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Vision Disorders and Phosphodiesterase Type 5 Inhibitors

A Review of the Evidence to Date

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Abstract

Phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, vardenafil and tadalafil) have been in widespread use for the safe and effective treatment of erectile dysfunction (ED) for nearly a decade. During that time, a relatively small number of patients have experienced adverse visual events, including nonarteritic anterior ischaemic optic neuropathy (NAION). In this article, post-marketing reports of adverse visual events along with other relevant literature on ocular safety related to PDE-5 inhibitor use are reviewed. Although a relatively small number of cases have been reported with a possible temporal association with PDE-5 inhibitor use, it has not been possible to conclude whether these events are coincidental or whether they are

associated with effects of PDE-5 inhibitors on ocular circulation or on other structures of the eye. A careful review of pooled data from clinical trials for all three PDE-5 inhibitors, which contain well documented information about the dose and duration of exposure to the drug for a large number of patients, yields no evidence for an increased risk of NAION or other adverse ocular events associated with PDE-5 inhibitor use. However, the inherent limitations in interpreting results from clinical trials and potentially incomplete information from post-marketing surveillance preclude a definitive declaration that ocular safety will not be a concern for some patients with ED and co-morbid disease states. Despite the absence of a proven link between PDE-5 use and serious ocular disorders, physicians should continue to advise patients to stop use of a PDE-5 inhibitor and seek immediate medical attention in the event of a sudden loss of vision as a safety measure.

Phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, vardenafil and tadalafil) have been in widespread use for the safe and effective treatment of erectile dysfunction (ED) for nearly a decade. During that time, a relatively small number of patients have experienced adverse visual events, including nonarteritic anterior ischaemic optic neuropathy (NAION). This article reviews the ocular safety profile of PDE-5 inhibitors prescribed for the treatment of ED, taking into consideration co-morbidities such as diabetes mellitus and cardiovascular disease (CVD), which may be shared risk factors that predispose some patients to visual disorders. A literature survey was conducted on MEDLINE from January 1991 to June 2008 using the terms 'central serous chorioretinopathy', 'nonarteritic anterior ischemic optic neuropathy', 'retinal artery branch occlusion' and 'phosphodiesterase type 5 inhibitors'. Results from clinical trials, post-marketing studies and published case reports are summarized.

1. Erectile Dysfunction

1.1 Risk Factors for Erectile Dysfunction

A cross-sectional analysis of 2126 adult male participants in the 2001–2 National Health and Nutrition Examination Survey (NHANES) estimates that ED affects 18 million men in the US.[1] The prevalence of ED was higher for men with one or more cardiovascular risk factors and was 51% among men with diabetes. The prevalence and severity of ED increase with age in men aged 40–70 years, as does the incidence of co-morbidities.[2] An increase in the prevalence of ED to over 300 million men worldwide is expected by 2025.[3] ED may result from psychogenic, or organic factors, or a combination of the two. Vascular disease is the most common organic cause of ED.[2,4]

A large managed-care claims database (1995–2002) of 272 325 patients with ED identified hypertension, hyperlipidaemia, diabetes and depression to be the most common co-morbid diagnoses.[5] Another recent survey of 22 086 men in the US using a questionnaire to evaluate the risk of developing ED found positive associations with obesity and cigarette smoking, and an inverse relationship with physical activity.[6] A survey of 8367 Australian men aged 18–59 years found a higher risk of ED for smokers compared with nonsmokers, with the highest risk for those smoking >20 cigarettes per day.[7] A more recent study of 2301 men in the Boston area (MA, USA) also found a significant trend for an increased risk of ED with cumulative pack-years of smoking, and a moderately increased risk for nonsmokers exposed to passive smoking, although not statistically significant.[8] In addition to hypertension, hyperlipidaemia and diabetes, lower urinary tract symptoms and psychological stress were also identified as risk factors for ED in a study of 2869 men in Vienna,

Austria.[9] Central obesity has been identified from anthropometric measurements to be a predictor of ED in men older than 60 years.[10] Results from the Massachusetts Male Aging Study found an association between ED and the metabolic syndrome, which is characterized by central obesity, insulin resistance, abnormal lipid levels and borderline hypertension.[11] The investigators concluded that ED may be an early warning sign for the development of the metabolic syndrome and might be an indication for providing early intervention to prevent CVD. A strong association between ED and subsequent development of clinical cardiovascular events was found in the placebo group (9457 men) in the 5-year Prostate Cancer Prevention Trial, with the authors concluding that ED is a harbinger of CVD in some men.[12]

1.2 Treatment of Erectile Dysfunction

Oral PDE-5 inhibitors are the current first-line treatment for ED, and their pharmacological mechanism of action is well understood. The physiological mechanism for penile erection during sexual stimulation involves release of nitric oxide (NO) from cavernous nerves and vascular endothelial cells in the corpus cavernosum.[13] Vascular dilation occurs through relaxation of vascular smooth muscle mediated by intracellular cyclic nucleotide/protein kinase messenger systems. NO activates the enzyme guanylate cyclase, leading to an increase in cyclic guanosine monophosphate (cGMP) and activation of cGMP-dependent protein kinase I. Activated kinases phosphorylate proteins that inhibit the calcium pump within the membrane of the sarcoplasmic reticulum, causing a reduction in free cytoplasmic calcium and smooth muscle relaxation leading to increased corporal blood flow and tumescence (erection). The enzyme PDE-5 is responsible for degradation of cGMP. Inhibition of PDE-5 slows cGMP degradation, leading to increased levels of cGMP and greater blood flow through the corpus cavernosum when NO is released during sexual stimulation. In the absence of sexual stimulation, PDE-5 inhibitors have little effect on corpus cavernosum blood flow.

The first PDE-5 inhibitor to be approved by the US FDA for the treatment of ED was sildenafil, approved in March 1998. The effectiveness and safety of sildenafil for treating ED has been established in over 100 manufacturer-sponsored clinical trials of sildenafil, with a cumulative exposure of over 13 000 patient-years, and from other independent studies.[14,15] To date, sildenafil has been prescribed to nearly 35 million men worldwide.[16] The recommended therapeutic dose is 50 mg, taken orally approximately 1 hour before sexual activity, and not more than once per day.[17] The dose can be increased to 100 mg, the maximum recommended dose, or decreased to 25 mg, depending on effectiveness and tolerability. The half-life of sildenafil after oral administration is about 4 hours.

The cardiovascular safety profile for sildenafil has been well defined for otherwise healthy men with ED and for individuals with co-morbid CVD.[18] No differences in adverse events with sildenafil have been found between men taking antihypertensive medications and men with hypertension who were not treated. There is no evidence that the use of sildenafil is associated with an increased risk of adverse cardiovascular events. However, men with ED and co-morbid CVD may be at greater risk for adverse cardiovascular events unrelated to sildenafil use. Recommendations for evaluating the degree of risk associated with sexual activity for men with CVD are provided by the Second Princeton Consensus Conference as a general guide for managing patients with ED with co-morbid CVD.[19,20]

The second PDE-5 inhibitor to be approved by the FDA for the treatment of ED was vardenafil, approved in August 2003. The efficacy and safety of vardenafil has been evaluated at doses of 5, 10 and 20 mg in four double-blind, placebo-controlled, multicentre trials with 2431 men aged 20–83 years.[21] Safety data are available from over 4430 men worldwide, with 880 patients treated for at least 1 year. The recommended therapeutic dose for most patients with ED is 10 mg, taken orally approximately 1 hour before sexual activity and not more than once a day. Its half-life after oral administration is similar to

sildenafil; approximately 4–5 hours. Lower doses of 2.5 and 5 mg are available as required for co-administration with other medications, and a higher dose of 20 mg is available for patients whose response to 10 mg is not adequate.

The third PDE-5 inhibitor to be approved by the FDA for the treatment of ED was tadalafil, approved in November 2003. The efficacy and safety of tadalafil has been evaluated in over 4000 patients in 22 clinical trials of up to 24 weeks' duration.[22] It is structurally different from the other two PDE-5 inhibitors and has a longer half-life of 17.5 hours. The recommended starting dose is 10 mg for most patients, which can be increased to 20 mg or decreased to 5 mg, depending on efficacy and tolerability. The prescribing information for tadalafil was updated in February 2008,[22] adding recommendations for once-daily use by some patients at a starting dose of 2.5 mg taken at approximately the same time each day. The daily dose may be increased to 5 mg, depending on efficacy and tolerability. Cautions for once-daily use are advised for patients with hepatic insufficiency or severe renal insufficiency, or patients taking concomitant potent inhibitors of cytochrome P450 3A4.[22]

1.2.1 Treatment-Related Adverse Events

Treatment-related adverse events with PDE-5 inhibitors are generally mild to moderate and consistent for this class of drugs. Headache, facial flushing, nasal congestion, dyspepsia and back pain are the most common adverse events.[23-26] An analysis of pooled data from a subset of 974 men with diabetes and ED from 11 placebo-controlled trials with sildenafil found similar adverse events.[27] Cardiovascular safety has been extensively evaluated for all three PDE-5 inhibitors. An analysis of pooled data collected prospectively from more than 120 clinical trials with sildenafil conducted worldwide from 1993 to 2001 showed no difference in the rate of myocardial infarction or cardiovascular death compared to placebo, with no significant increase in relative risk.[18,28,29] Sildenafil was not associated with short-term risk of myocardial infarction within 6 hours, or within 24 hours following sexual intercourse. An analysis of pooled data from 28 placebo-controlled clinical trials with tadalafil shows a similar cardiovascular safety profile.[30] However, caution is advised in prescribing PDE-5 inhibitors to patients who have had a myocardial infarction or stroke, or who have resting hypotension or hypertension, unstable angina or cardiac failure, as there are no controlled clinical data in these patient types.

1.2.2 Post-marketing Reports of Adverse Events

Although it is crucial to identify adverse events, there are many limitations to clinical trials, including relatively short duration of therapeutic exposure when the drug is under study, limited numbers of subjects and arbitrary times for analysing the incidence of adverse events. Consequently, premarketing clinical trials do not identify all potential clinically relevant adverse events. Post-marketing surveillance is encouraged by the FDA through the MedWatch programme, relying on healthcare providers to voluntarily report serious, clinically significant adverse events that are suspected to be related to the use of medical products, either to the manufacturer or directly to the FDA.[31] The system often identifies unsuspected adverse events and is a valuable tool for continuous monitoring of product safety. However, the limitations of post-marketing surveillance are recognized, including the subjective nature of spontaneous reports and possible bias of the healthcare professional, the probability that adverse events are under-reported, lack of detail concerning exposure to the product and onset of the adverse event, inadequate or insufficient follow-up after the event or whether there are other potential confounding factors. Publications of adverse events can also lack sufficient detail to evaluate whether there is reason for causality. The eventual goal of post-marketing surveillance should be to generate testable hypotheses to explain the association between the adverse event and the product. However, it may not be feasible to design or conduct an appropriate clinical study for the specific population that might be at risk. Thus, it is difficult to discriminate whether an isolated,

rare adverse event is due to an unknown effect of the drug or whether it is a coincidental event.

Post-marketing surveillance of PDE-5 inhibitors has provided additional data on safety profiles that have been generally consistent with adverse events that have been reported in pre-marketing clinical studies. Post-marketing safety analyses have been conducted for sildenafil for more than 28 000 patients with ED in the UK and 3813 patients with ED in the EU, as recently reviewed.[18] Additional post-marketing safety studies for vardenafil include results for over 30 000 patients with ED in the Real Life Safety and Efficacy study in the US,[32] 29 358 patients with ED in Germany[33] and 384 patients with ED in Korea.[34] Prescription event monitoring of tadalafil was used to evaluate cardiovascular safety for 6266 patients with ED in the UK, finding that the mortality rate from myocardial infarction and ischaemic heart disease was similar to the general male population in the UK.[35]

Post-marketing reports of adverse visual events in patients with ED treated with PDE-5 inhibitors have also appeared in the literature, often in the form of individual case reports, with variable quality of information available to evaluate whether there is a direct association with PDE-5 inhibitor exposure or whether the events are coincidental.

2. Phosphodiesterase Type 5 (PDE-5) Inhibitors and Visual Function

The NO/cGMP pathway is important for the normal physiology of the eye, not only for regulation of ocular blood flow, but also for phototransduction. Disturbances in the normal balance of NO and cGMP, or in oxygen delivery by the ocular circulation, can have an effect on vision. Experimental and clinical evidence for the role of NO in glaucoma, retinal ischaemia and diabetic retinopathy has been recently reviewed.[36] Clinical studies in diabetic patients suggest that basal NO release is reduced, the vascular system is less sensitive to NO or that increased oxidative stress inactivates NO. Altered NO production and impaired ocular blood flow due to increased intraocular pressure are both postulated to be involved in the pathogenesis of glaucoma. Increased levels of NO from sources other than the endothelium may contribute to the pathophysiology of some ocular diseases. Additional NO can be released from nitrergic efferent nerves or produced in high amounts from the immune isoform of NO synthase during inflammation.

2.1 A Tale of Two PDEs

Currently, 11 families of PDE enzymes (PDE-1 to PDE-11) have been identified. Three families (PDE-5, PDE-6 and PDE-9) selectively hydrolyse cGMP, and five other families (PDE-1, PDE-2, PDE-3, PDE-10 and PDE-11) can hydrolyse both cGMP and cyclic adenosine monophosphate with varying degrees of efficiency.[37] Two PDEs found in the eye (PDE-5 and PDE-6) are important for visual function. As elsewhere in the vascular system, PDE-5 is located in the smooth muscle of ocular blood vessels. PDE-6 is present in rod and cone photoreceptors and in bipolar cells but is not found in the vasculature. PDE-6 regulates cGMP required for normal operation of the visual transduction cascade. Severe and persistent disturbances in either the synthesis or degradation of cGMP can lead to photoreceptor cell death and retinal degeneration, for example, in a form of retinitis pigmentosa.[38]

It is known that PDE-5 inhibitors can also partially inhibit the PDE-6 enzyme.[38] A study with purified rod and cone PDE-6 enzymes reports that competitive inhibition of rod PDE-6 by PDE-5 inhibitors is two to three times greater than for cones.[39] The greatest competitive inhibition was found for vardenafil, with average inhibition constants (K_i) of 0.71 nM and 0.3 nM for rod and cone PDE-6, respectively. Less competitive inhibition was found for sildenafil, with average K_i an order of magnitude higher at 11 nM and 4.7 nM for rod and cone PDE-6, respectively. The lowest competitive inhibition was found for tadalafil, with average K_i of 2100 nM and 700 nM for rod and cone PDE-6, respectively.

The potential for nonselective inhibition of the PDE-6 enzyme was an initial concern for ocular

safety. As a result, the effects of PDE-5 inhibitors on vision were carefully monitored in pre-marketing clinical studies. The relative selectivity of PDE-5 inhibitors for PDE-5 over PDE-6 indicated in prescribing information for each product is 10-fold for sildenafil,[17] 15-fold for vardenafil[21] and 700-fold for tadalafil.[22] As a result of this, this class of drugs is not recommended for patients with hereditary degenerative retinal disorders, including retinitis pigmentosa.[17,21,22]

2.2 Colour Vision Changes

Minor disturbances in colour vision were reported for a small percentage (2%) of subjects in pooled data from clinical trials with sildenafil.[18] Sildenafil can cause transient, fully reversible, mild impairment of colour discrimination (assessed by Farnsworth-Munsell 100-hue test) that is often, but not exclusively, in the green-blue to blue-purple range of the light spectrum.[40,41] The greatest changes in colour discrimination occur when sildenafil plasma concentration is highest, approximately 1-hour post-dose, returning to baseline in 4–8 hours.[42]

A pooled analysis of 25 double-blind, placebo-controlled clinical trials with 5918 patients found that transient visual events (colour tinge, sensitivity to light, blurred vision) were reported by 5% of 3545 patients receiving sildenafil compared with <1% of 2373 patients receiving placebo.[42,43] The visual events were dose dependent, suggesting greater competitive inhibition of PDE-6 at higher doses of sildenafil, especially at 200 mg (twice the maximum recommended therapeutic dose). Fewer reports of abnormal vision were observed in an analysis of pooled data from 37 double-blind, placebo-controlled, phase II, III and IV clinical trials for sildenafil for all 8350 patients (2.3% vs 0.47% for placebo). Lower incidences were observed for the 2312 patients with diabetes (1.5% vs 0.4%), the 3036 patients with hypertension (2% vs 0.5%) and the 971 patients with ischaemic heart disease (2% vs 0.7%).[18] No more than 2% of 608 patients receiving vardenafil in clinical trials reported adverse visual events.[25] Lower incidences of 0.46%[32] and 0.3%[34] have been found in post-marketing surveillance of vardenafil. In an integrated analysis of clinical trials for tadalafil, only 1 (0.1%) of 804 men receiving tadalafil reported abnormal colour vision.[24]

2.3 Electroretinogram Changes

As recently reviewed,[14] there is no evidence that sildenafil produces any clinically significant changes in visual function from either pre-marketing clinical trials or post-marketing reports. Transient changes in the electroretinogram (ERG), such as modest prolongation of rod (scotopic) a-wave and cone (photopic) b-wave implicit times that correlated with dose and peak plasma concentration of sildenafil have been reported from a double-blind, placebo-controlled study in 20 healthy men.[44] No visual adverse events were found, and all electrophysiological effects returned to normal within 24 hours. Comparable ERG studies have not been reported for vardenafil and tadalafil.

Other studies examining the effects of sildenafil on visual function, including visual acuity and Humphrey visual field, have been recently summarized.[14] However, only limited information on changes in visual function with vardenafil[24] or tadalafil[45,46] is available in the literature.

3. PDE-5 Inhibitors and Ocular Circulation

Because patients with ED often have multiple cardiovascular-related risk factors, it should not be surprising that patients with ED might also incur vision disorders due to vascular disease of ocular blood vessels. Isolated cases of more serious visual disorders have been reported for a small number of patients using PDE-5 inhibitors, although a causal link has not been established. Circulatory disorders are major causes of blindness or impaired vision. The blood supply to the optic nerve head (ONH) is complex and is derived primarily from posterior ciliary arteries.[47] Nerve fibres at the surface of the optic disc are supplied mainly by retinal arterioles derived from branches of the central retinal artery. The prelaminar region between the surface layer and the lamina cribrosa is supplied by the peripapillary choroid, without contribution from the central retinal

artery. The entire lamina cribrosa region is a highly vascular structure supplied solely from branches of short posterior ciliary arteries. In addition, the retrolaminar region immediately behind the lamina cribrosa is supplied by pial arteries, some of which branch from the circle of Zinn and Haller. Pial arteries can also branch from short posterior ciliary arteries or the central retinal artery.

Normal visual function depends on adequate delivery of oxygen and nutrients to the retina and optic nerve. Ocular blood flow and oxygen supply depend on the balance between systemic blood pressure and intraocular pressure and can be compromised if either the intraocular pressure is elevated or systemic blood pressure is reduced.[48] The actual form of the optic disc ('crowded disc') and the scleral canal are postulated to affect blood flow to the eye, although specific mechanisms for a vasculopathy are not defined.[49] The effect of sildenafil on ocular circulation has been investigated as a factor for possible adverse visual events in several different populations, as described below in sections 3.1–3.3, with only limited investigations for the other PDE-5 inhibitors.

3.1 Healthy Subjects

A number of small-scale studies (typically <20 subjects) measuring the effects of sildenafil on intraocular pressure and ocular blood flow conducted in healthy subjects have been recently reviewed.[14] Virtually all found no significant effects of sildenafil on ocular blood flow. As expected, there were some minor inconsistencies among the studies, which probably reflect technical difficulties in measuring relatively small changes with the various techniques that were used. In one randomized, placebo-controlled study, retinal blood vessel diameters were measured along with blood flow velocities by laser Doppler flowmetry following a single dose of sildenafil 100 mg in 12 healthy male subjects.[50] After baseline measurements, data were collected every 20 minutes for 3 hours, with an endpoint at 6 hours. Blood flow responses to a 60-second period of 8-Hz flicker were also assessed. There was a tendency for an increase in the retinal artery diameter, with a maximum increase of 3.7% at 1-hour post-dose, but the changes were not statistically significant. Retinal artery blood flow velocity also tended to increase, with a peak increase of 8.9% at 40 minutes, again not statistically significant. There was a significant increase in retinal blood flow ($p = 0.029$), with a peak increase of 15.7% that occurred 80 minutes after administration. In another randomized, placebo-controlled study using laser Doppler flowmetry to follow changes in choroidal and ONH blood flow, there was a tendency for a decrease in choroidal blood flow and an increase in ONH blood flow at 1 hour after administration of sildenafil 100 mg.[51] However, these blood flow changes were not statistically significant, and similar trends were observed with placebo. In addition, no significant changes were found in intraocular pressure, mean blood pressure or perfusion pressure. It was estimated that the laser Doppler flowmetry method was able to detect a 20% change in blood flow.

In a more recent double-blind, placebo-controlled study, colour Doppler ultrasonography was used to assess changes in ophthalmic artery blood flow following administration of sildenafil 100 mg, tadalafil 20 mg or placebo in 30 healthy subjects.[52] Measurements were made at baseline, and at 1, 4, 8, 12, 24, 36 and 48 hours after administration of the study drug. There was a significant increase ($p < 0.01$) in both end diastolic and peak systolic blood velocities at 1 hour for sildenafil 100 mg. However, both end diastolic and peak systolic blood velocities were significantly increased from baseline at 1, 4, 8, 12 and 24 hours after administration of tadalafil 20 mg, with the largest increase at 1 hour. The peak systolic blood velocity was significantly elevated at 36 hours after tadalafil administration. No significant changes were found with placebo. It is not possible to assess how blood flow to the optic nerve was altered in this study, because the ophthalmic artery not only supplies the eye, but also the orbit and some adjacent structures.

3.2 Patients with Pre-existing Ocular Disorders

In a randomized, double-blind, placebo-controlled study of 15 men with open-angle

glaucoma, no significant change in intraocular pressure was observed with the maximum therapeutic dose of sildenafil 100 mg.[53] The effects of sildenafil on foveolar choroidal blood flow were investigated in a randomized, double-blind, placebo-controlled, crossover study in 15 male patients with age-related macular degeneration (AMD) using laser Doppler flowmetry.[54] No significant changes were observed. In another randomized, double-blind, placebo-controlled, crossover study of 14 male patients with AMD, major retinal vein diameter measurements were obtained from computer analysis of digitized fundus photographs following sildenafil 100 mg.[55] Minor, but statistically significant increases in average retinal vein diameter by 4.7%, 5.5% and 5.8% were found at 90, 180 and 300 minutes, respectively. It was not determined whether there were also blood flow increases in the retinal microcirculation.

3.3 Individuals with Erectile Dysfunction

A combined analysis of data from clinical trials of sildenafil identified 66 patients with ED with pre-existing ocular disorders, including 33 men with glaucoma, 16 with diabetic retinopathy and 12 with AMD. No difference in adverse visual events was noted for those receiving sildenafil or placebo.[56] No ocular effects of sildenafil were found in a small study of six patients with ED and glaucoma.[57] In a study of 38 men with ED using colour Doppler ultrasonography to evaluate ocular blood flow, no significant change from baseline in retinal artery diameter or maximal blood flow velocity was found 60 minutes and 75 minutes after taking sildenafil 100 mg.[58] In a study of 15 patients with ED receiving sildenafil 50 mg two times per week for 3 months, ocular blood flow was evaluated using colour Doppler imaging, and no effect on ocular haemodynamics was found.[59] A randomized study of 30 men with ED (20 receiving sildenafil, 10 receiving placebo) using colour Doppler ultrasound to measure ocular blood flow reported statistically significant higher mean blood flow velocities 1 hour after administration of sildenafil 100 mg in the ophthalmic and short posterior ciliary arteries with no difference in mean blood flow velocity in the central retinal artery, compared with measurements from the same blood vessels in the group receiving placebo.[60] Although the largest difference in mean blood flow velocity between groups was for the short posterior ciliary artery, the relative increase from baseline was 28% for the sildenafil group. A larger relative change was found for the ophthalmic artery, with a 41% increase from baseline for the sildenafil group.

4. Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)

Nonarteritic anterior ischaemic optic neuropathy (NAION) is a relatively uncommon visual disorder mostly affecting individuals between the ages of 55 and 70 years, although it can also occur in younger patients.[61] The annual incidence rate in the US is between 2.52 and 11.8 men and between 2.14 and 9.2 women per 100 000 of the population aged ≥50 years.[62,63] The incidence rate in China is similar. The Beijing Eye Study reports an annual incidence of new NAION for 1 in 16 000 Chinese adults (age >40 years), or about 6 per 100 000 of the population.[64] The incidence of NAION has been estimated to be 2.8 cases per 100 000 patient-years of exposure to sildenafil,[65] which is not higher than the estimated annual incidence rate in the general population of men aged ≥50 years.[62,63]

NAION is usually characterized by a history of painless decrease in vision in one eye, often discovered upon awakening. When the patient is examined, an afferent pupillary defect, pale swollen optic disc and a loss of visual acuity and/or a partial loss of visual field are typically found in the affected eye. However, the presence of normal visual acuity does not rule out NAION. A large cohort study of 340 patients (386 eyes) with NAION recently reported that nearly half of the eyes with NAION (49%) had almost normal visual acuity (20/15 to 20/30).[66] Importantly, to make a diagnosis of NAION, it is essential to rule out other ocular, systemic and neurological diseases that could account for the

patient's visual symptoms. In this regard, NAION differs from arteritic anterior ischaemic optic neuropathy (AAION), which is most commonly caused by a granulomatous vasculitis affecting medium and large arteries, particularly cranial branches from the aortic arch.[61] Sudden and catastrophic vision loss can occur with AAION, frequently (but not always) preceded by systemic and/or focal symptoms, including jaw claudication, headache, scalp tenderness, malaise, weight loss and fever. Oedema of the optic disc is typically observed. Irreversible vision loss in the fellow eye can occur within hours or days. The degree of visual loss for AAION tends to be greater than for NAION. For this reason, AAION represents a true medical emergency as immediate treatment with corticosteroids can prevent blindness.

4.1 Risk Factors for NAION

Although the pathology underlying NAION remains poorly understood, it is generally thought to represent a blockage of blood supply to the anterior part of the optic nerve derived from short posterior ciliary arteries at or near the lamina cribrosa.[61,67] An established risk factor for NAION is a 'disc at risk' or 'crowded disc', an anatomical variant of the ONH with either an absent or small physiological cup (small cup-to-disc ratio).[68] The utility of cup-to-disc ratio is hampered by the degree of expertise required for its accurate ascertainment. In a recent study, Jonas and Laties[69] found that over a wide range of cup-to-disc ratios, disagreement among a group of comprehensive ophthalmologists was unacceptably high. In contrast, clinical observation by experts appears to be valid. As to pathogenesis, current explanations for NAION remain speculative. Chief among them is a theory of local crowding as nerve fibres pass through a restricted space in the rigid opening of the scleral canal. Swelling of axons from stasis of axoplasmic flow could compress capillaries and other small blood vessels, which could compromise local blood supply.[70]

Recent studies suggest that optical coherence tomography (OCT) may be useful for evaluating optic disc oedema from measurements of retinal nerve fibre layer (RNFL) thickness.[71,72] An OCT study of 27 patients with NAION examined within a mean of 5 days after onset found that the RNFL in the affected eye was nearly twice as thick as the fellow eye.[71] At 1.5 months after the initial visit, the RNFL thickness in the affected eye decreased towards a value similar to that in the fellow eye, and plateaued at an almost 40% lower thickness than the fellow eye after 6 months to 1 year, consistent with damage and optic head atrophy. Another combined OCT and visual field defect study of 21 patients with NAION and 32 healthy control patients found decreased RNFL thickness in the eyes of patients with NAION even in sectors of the optic disc with relatively normal visual fields, suggesting that the extent of damage is more extensive than that estimated by visual field methods alone.[72]

However, it is not clear whether oedema occurs first to directly cause an ischaemic event or contributes to a further reduction in blood flow secondary to an initial ischaemic event. Support for this possible mechanism of injury is provided from a single pathophysiology study that performed a three-dimensional digital reconstruction of morphological images for a serially sectioned optic nerve removed from the infarcted eye of a 70-year-old man who died 20 days after an initial diagnosis of NAION.[73] The infarct was greatest in the anterior region and was contained within the boundaries of the sclera. Peripheral regions were spared, and there was relatively little damage adjacent to the central retinal artery. The infarct appeared to be located in a watershed zone between the central retinal artery and the pial arteries. These observations support the concept of a compartment syndrome, where oedema in the confined space of the sclera results in mechanical compression of optic nerve fibres. The histological evidence from this individual suggested that, at least in this instance, NAION is not a disease of small-vessel ischaemia associated with vasculitis or hypertensive changes, nor a disease of large-vessel ischaemia associated with emboli, thrombosis, hypotension, vasculitis or hypertensive changes, although the possibility of vasospasm could not be ruled out.

The fellow eye of patients with NAION is also at risk for vision loss. Observations of 386 patients with NAION with no history of NAION in the other eye found an overall incidence of 14.7% of new cases of NAION occurring in the second eye at a mean interval of 2.1 years during more than 5 years of follow-up.[74]

Although laser Doppler measurements indicate a reduction in ONH blood flow in temporal and nasal sites in affected eyes of patients with NAION, the same does not hold for the contralateral eye, which often has a similar ONH configuration.[75] Mild optic disc oedema can be a premonitory sign of NAION. However, it is not possible to determine how long this condition existed before visual loss occurred. In one report, optic disc oedema was observed in a cohort of 54 patients (60 eyes) who had normal visual fields, suggesting that incipient NAION is a distinct clinical entity.[76] Follow-up information was available for 55 eyes. Fourteen eyes (25%) developed visual field defects and progressed to classic NAION within a median time of 5.8 weeks from the initial visit. A review of 591 patients with NAION found that optic disc oedema more often involves the superior rather than the inferior portion of the disc.[70] Optic disc oedema resolved spontaneously with a median time of 8.5 weeks in patients with untreated NAION. However, the time for optic disc oedema to resolve was found to be significantly faster with corticosteroid therapy initiated within 2 weeks of onset, with a median time of 7.1 weeks for 237 eyes of patients with NAION in this study. Similarly, for diabetic patients with NAION who received corticosteroid therapy within 2 weeks of onset, a shorter time for oedema to resolve (median 7.8 weeks) was required compared with diabetic patients who were not treated (median 9.4 weeks). The time course for resolution of optic disc oedema was found to be shorter with greater severity of initial visual field and visual acuity loss. The authors did not indicate whether there were improvements in visual acuity or visual field defects after resolution of optic disc oedema.[70]

Other risk factors for NAION include diabetes, hypertension, hypercholesterolaemia, atherosclerosis, ischaemic heart disease, stroke, prothrombotic factors, elevated homocysteine levels, sleep apnoea and nocturnal hypotension, as summarized in a number of reviews.[14,49,61,77,78] Many of the same cardiovascular risk factors are also associated with ED, as reviewed in section 1.1. In one recent study, blood samples from 36 patients with NAION and 81 age- and sex-matched controls were evaluated for thrombophilic factors.[79] Compared with controls, significantly higher levels of cholesterol, fibrinogen and von Willebrand factor were measured from blood samples taken 6 weeks after the starting date of ophthalmological symptoms for the patients with NAION. Additional analysis at first found that diabetes, the Leiden mutation of factor V in the heterozygous form, and elevated lipoprotein A levels increased the odds of developing NAION. However, when conventionally accepted cut-off levels were used for elevated cholesterol, fibrinogen, lipoprotein-A and von Willebrand factors, only hyperfibrinogenaemia remained as a significant risk factor for developing NAION. A deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD) has been reported to be a potentially protective factor for NAION from a study of 140 patients with NAION and 280 control patients in Sardinia, Italy where G6PD deficiency is relatively common.[80] Although further research is needed for a better understanding of the mechanism involved, there is evidence for protection against other vascular disorders as well, possibly linked to changes in cholesterol metabolism with G6PD deficiency (not reviewed here).

Smoking has been identified to be a risk factor for ED (section 1.1) but has not been established to be a risk factor for NAION. A study of 418 patients with NAION found no association between smoking and the risk for NAION in the fellow eye.[74] A large systematic study of tobacco use in a cohort of 624 patients with NAION found no significant difference in the amount of visual field loss and no significant difference in initial visual acuity among nonsmokers, former smokers and current smokers.[81] The prevalence of smoking in these patients with NAION was not different from that of the general population in the US. Current smokers did have a diagnosis of NAION in the first eye at a significantly

younger age compared with former smokers or nonsmokers, but there was no significant difference in the risk of developing NAION in the other eye between current smokers and nonsmokers. However, this cohort of patients with NAION had a higher prevalence of diabetes, ischaemic heart disease, hypertension and cerebrovascular disease compared with the prevalence of these diseases in the general US population. The prevalence of ED in the 369 men with NAION in this cohort was not evaluated.[81]

Sleep apnoea is a risk factor for ED and may also be a risk factor for NAION. A recent study of 50 men with sleep apnoea syndrome found that the severity of ED correlated strongly with the severity of sleep apnoea.[82] In two studies of patients with NAION, a high incidence of obstructive sleep apnoea (OSA) was reported.[83,84] Because repeated episodes of ocular hypoxia with decreased arterial blood oxygen saturation and increased carbon dioxide levels during OSA might be a confounding factor in the development of NAION, it was speculated that continuous positive airway pressure (CPAP) treatment for OSA might prevent NAION.[83] However, this was not supported from a study of 108 patients newly diagnosed with NAION.[85] Three patients were identified who had OSA and had been treated with CPAP for 4 months, 2 years and 6 years, respectively, before their diagnosis of NAION. A recent review of the possible link between OSA and ocular health, including glaucoma, NAION and other visual disorders, concludes that there is not a causal relationship based on current evidence.[86] Nonetheless, the association between OSA and hypertension, and the possible link to progression of CVD, are beginning to be recognized along with a greater awareness of the need to diagnose and treat OSA.[87] CPAP therapy for patients with OSA may yet prove to have some benefit for their long-term ocular health.

4.2 PDE-5 Inhibitor Use and Vision Loss with NAION

Sildenafil became available 5 years earlier than the other PDE-5 inhibitors and received massive publicity at its introduction. As a result, it is not surprising that most published reports that associate vision loss with PDE-5 inhibitor use are for patients using sildenafil. A total of 18 patients with suspected NAION related to sildenafil have been identified in the literature, published primarily as case studies (table I).[88-97] Patient ages ranged from 36 to 69 years, with sildenafil doses ranging between 25 and 100 mg. Loss of vision was reported to occur within several hours to 24 hours after the sildenafil dose, except for one case in which symptoms occurred 36 hours later. The temporal relationship is not known for four cases. 'Crowded disc' was a frequent risk factor in these patients, and the other co-morbidities, such as diabetes, hypertension, CVD, smoking or history of NAION in the other eye, are frequently present, as summarized in table I. In one case study, the clinical evidence suggested that the patient had a branch retinal artery occlusion in addition to NAION.[96] In another case study, two separate adverse visual events were experienced by a patient who was also receiving haemodialysis treatments for chronic renal failure.[97] The first event occurred the following day after taking sildenafil 100 mg for the first time. The second event occurred 4 months later, the day after taking sildenafil 100 mg for a second time, having ignored physician warnings to discontinue PDE-5 inhibitor therapy.

Three patients using tadalafil with diagnosed NAION have been identified in the literature (table I).[45,98,99] Two of the patients had undergone prostatectomies. In one case study, the patient had an adverse visual event on several occasions, each occurring shortly after taking tadalafil 20 mg.[45] Four times the visual disturbance resolved within 24 hours. Unfortunately, it persisted after the fifth time that the patient used tadalafil.

A small study comparing 38 men with NAION using sildenafil or tadalafil with age-matched control subjects without a history of NAION found no significant associations between NAION and PDE-5 inhibitor use, except for a prior history of myocardial infarction.[100] However, the methodological limitations of this study have been pointed out, especially the lack of

Table I. Summary findings for suspected nonarteritic anterior ischaemic optic neuropathy (NAION) in 21 patients[a] prescribed phosphodiesterase type 5 inhibitors[45,88-99]

Characteristic	Number of patients
Dose (mg)	
Sildenafil 25	1
Sildenafil 50	8
Sildenafil 100	5
Tadalafil 20	3
Unknown	4
Time to event (h)	
≤1	3
>1 to ≤4	2
>4 to ≤12	3
>12 to ≤24	5
>24	3
'Several hours'	1
Unknown	4
Symptoms	
Decrease in vision	10
Flashes, bright colours	6
Visual field defect	7
Blurry vision	3
Decrease in colour vision	3
Pain	2
Risk factors/co-morbidities	
Crowded disc/NAION other eye	9
Cardiovascular disease/risk factor[b]	11
Previous eye disorder[c]	6
Prostate surgery/radiation	4
Depression	3
Visual acuity affected eye[d]	
20/20	8
20/25 to 20/50	6
20/125 to 20/400	4
Count fingers/hand motion	4
Light perception	1

a Mean age of patients 58.2 years ± standard deviation 8.8.

b Ischaemic heart disease, coronary artery disease, prior myocardial infarction, hypertension, diabetes mellitus, atrial flutter, cardiac dysrhythmia, smoking, obesity and high cholesterol.

c Amblyopia, optic nerve hypoplasia, retinal buckle surgery, retinal detachment and colour blindness.

d Some patients had more than one affected eye.

information with regard to timing, dose and duration of drug use with respect to event onset.[101] A recent retrospective analysis of over 4 million men aged 50 years or older without a history of previous optic nerve disease in the National Veterans Health Administration pharmacy and clinical databases from 2004 to 2005 found that 11.5% of these men had been prescribed PDE-5 inhibitors.[102] The average length of exposure time to PDE-5 inhibitors for this group was not described. Most of the prescriptions (99.4%) were for sildenafil 100 mg. During these 2 years, 0.09% of this large cohort were identified as having a diagnosis of new ischaemic optic neuropathy, excluding new diagnoses for temporal arteritis or polymyalgia rheumatica. The percentage of men in the subgroup using PDE-5 inhibitors was slightly higher at 0.09%, yielding a nonsignificant relative risk factor of 1.02 (95% CI 0.92, 1.12). The authors speculate that it might be possible to evaluate the risk of NAION in persons taking PDE-5 inhibitors from a case-control study involving only a few hundred patients at most. However, even if specific risk factors can be determined, prognostic tests may not have the necessary sensitivity[103] to predict individuals at risk for NAION. The case-crossover approach[104] may be the most appropriate way to study rare events with abrupt outcomes that may or may not be associated with intermittent exposure.

4.3 US FDA Product Warning

In 2005, the FDA recommended the following label addition for the three currently marketed PDE-5 inhibitors:[17,21,22] "Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of PDE-5 inhibitors. 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 mellitus, hypertension, coronary artery disease, hyperlipidaemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects,

to a combination of these factors, or to other factors.'' Additional information has been added to the product labelling for each PDE-5 inhibitor (under the section ''PRECAUTIONS, Info for Physicians'') regarding how physicians should advise patients to discontinue use of all PDE-5 inhibitors and seek medical attention in the event of sudden vision loss in one or both eyes.[17,21,22]

5. Other Reported Vision Disorders

A case of optic atrophy of unknown origin has been reported,[105] in which a 69-year-old patient used sildenafil three times during a 6-month period before diagnosis. The patient did not recall any unusual visual effects during the times that he used sildenafil. The dose and any temporal association with dosing were not reported. The visual field loss was not consistent with NAION, and the patient did not have anatomical features of 'crowded disc'. Although intraocular pressure was elevated, the patient did not have glaucoma.

A case of acute angle-closure glaucoma with painful loss of vision in the left eye was reported for a 71-year-old man who had taken sildenafil 50 mg at 11:00 pm, followed by sexual intercourse.[106] Ocular symptoms were experienced approximately 1 hour after taking sildenafil. Upon examination the next day, intraocular pressure in the left eye was 60 mmHg but was normal in the right eye. The patient had a narrow angle in the fellow eye, suggesting a predisposition for angle-closure glaucoma. The patient was treated with systemic and ocular hypotensive medications (not specified in report), and at a later date had cataract removal with simultaneous glaucoma surgery for the left eye. The patient had normal intraocular pressures in both eyes upon examination 4.5 years after the initial adverse visual event.

A case of a visual field defect due to intracerebral haemorrhage has been reported for a 66-year-old patient who had taken a dose of vardenafil 20 mg and had sexual intercourse approximately 6 hours later.[107] The patient had experienced a mild headache after taking vardenafil, and the symptoms moderately worsened after sexual activity. The next morning upon awakening, the patient continued to experience headache, was unable to see to the left, had difficulties with balance and had a slow and unsteady gait when admitted to the emergency room. A CT scan of the head was taken without contrast material, and a right posterior parietal primary intracerebral haemorrhage was found. There was no evidence of arteriovenous malformation, aneurysm or other irregularity that could account for the haemorrhage.

5.1 Retinal Artery Branch Occlusion

Two cases of retinal artery branch occlusion have been reported for patients who were taking sildenafil.[108,109] This does not include a possible case of simultaneous retinal artery occlusion and NAION (included in table I).[96]

5.2 Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSR) is characterized by a well demarcated, shallow, serous elevation of the neurosensory retina, which is believed to be caused by an osmotic gradient from a high protein concentration in the subretinal fluid. The serous detachment can be identified by fluorescein angiography[110] and confirmed by noninvasive OCT.[111] CSR often occurs in young or middle-aged adults. The cause of CSR is presently unknown. Risk factors include corticosteroid use, hypertension, psychopharmacological medication use[112] and possibly type A personality.[113]

Four individual cases of CSR have been published for patients using PDE-5 inhibitors.[114-116] Sildenafil was used in all four cases. Medical histories were not fully described, and any concomitant medications taken by these four patients were not identified. The first reported case of CSR[110] was for a 33-year-old man using sildenafil who experienced two visual disturbances in the same eye approximately 1 year apart, which appears to meet accepted criteria for positive rechallenge. The dosage used before each visual disturbance and the frequency of sildenafil

use during the year between these two events were not reported. The first event resolved spontaneously. After the second event, which occurred the day after sildenafil use, a diagnosis of CSR was made based on fluorescein angiography. Dilation of a choroidal vein was observed near the region of dye leakage. The patient started a course of oral vitamin E with improvement in symptoms and mild fluorescein dye leakage observed on follow-up examination. The second reported case of CSR[111] was for a 37-year-old man who was initially prescribed sildenafil 100 mg. The dose was reduced to 50 mg after complaints of lightheadedness, heartburn, nasal congestion and visual disturbances, including increased sensitivity to light and a bluish tinge to his vision. He continued using sildenafil 50 mg for 3 months without experiencing adverse events. During the week before experiencing an acute loss of vision, he used sildenafil six times, with the last dose taken 6 hours before the event. An initial diagnosis of CSR was made based on Amsler grid testing, and the patient was advised to discontinue using sildenafil. One week after experiencing the vision loss, a diagnosis of CSR was confirmed by fluorescein angiography. Within 3 weeks, there was a complete resolution of the CSR. In two CSR cases in elderly men,[112] the subretinal detachments and vitelliform lesions were reported to have resolved for both patients after they discontinued taking sildenafil. It was not reported whether there was any temporal relationship to sildenafil use with the initial adverse visual events. In the first case, the 68-year-old man had been using sildenafil 50 or 100 mg at a frequency of two times per week for approximately 1 year. He was advised to discontinue sildenafil use and the CSR resolved without further recurrences over a follow-up period of 16 months. The other case was a 70-year-old man with medically controlled hypertension. He used sildenafil 50 or 100 mg at a frequency of three to four times per week for at least 1 year. The patient temporarily discontinued sildenafil use for 2 months with improvement in visual acuity. He then resumed his previous sildenafil use at a frequency of three to four times per week. An increase in subretinal fluid was observed upon reexamination several months later. The investigators speculated that engorgement of the choroidal vasculature might have led to increased fluid leakage across the retinal pigment epithelium to increase subretinal fluid at detachment sites in this patient.

6. Conclusions

Because ED is often a vascular disorder, and patients with ED have multiple cardiovascular-related risk factors, it should not be surprising that vascular events in the eye might also be experienced. However, there has been no consistent pattern of physiological effects on ocular circulation or retinal function that can conclusively link PDE-5 use to the pathogenesis of serious ocular vascular disorders. To date, there is no compelling statistical evidence that there is any greater risk for adverse visual events with PDE-5 inhibitor use compared with that for the population of men with ED who are not using PDE-5 inhibitors. Patient counselling information provided for all PDE-5 inhibitors gives clear guidance to physicians with regard to potential areas of concern. Physicians should continue to advise patients to stop use of a PDE-5 inhibitor and seek immediate medical attention in the event of a sudden loss of vision as a safety measure despite the absence of a proven link between PDE-5 use and serious ocular disorders.

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