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EXTENDED REPORT

Non-arteritic anterior ischaemic optic neuropathy and the treatment of erectile dysfunction

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Aim: To determine the association between Viagra (sildenafil) and Cialis (tadalafil) and non-arteritic anterior ischaemic optic neuropathy (NAION).

Methods: A retrospective matched case-control study was conducted. 38 cases of NAION in males were identified from an academic ophthalmology practice in Birmingham, Alabama, and matched (on age) to 38 controls without a history of NAION. Self reported information regarding past and current use of Viagra and/or Cialis was obtained via a telephone questionnaire from interviewers who were not blind to case status.

Results: Overall, males with NAION were no more likely to report a history of Viagra or Cialis use compared to similarly aged controls (odds ratio (OR) 1.75, 95% confidence interval (CI) 0.48 to 6.30 and OR 1.82, 95% CI 0.21 to 15.39). However, for those with a history of myocardial infarction, a statistically significant association was observed (OR 10.7, 95% CI 1.3 to 95.8). A similar association was observed for those with a history of hypertension though it lacked statistical significance (OR 6.9, 95% CI 0.8 to 63.6).

Conclusions: For men with a history of myocardial infarction or hypertension the use of Viagra or Cialis may increase the risk of NAION. Physicians prescribing these medications to patients with these conditions should warn them about the potential risk of NAION.

Non-arteritic anterior ischaemic optic neuropathy (NAION) is the most common acute optic neuropathy among older adults in the United States.^{1–3} An estimated 1500–6000 people develop NAION annually,^{4–6} of which one in four patients will go on to experience NAION in the fellow eye.⁷ NAION manifests as acute painless monocular vision loss, optic disc oedema, and a relative afferent pupillary defect. Presenting visual acuity is worse than 20/64 in about 50% of patients and may subsequently improve (in 30%–40% of patients), worsen (in 12%–22% of patients), or remain unchanged (in about 45% of patients).^{7–8}

There have been several case reports suggesting a link between certain phosphodiesterase inhibitor erectile dysfunction (ED) medications (Viagra (sildenafil) and Cialis (tadalafil)) and NAION.^{9–13} Visual side effects (for example, light sensitivity, colour vision abnormalities) associated with these medications are well documented but these effects, which have been traced to the fact that phosphodiesterase inhibitors appears to have an inhibitory influence, albeit weak, on enzymatic activity in the rod and cone cells, appear to be transient in nature.^{14–15} However, the mechanism by which these medications might damage the optic nerve is not as well understood. It has been theorised that sildenafil, which works through the nitric oxide-cyclic GMP pathway, may alter the perfusion of the optic nerve head by modifying nitric oxide levels.¹¹ Given their similar properties, it can also be theorised that tadalafil might act similarly though no explicit theories have been proposed.

Unfortunately, to date there is no empirical evidence for or against an association between sildenafil or tadalafil and NAION. The only published studies have been case reports and series,^{9–13} which, by their nature, do not provide a comparison group. Therefore, we conducted a retrospective matched case-control study to investigate the association between NAION and the self reported use of these medications.

METHODS

Selection of cases and controls

Cases and controls were selected from the University of Alabama at Birmingham, Department of Ophthalmology Clinic located at the Callahan Eye Foundation Hospital in Birmingham, Alabama, USA. This facility constitutes the most popular tertiary referral centre for people suspected of having a neuro-ophthalmological disorder in the state of Alabama.

Cases were initially identified by the clinic's electronic database for records containing the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) code 377.41 (ischaemic optic neuropathy) during the time period January 2000 to February 2004. Medical record abstraction was then performed in order to confirm the diagnosis of NAION. Our inclusion criteria for the diagnosis of NAION are as follows: (1) history of sudden painless monocular loss of vision; (2) optic disc oedema noted on ophthalmological examination that eventually resolved leaving optic disc pallor; (3) a visual field defect in keeping with pathology at the level of the optic nerve head; (4) lack of findings on examination suggesting another disorder that could be causing the symptoms; (5) exclusion of arteritic anterior ischaemic optic neuropathy by clinical history, examination, and erythrocyte sedimentation rate. Subjects were not eligible if a previous diagnosis of optic neuropathy of any aetiology was listed in a previous visit's chart notes.

Controls were randomly selected from patients seen in the clinic for reasons other than NAION during the same time period used to select cases (that is, January 2000 to February 2004). Cases and controls were matched based on age (within 1 year) and sex.

Abbreviations: ED, erectile dysfunction; NAION, non-arteritic anterior ischaemic optic neuropathy

Table 1 Demographic, health behaviour, and medical characteristics among cases and matched controls

	Cases (n = 38)	Controls (n = 38)	p Value
Age (years), mean (SD)	61.4 (10.4)	61.2 (10.5)	0.94
Race, % (n)			0.21
White	89.5 (34)	79.0 (30)	
African American	10.5 (4)	21.1 (8)	
Smoking, yes, % (n)	60.5 (23)	50.0 (19)	0.36
Alcohol consumption, yes, % (n)	76.3 (29)	76.3 (29)	0.99
Diabetes, yes, % (n)	26.3 (10)	34.2 (13)	0.45
Hypertension, yes, % (n)	68.4 (26)	57.9 (22)	0.34
Coronary artery disease, yes, % (n)	18.4 (7)	13.2 (5)	0.53
Myocardial infarction, % (n)	52.6 (20)	26.3 (10)	0.02
High cholesterol, yes, % (n)	65.8 (25)	50.0 (19)	0.16

Eighty eight individuals (males and females) with a diagnosis of NAION were initially identified as eligible and contacted for participation in the study, of whom 73 were ultimately enrolled, the remaining individuals refused to participate in the study. For each case a single control matched on age within 1 year and sex was randomly identified and contacted for participation in the study. If the first randomly selected control did not choose to participate in the study, another control was randomly selected. In total, 130 people as potential controls were contacted, of whom 42 refused to participate. Given this study's interest in ED medications, females were excluded from the analysis, thereby leaving 38 cases and 38 controls.

The institutional review board of the University of Alabama at Birmingham approved the study design and procedures.

Data collection

A telephone survey was designed to collect information regarding sociodemographic, health behaviour, and medical characteristics. A research interviewer trained in the administration of medical telephone questionnaires administered the survey. The interviewer was not masked to the status of the subject as a case or control. Sociodemographic information was collected with standard items addressing age, sex, race, and education. Health behaviours were assessed with questions concerning cigarette smoking and alcohol consumption. Medical characteristics were obtained with questions regarding whether the respondent had ever been diagnosed with various chronic conditions (for example, heart disease, high blood pressure, diabetes) and if they were currently taking medications for these conditions. Male patients were specifically asked about past and present use of phosphodiesterase inhibitor ED medications, specifically Viagra and Cilais. Specifically, subjects were queried as to the date they first used each of the medications and their frequency of use since that time. For the purposes of this study, only the medication use that occurred before the NAION diagnosis date was considered; for controls, the diagnosis date of the matched control was used to similarly truncate medication use.

Statistical analysis

Cases and matched controls were compared with respect to demographic and medical characteristics using paired *t* tests and McNemar's test for continuous and categorical variables, respectively. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between NAION and the use of ED medications. *p* Values of ≤ 0.05 (two sided) were considered statistically significant.

RESULTS

By design the mean ages of the cases and controls were similar (table 1); however, they were also similar with respect to race, with the majority of both groups being white. The prevalence of smoking and alcohol consumption also did not differ between cases and controls. Cases were more likely to report a history of hypertension, coronary artery disease, myocardial infarction, and high cholesterol, although the only significant difference was observed for myocardial infarction. Diabetes was more common among controls but not significantly so.

Table 2 presents the proportion of cases and controls that reported using Viagra and/or Cialis. While the ORs suggested an approximately 75–80% increased risk of NAION associated with the use of either or both of these medications, none of the associations were statistically significant. Given the similarity of the estimates for Viagra and Cialis, a single variable representing use of either medication was created and used in subsequent analyses.

An interaction between Viagra and/or Cialis use and two medical conditions was observed, specifically, history of myocardial infarction ($p = 0.04$) and hypertension ($p = 0.07$). Compared to individuals reporting neither Viagra and/or Cialis use nor a history of myocardial infarction, those who reported both using Viagra and/or Cialis and a history of myocardial infarction were 10.7 times (95% CI 1.3 to 95.8) more likely to have NAION, whereas no association was observed among those who also reported using Viagra and/or Cialis but did not have a history of myocardial infarction (OR 0.7, 95% CI 0.2 to 2.6). Those with a history of myocardial infarction who did not report use of

Table 2 Proportion of cases and matched controls reporting erectile dysfunction medication use and associated odds ratios (OR) and 95% confidence intervals (CI)

	Cases (n = 38)	Controls (n = 38)	p Value	OR (95% CI)	OR (95% CI)*
Viagra use, yes, % (n)	36.8 (14)	31.6 (14)	0.64	1.25 (0.49 to 3.17)	1.75 (0.48 to 6.30)
Cialis use, yes, % (n)	10.5 (4)	5.3 (2)	0.42	2.00 (0.37 to 10.92)	1.82 (0.21 to 15.39)
Viagra or Cialis, yes, % (n)	39.5 (15)	31.6 (12)	0.49	1.38 (0.55 to 3.42)	1.81 (0.51 to 6.37)

*Adjusted for all of the variables in table 1 (except age).

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for the association between NAION and Viagra/Cialis use without and without history of myocardial infarction or hypertension

	Viagra or Cialis use	
	Yes	No
Myocardial infarction		
Yes	10.7 (1.3 to 95.8)	2.2 (0.6 to 7.6)
No	0.7 (0.2 to 2.6)	—
Hypertension		
Yes	6.9 (0.8 to 63.6)	0.9 (0.3 to 3.0)
No	0.5 (0.1 to 2.4)	—

Viagra and/or Cialis demonstrated an increased risk of NAION (OR 2.2, 95% CI 0.6 to 7.6) but the association was not statistically significant. With respect to hypertension, for those who also reported Viagra and/or Cialis use, a nearly sevenfold (95% CI 0.8 to 63.6) risk of NAION was observed though this association was of borderline statistical significance ($p = 0.08$). The ORs for those who reported using these medications who also did not report a history of hypertension or the converse were 0.5 (95% CI 0.1 to 2.4) and 0.9 (95% CI 0.3 to 3.0), respectively.

DISCUSSION

Overall, we observed positive yet not statistically significant associations between Viagra and/or Cialis use and the occurrence of NAION. However, for patients with a history of myocardial infarction, we did observe a strong and statistically significant association suggestive of a link between the use of Viagra and/or Cialis and an increased risk of NAION. A similar association was also observed for patients with a history of hypertension but it was of borderline statistical significance ($p = 0.08$). These results must be interpreted in light of several potential limitations, the most apparent of which is the study's small sample size. This provided limited statistical power to detect associations that were small and moderate in magnitude and yielded estimates that lacked precision. However, we were able to observe one statistically significant association and another of borderline significance; both associations suggest modest to strong associations. Yet despite the magnitude of these associations, the lack of precision associated with these estimates provides little evidence regarding the true strength of the association should it truly exist.

Not all of the eligible cases or controls opted to participate in the study, the response rates were 83% and 68%, respectively. There were no apparent differences with respect to age or race between those who did and did not choose to participate and we have little reason to suspect selection bias with respect to the primary risk factor of interest.

Information on Viagra and Cialis (and other characteristics) was obtained via telephone interview. Given recent media attention regarding a possible link between Viagra and NAION the potential for information bias would seem to exist; however, the telephone interview was conducted before this issue reached the mainstream media, therefore we do not believe bias explains the observed results. We also have no reason to believe that any bias associated with failure to accurately recall or report the use of Viagra or Cialis is differential. Many of the existing case reports and series regarding Viagra or Cialis and NAION have been able to isolate the exact timing of use relative to the onset of NAION associated symptoms. The retrospective nature of the current study makes collecting information with this degree of precision difficult. However, when defining the primary exposure variable—that is, Viagra and/or Cialis use, we were

able to define as exposed only those subjects who reported using Viagra and/or Cialis before NAION diagnosis. This allowed us to minimise misclassification by limiting the definition of exposed to aetiologically relevant medication use. Ultimately, future research seeking to further explore this relation should consider the case-crossover design wherein such issues of temporality would be more easily addressed.

This is the first study to investigate the association between Viagra and Cialis and NAION, therefore placing the results in context is difficult. The only evidence regarding this relation is in the form of case reports and series that, by their nature, do not explicitly test whether such an association might exist. Despite this, these studies lend some support to the results reported herein. Pomeranz and Bhavsar describe 14 cases of NAION that occurred shortly after Viagra use.¹² Of interest is the fact that eight of these patients had a history of hypertension and six had history of elevated lipids; only two had a history of coronary artery disease or myocardial infarction. This provides support, albeit indirect, that should an association exist between Viagra and NAION, it may be limited to individuals with a history of cardiovascular disease.

One hypothesis regarding the cause of NAION is vascular insufficiency at the optic nerve head; this insufficiency and the resulting ischaemia may be more frequent in those with certain anatomical characteristics (for example, small physiological cup).¹¹ Viagra and Cialis may cause damage to the optic nerve head via its ability to increase nitric oxide levels that in turn cause reduced perfusion. However, this does not satisfactorily explain why we observed the strongest effect among those with a history of myocardial infarction or hypertension. Insight regarding this issue can be gleaned from the fact that certain chronic medical conditions such as hypertension, diabetes, heart disease, are thought to be risk factors for optic nerve head vascular insufficiency.¹⁶ Therefore, individuals with these conditions, or specifically the pharmacological treatments for these conditions, who may already be at increased risk of NAION, may have their risk exacerbated in the presence of Viagra or Cialis.

The Food and Drug Administration has issued a statement regarding reports of patients experiencing a sudden loss of vision attributed to NAION after taking Viagra, Cialis, and Levitra.¹⁷ This statement is clear that no link has been established between these medications and the occurrence of NAION. However, it advises patients "...to stop taking these medicines, and call a doctor or healthcare provider right away if they experience sudden or decreased vision loss in one or both eyes. Further, patients taking or considering taking these products should inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION. Such patients are at an increased risk of developing NAION again." Similarly, recent publications have suggested that ophthalmologists ask all men with

NAION about the use of sildenafil (Viagra) and that patients with a history of monocular NAION be cautioned that sildenafil may increase the risk of NAION in the fellow eye.¹² Given the results of the current study, patients with a history of myocardial infarction or hypertension who are prescribed Viagra or Cialis should be warned about the elevated risk of NAION associated with the use of these medications. Though NAION is a rare condition, the large number of men using Viagra or Cialis suggests that, should an association truly exist, the incidence of NAION could rise dramatically.

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