2)

Half of the patients in the current study had a primary episode of unilateral ischemic optic neuropathy; after this episode, they did not seek care from an ophthalmologist or the episode was somehow unnoticed or subclinical to the patients. For three of these patients, after the first episode of ischemic optic neuropathy, the ophthalmologist in charge of emergencies did inquire about Sildenafil intake. Due to this oversight, discontinuation of Sildenafil was not recommended. These three patients suffered from a second episode of ischemic optic neuropathy, at which time they were queried about Sildenafil intake.

Of note, we found spontaneous reporting by the patient that the use of PDE-5 continues to be a source of embarrassment, especially if his wife or son/daughter are present during the consult. This observation has been reported previously.[13,16] This fact indicates that ophthalmologists assessing a patient after an episode of unilateral ischemic optic neuropathy must inquire about the use of PDE-5.

We believe that this is the largest series published to date and the observations reinforce the general consensus for the contraindication of PDE-5 in patients with a history of unilateral NAION.

Conflict of interest

The authors declared that there is no conflict of interest.

Financial Disclosure

The authors have no relevant financial interests to report.

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