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Sildenafil citrate use and the incidence of nonarteritic anterior ischemic optic neuropathy

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SUMMARY

Nonarteritic anterior ischemic optic neuropathy (NAION) has been reported rarely in men after taking sildenafil or other phosphodiesterase 5 inhibitors for erectile dysfunction (ED). The incidence of NAION in men receiving sildenafil treatment for ED was estimated using pooled safety data from global clinical trials and European observational studies. Based on clinical trial data in more than 13,000 men and on more than 35,000 patient-years of observation in epidemiologic studies, we estimated an incidence of 2.8 cases of NAION per 100,000 patient-years of sildenafil exposure. This is similar to estimates reported in general US population samples (2.52 and 11.8 cases per 100,000 men aged $\geq$50 years). The data cited herein do not suggest an increased incidence of NAION in men who took sildenafil for ED.

Keywords: Diabetes; erectile dysfunction; hypertension; optic neuropathy; ischemic; phosphodiesterase type 5 inhibitors; sildenafil citrate

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Although nonarteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in people older than 50 years, it is actually a rare event in the general population, with only between 1500 and 6000 cases reported in the US each year (1,2). It is characterised by sudden, usually painless, partial loss of vision in one eye (3), which confers an increased risk of vision loss in the contralateral eye (4). Although a definitive cause has not been determined, NAION is thought to occur following an idiopathic ischemic event involving the short posterior ciliary arteries that supply blood to the most anterior part of the optic nerve (3). A complete loss of vision is rare, but partial loss of visual field or acuity can result from NAION in the affected eye(s) (5).

Patients who have a 'disc at risk' or 'crowded disc' (small cup : disc ratio) (6) are at increased risk for developing NAION. The optic disc is the region in which the optic nerve attaches to the back of the eye, and the optic cup is a smaller circular region within the disc. The optic nerve fibres that make up the cup allow the central retinal artery to pass through the optic disc to supply blood to the retina and are supplied themselves by very small branching vessels from the posterior ciliary arteries. If the optic nerve fibres are crowded by a small scleral channel, then an ischemic event in the small vessels that supply the optic nerve increases the risk of NAION.

In addition to a crowded disc, other established risk factors for NAION include age greater than 50 years and white race (an estimated 95% of cases occur in the latter group) (5). Hypertension and diabetes also predispose to NAION development (5). Other factors that have been hypothesised to associate with NAION include high cholesterol, arteriosclerosis, stroke, cardiac and intraocular surgery, tobacco use, nocturnal hypotension, blood loss, glaucoma, elevated homocysteine and sleep apnea (3). The association between NAION and hypertension, high cholesterol and diabetes is stronger in individuals younger than 50 years than in older persons (3).

Many of the risk factors for developing NAION also predict the occurrence of erectile dysfunction (ED), such as hypertension, diabetes, hyperlipidemia and smoking (7–9). Oral phosphodiesterase 5 inhibitors such as sildenafil citrate (Viagra®, Pfizer Inc, New York, NY, USA) are the first-line treatment for ED in patients without contraindications. Vascular risk factors associated with ED clearly indicate that consumers of sildenafil are not a random sample of the general US male population, even of the population of those aged $\geq$50 years. The prevalence of hypertension and diabetes in the general US adult population, according to data analysed from the National Health and Nutrition Examination Survey (NHANES) for 1999–2002, is estimated to be 29% (10) and 7% (11), respectively. In contrast, in a large population of ED patients ($n = 272{,}325$), the prevalence of diagnosed hypertension and diabetes in men

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aged 56–65 years ($n = 91,280$) was 51% and 23%, respectively (7). Similar baseline prevalences were observed in the 420 patients with NAION eligible for the 26-centre Ischemic Optic Neuropathy Decompression Trial: 47% and 24%, respectively (5). Furthermore, the joint occurrence of hypertension and diabetes is higher in the ED population (12.8%) (7) and in the NAION population (13%) (12) than in the general population (5.4% [data derived from NHANES 1999–2002 (13)]). Thus, based on the increased prevalence of underlying NAION risk factors, the incidence of NAION in men with ED would be expected to be higher than the incidence of NAION in the general population, and some men being treated for ED would be expected to coincidentally experience NAION.

Sildenafil has been approved for the treatment of ED since 1998, and more than 150 million prescriptions have been written for more than 27 million men worldwide since its approval (14). The results of more than 100 manufacturer-sponsored clinical trials of sildenafil for the treatment of ED demonstrate that it is well tolerated in patients with ED of various aetiologies and comorbid conditions. However, because sildenafil may potentiate the hypotensive effects of nitrates, sildenafil use in patients receiving organic nitrates in any form, at any time, is contraindicated.

Because of the implied relationship between ED and cardiovascular disease, the cardiovascular risk associated with sildenafil use has been studied extensively. Acute or long-term (as needed) treatment of ED with sildenafil has not been causally associated with the onset of cardiovascular ischemic events (15–18).

There have been rare postmarketing reports of patients developing NAION after taking sildenafil or other phosphodiesterase 5 inhibitors (i.e. tadalafil [Cialis®, Lilly ICOS LLC] and vardenafil [Levitra®, Bayer Pharmaceuticals Corporation]) for ED. Consequently, the US Food and Drug Administration and several other regulatory agencies requested that the prescribing information for all three marketed phosphodiesterase 5 inhibitors be updated. The manufacturer has modified the prescribing information for Viagra globally. The Viagra US prescribing information was updated (Adverse Reactions/ Postmarketing Experience section) as follows:

> NAION, a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to low cup to disc ratio ('crowded disc'), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors or to other factors (19).

The Precautions/Information for Patients section of US prescribing information was also updated, directing physicians to 'advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes' (19) and to 'discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by the use of vasodilators, such as PDE5 inhibitors' (19).

Although no cases of NAION have been reported in patients treated with Revatio® (sildenafil citrate, Pfizer Inc, New York, NY, USA) for pulmonary hypertension, the manufacturer has also modified the Revatio prescribing information (20).

Spontaneous reports, while useful for identifying potential signals of drug adverse events, are subject to a number of limitations. Spontaneous reports may under-report or over-report events; may lack medical confirmation; can be influenced by factors such as time on market, popularity of a drug, severity of event, or media attention; and cannot provide incidence rates. To better understand this event in men who use sildenafil, we used pooled global clinical trial and European epidemiologic data to compare the estimated incidence of NAION in the general US population of men with the estimated incidence in men who took sildenafil for ED worldwide.

INCIDENCE OF NAION IN THE GENERAL US POPULATION

Only two studies have investigated the incidence of spontaneous NAION in the general US population. As part of the Rochester Epidemiology Project conducted from 1981 to 1990, Hattenhauer et al. (1) conducted a retrospective analysis of residents of Olmstead County, MN, aged 50 years or older. Only 22 NAION cases were observed, which yielded an annual estimated incidence in men and women of 10.3 cases (95% confidence interval [CI], 6.5–15.6) per 100,000 population aged $\geq$50 years. The estimated incidence was slightly higher among men [11.8 per 100,000 aged $\geq$50 years (95% CI, 5.9–21.1)] compared with women [9.2 per 100,000 aged $\geq$50 years (95% CI, 4.6–16.5)].

Johnson and Arnold (2) sampled a larger population in two different regions of the US, resulting in greater racial diversity and a more accurate representation of US population. Monthly written surveys were sent during a 12-month period to an average of 198 ophthalmologists in Missouri and during a 6-month period to an average of 336 ophthalmologists in

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Los Angeles County. Analysis of 1814 written responses provided an estimated annual NAION incidence in men and women of 2.3 cases per 100,000 population aged ≥50 years (95% CI, 1.78–2.82) (2). Similar to the results of Hattenhauer et al., the estimated incidence was slightly higher among men [2.52 per 100,000 men aged ≥50 years (95% CI, 1.69–3.33)] than in women [2.14 per 100,000 women aged ≥50 years (95% CI, 1.48–2.81)].

Follow-up telephone interviewing to resolve 130 of 579 nonresponses from the first 5 months of the Missouri survey yielded one additional case of NAION. The results from this follow-up sample were extrapolated to the 1293 nonresponses during the entire 12-month Missouri survey, resulting in 10 additional cases and a corrected estimated annual incidence of 3.06 per 100,000 men and women aged ≥50 years (2).

INCIDENCE OF NAION IN STUDIES OF SILDENAFIL

To determine the incidence of NAION in men receiving sildenafil for the treatment of ED, we reviewed safety data from global clinical trials and European observational studies. Clinical trial data and epidemiologic data are both necessary to evaluate a drug's safety profile. Clinical trial data have the advantage of capturing more frequent and more detailed patient assessments than observational epidemiologic studies, but observational studies generally reflect 'real-life' use in a greater number of patients followed for a longer period of time. Clinical trials and observational studies both have mechanisms to reliably capture incident, serious, adverse events, including cases of NAION.

A review of a collective database of 103 double-blind or open-label trials of sildenafil conducted between 1993 and 2003, which included more than 13,400 men with ED, 76% of whom were from non-US (international) sites, revealed no cases of reported or observed NAION in more than 13,300 patient-years of observation (14).

The International Men's Health Study, a prospective cohort study of 3813 men (mean age 57 years; range 18–100 years) who received a sildenafil prescription in Germany, France, Spain or Sweden was conducted by the manufacturer between 2001 and 2004 (21). This cohort study had broad inclusion criteria (receipt of a sildenafil prescription as part of normal care by general practitioners or urologists) and minimal exclusion criteria (inability to understand or complete informed consent or questionnaires). Detailed information on health status was obtained from participants via a quarterly postal questionnaire, and all serious events received medical confirmation. No cases of NAION were reported during 2935 patient-years of follow-up (14).

A study of patients who received sildenafil from the UK National Health Service was independently conducted by the Drug Safety Research Unit at the University of Southampton between 1998 and 2001 (22–24). In this prescription event monitoring (PEM) study, physicians were asked to provide, via postal questionnaire, brief demographic and clinical information on patients who had filled an initial sildenafil prescription between September 1998 and March 1999 (phase I) and April 1999 and August 1999 (phase II). Response rates were typical of a PEM study and ranged from 54.7% to 61.0%. The mean follow-up time was 6.0 months for the 5601 patients in phase I and 17.5 months for the 22,473 patients in phase II. One case of NAION was reported to the Drug Safety Research Unit during the 35,500 patient-years of observation (24,25). This patient was 61 years of age, had significant predisposing factors for NAION (i.e. a smoker being treated for hypertension, ischemic heart disease diagnosed following myocardial infarction and reported multiple concomitant medications) and did not experience the NAION event until more than a year (368 days) after first being prescribed sildenafil. Based on the report of one NAION case in a total of 35,500 patient-years of observation in the PEM, the unadjusted incidence of NAION is estimated to be 2.8 cases per 100,000 patient-years of exposure to sildenafil.

DISCUSSION

An association between medication use and NAION has been considered previously but has not been well supported. In a recent review of the ischemic optic neuropathies, Rucker, Biousse and Newman concluded, 'Rarely, medications have been implicated in the pathogenesis of NAION, including sumatriptan, sildenafil, amiodarone and nasal decongestants. Establishing a direct relationship between the use of a specific medication and NAION is problematic, however, since most patients have concurrent vascular risk factors and an underlying disc-at-risk.' (3)

Using extensive epidemiologic and clinical trial data, we estimated an incidence of 2.8 cases of NAION per 100,000 patient-years of exposure to sildenafil for the treatment of ED. Compared with estimates in general population samples, this finding is similar to those of Johnson and Arnold (2.52 per 100,000 men aged ≥50 years initially; 3.06 per 100,000 individuals [men and women] aged ≥50 years when corrected for missing respondents) but lower than that of Hattenhauer et al. (11.8 cases per 100,000 men aged ≥50 years). Therefore, the data cited herein do not suggest an increased incidence of NAION in men who took sildenafil for their ED.

Based on the similar risk profiles for NAION and ED, it is not unexpected to observe NAION cases in men with ED. Rather than supporting an increased incidence of NAION associated with sildenafil use, this analysis of clinical trial and epidemiologic data representing approximately 52,000 patient-years of observation indicates that the NAION incidence in men with ED who took sildenafil worldwide is

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consistent with the range of estimated NAION incidence in the general US population. Extensive European epidemiologic and global clinical trial data suggest that there is no increased incidence of NAION associated with sildenafil use.

DISCLOSURES

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