Effects of phosphodiesterase type 5 inhibitors on choroid and ocular vasculature: a literature review

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Abstract
To provide information on the effects of phosphodiesterase type 5 (PDE5) inhibitors on choroidal vessels and central serous chorioretinopathy (CSC) and possible implications for development of exudative age-related macular degeneration (AMD). Two independent investigators conducted a qualitative review of PubMed to identify studies on the choroidal effect of PDE5 inhibitors in June 2019. The search used key words that included PDE5 inhibitors, sildenafil, tadalafil, vardenafil, choroid, choroidal flow, choroidal vessels, choroidal thickness, CSC, AMD or a combination. Only studies which assessed choroidal findings were included. Many ocular diseases are related to changes in choroidal thickness and perfusion. Patients with AMD, who have decreased choroidal perfusion, may manifest more severely diminished choroidal ability to deliver oxygen and other metabolites to the retina, leading to growth of neovascular tissue. As a result of this engorgement of the choroidal vasculature, some patients may have leakage across the retinal pigment epithelium (RPE) and accumulation of subretinal fluid, resulting in CSC. Transient visual symptoms, i.e., changes in color perception and increased light sensitivity, are well-known adverse effects, but there have been rare reports of vision-threatening ocular complications in users of PDE5 inhibitors, such as nonarteritic anterior ischemic optic neuropathy and cilioretinal artery occlusion. The choroid is a vascular tissue analogous in many respects to the corpus cavernosum, and PDE5 inhibitors may increase the choroidal thickness and perfusion. While it is intuitively obvious that thickness of the choroid alone does not guarantee better choriocapillaris oxygenation, it is a reasonable step towards ameliorating ischemia. These drugs have numerous physiologic effects on the choroid related to blood flow, such as clinical consequences in CSC and AMD.

Keywords: Choroidal thickness, Enhanced depth imaging, Optical coherence tomography, PDE5 inhibitors

Introduction
Sildenafil (Viagra, Pfizer Pharmaceuticals, Secaucus, NJ, USA), tadalafil (Cialis, Eli Lilly Medical, Indianapolis, IN, USA), vardenafil (Levitra, Bayer Pharmaceuticals, Whippany, NJ, USA), and avanafil (Stendra, Vivus, Inc., Campbell, CA, USA) are used widely to treat pulmonary arterial hypertension and are currently the first-line pharmacologic treatments for erectile dysfunction (ED). These drugs are selective cyclic guanosine monophosphate (cGMP)-dependent PDE5 inhibitors, which induce vasodilation by enhancing the smooth muscle relaxant effects of nitric oxide (NO) [7, 64, 70, 78]. The enhanced dilation of blood vessels and lacunar spaces in the corpus cavernosum, and PDE5 inhibitors may increase the choroidal thickness and perfusion. While it is intuitively obvious that thickness of the choroid alone does not guarantee better choriocapillaris oxygenation, it is a reasonable step towards ameliorating ischemia. These drugs have numerous physiologic effects on the choroid related to blood flow, such as clinical consequences in CSC and AMD.

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The ocular adverse reactions of this drug class are often mild and related to color and brightness perception in 3–11% of men taking sildenafil 25–100 mg [27], 0.3–2% of those taking vardenafil [54, 59], and 0.1% of tadalafil users [16]. Although rare, some severe reactions may occur, i.e., nonarteritic anterior ischemic optic neuropathy (NAION) with attendant visual loss, cilioretinal artery occlusion, central retinal vein occlusion, pupil-sparing third nerve palsy and glaucoma [2, 9, 14, 27, 39, 46, 58, 69, 70, 87, 92, 99]. Quiram et al. [89] also reported a case of Viagra-associated serous macular detachment. Even though these complications have been reported, men who use PDE5 inhibitors appear to have vision-threatening complications at the same frequency as the general population [6, 12].

PDE5 inhibitors decrease systemic BP, which can potentially lead to decreased choroidal circulation [75] that is deleterious in patients who may have compromised choroidal circulation or be at risk of ocular ischemic conditions. Indeed, several cases of NAION have been reported in patients taking sildenafil [15, 23, 29, 88]. In 2005, 43 cases of NAION in patients taking PDE5 inhibitors were reported to the Food and Drug Administration Adverse Event Reporting System [30]. Sildenafil was reported the most often, with 38 cases versus four cases for tadalafil and one case for vardenafil [6].

The possible effect of sildenafil in the choroid remains unknown. The current report reviews published studies that examined the effects of PDE5 inhibitors on the choroidal vessels, CSC, and their possible implications for exudative AMD, diseases that are associated with changes in choroidal thickness and perfusion.

Results and discussion
Pharmacology of PDE5 inhibitors
PDE5 inhibition increases the level of cGMP, an intracellular messenger affecting vasodilation by relaxation of smooth muscle in the arterioles. Production of cGMP from guanosine triphosphate is mediated through the NO signaling pathway. PDE5 inhibitors increase the cGMP levels, thereby potentiating the NO-elicited effect on sinusoidal vessels of the corpus cavernosum [43, 56].

PDE5 is largely expressed in the corpora cavernosa of the penis, but many other organs such as the pulmonary and coronary vasculature, sympathetic nervous system, and Purkinje neurons express the PDE5 enzyme, where its effect is less known [68, 91, 107]. PDE5 also directly affects the dilation of the retinal and choroidal vessels (smooth muscle and endothelial cells) and the ganglion (III neuron) and bipolar cell layers (II neuron). This is noteworthy because ganglion and bipolar cell layers act as filters in the visual signals and provide a first codification of the neural signal [24, 37, 81, 82, 102]. Other studies also have reported that PDE5 inhibitors significantly increase choroidal blood flow (CBF) [53, 61, 84, 96, 105].

These drugs also weakly inhibit PDE6 (Phosphodiesterase type 6), reflecting an affinity for PDE6 one-tenth that of PDE5 [7]. Because PDE6 is present in high concentrations in cone and rod cells and plays a key role in retinal light signal phototransduction [5, 17, 44, 110], its partial inhibition may account for the visual effects, such as impaired color discrimination and depressed scotopic responses [65, 106, 108] observed in flexible-dose controlled clinical trials of sildenafil in men with ED [22, 57, 70, 77, 97, 106] Fig. 1.

Systemic and ocular effects
The standard recommended doses of Viagra range from 25 to 100 mg three times weekly. The peak plasma level after oral intake occurs at about 60 min with an elimination half-life of 3–5 h [34, 35]. The systemic side effects have been reported with an incidence of 2% or greater at doses of sildenafil up to 100 mg and include headache, flushing, dyspepsia, nasal congestion, urinary tract infection, diarrhea, dizziness, and rash [31–34]. Subjects also have been reported to have a 10-mmHg decrease in systemic BP [115]. Visual symptoms, including blue-tinted vision and/or increased light sensitivity, have been reported in 3% of men taking 25 mg of the drug, 11% taking 100 mg, and almost 50% taking 200 mg [36].

Choroidal effect
The choroid, which supports the metabolic function of the outer retina, has been described as an erectile tissue, analogous to the corpus cavernosum. The fenestrated choroidal vasculature is highly responsive to
local and neurogenic stimuli, and the uveal system may hold up to 97% of the intraocular blood volume [84]. Theoretically, because sildenafil has a strong systemic vasodilating effect that decreases systemic BP, this can result in decreased CBF [60]. However, since the choroid is similar to the corpus cavernosum, sildenafil could have a strong vasodilatory effect resulting in increased CBF as the result of a direct effect on the smooth muscle relaxation in the choroidal vessel walls [84]. The small variable effects we observed may be due to a different balance of these factors among individuals.

McCulley et al. [73], who assessed the choroidal thickness with ultrasonography with ultrasonography to correlate it with color vision and contrast sensitivity changes in a group of healthy subjects, did not report a consistent increase in the choroidal thickness after administration of 200 mg of sildenafil, a dose that is twice that of the highest recommended dose for treating ED. The study found only one subject who experienced a marked increase of 33% in the choroidal thickness, suggesting that some individuals could be especially responsive to sildenafil therapy. However, when the choroidal thickness was measured by enhanced-depth imaging-optical coherence tomography (EDI-OCT), the significant increases varied from 9.3 to 12.3% 1–3 h after ingesting 50–100 mg of sildenafil. This difference is likely due to low-resolution ultrasonography with small choroidal measurements compared to OCT, which has an approximate resolution of 5 microns. Other studies, however, showed no significant difference between the 1- and 3-h time points [60, 104] Fig. 2.

Interestingly, another study investigated the histopathologic effect of chronic sildenafil citrate use on the choroidal circulation in male rats and found a significant increase in the choroidal vascular dilation and congestion [105]. However, Vance et al. [104] noticed that choroidal vessels’ caliber changes after sildenafil assessed by EDI-OCT were not consistent for all study participants.

Vascular effects
Most studies have reported increased CBF, with a lesser effect on the retinal vasculature. This differential effect may be due to differences in vascular innervation. Choroidal vessels are innervated by the autonomic nervous system, while innervation of the retinal vasculature is limited to the central retinal artery (CRA) posterior to the lamina cribrosa [10, 11, 66, 67]. In this respect, the innervation of the choriocapillaris resembles that of the corpus cavernosum. Nitric oxide triggers cGMP within smooth muscle cells as part of the signal transduction pathway in neural control of the choroidal vasculature, as it does in the vascular bed of the corpus cavernosum [84]. The retinal vessel endothelium continuously produces NO, which maintains the retinal vessels in a constantly dilated state [52]. Functionally, the retinal arteries and veins act as arterioles and venules. Because vascular resistance is correlated inversely with the fourth power of the radius of a blood vessel, small changes in diameter have a substantial effect on blood flow through the vessel by affecting the blood flow velocity in the ophthalmic artery (OA) and choroidal and retinal flow [26]. Therefore, the increase in retinal vessel diameter should lead to a considerable increase in the retinal blood flow (RBF) if the blood velocity is assumed to be constant [83].

Techniques to assess vascularization and perfusion
Several studies have focused on the effects of sildenafil on the RBF and retinal vessel diameter in normal subjects. Despite these apparent discrepancies, this may result from different methods, techniques and/or sensitivities in measuring ocular blood velocity/flow, vascular diameter, or different medication times and doses.

Color Doppler image (CDI), one method to analyze the speed and direction of blood flow, showed significant increases in the OA peak systolic velocity (PSV) and the end diastolic velocity (EDV). Parallel increases in PSV and EDV can be interpreted as increased volumetric blood flow within a vessel [95].

CDI was used in some studies to elucidate the effect of sildenafil on blood flow. Dundar et al. [28] showed an
da Cruz et al. Int J Retin Vitr (2020) 6:38

increase in flow in the OA caused by 50 mg of sildenafil but failed to show increased flow in the CRA or temporal short posterior ciliary artery (SPCA), since it is technically difficult to locate and assess the SPCA using CDI.

Kurtulan et al. [63] noted that although sildenafil increased the mean cavernous artery PSV and also reduced systemic systolic and diastolic BP, it had no effect on CRA circulation even in subjects with ocular side effects. The alterations in choroidal perfusion and sildenafil-mediated inhibition of PDE6 were associated with ocular symptoms.

In a study similar to that of Kurtulan et al. [63], Koksal et al. [61] reinforced that sildenafil caused a significant increase in blood flow in the OA in a time-dependent manner, probably as a result of PDE5 inhibition on smooth muscle cells. Once again, vessels associated with the choroidal vasculature showed significantly greater volumetric blood flow when treated with sildenafil, while no effect was observed in the CRA.

In 2008, Foresta et al. reported that tadalafil and sildenafil modified the OA flow in a time-dependent manner. The administration of sildenafil increased PSV and EDV in the OA 60 min after administration. After 4 h, OA blood-flow velocity no longer differed from baseline. Tadalafil increased the PSV and EDV in the OA for at least 48 h. This result was consistent with the drug half-life (4 h for sildenafil and 48 h for tadalafil), so the modifications are not drug-specific but class-specific.

Taner et al. [98], also using CDI, studied the effect of 50 mg of sildenafil on the retrolubar and systemic hemodynamics during postural changes in healthy volunteers. However, no change was found in the OA, CRA, and SPCA blood-flow velocities between subjects taking 50 mg of sildenafil and controls.

Later in 2016, Matieli et al. [72] found no effects on blood flow in the OA, CRA, and ciliary arteries in patients who used sildenafil chronically for pulmonary arterial hypertension, when compared to controls. These results corroborated Taner et al.’s previous findings [98].

Sponsel et al. [96] and Paris et al. [84] used Heidelberg retina flowmetry (HRF) to assess the retina and pulsatile ocular blood flowmetry to evaluate the choroid flow.

HRF provides a two-dimensional map of blood flow to the optic nerve and surroundings of the retina. This technique, however, is most sensitive to blood flow changes in the superficial layers and therefore provides only limited information about deeper regions, which limits the ability to account for the RBF that is supplied by the choriocapillaris from the uveal system [8]. The authors found no changes in retinal capillary blood flow measured with the HRF and did not detect any change in the systemic BP.

Pulsatile ocular blood flow (POBF) determines the real-time changes in ocular volume based on real-time measurement of intraocular pressure. Most blood flow in the eye is in the choroidal circulation; therefore, it is presumed that POBF primarily measures the pulsatile component of the choroidal perfusion independent of the retinal or retrobulbar circulation [55]. Those authors found significant increases in the POBF in patients taking sildenafil that likely represents an increase in choroidal hemodynamics, though it is impossible to state with certainty the source of the changes in the ocular pulsatility.
Since the CBF accounts for about 85% of the total ocular blood flow, significant changes in the POBF may be due to changes in the choroidal circulation. These data suggest that sildenafil produces an increased CBF [84, 96].

Laser Doppler Flowmetry (LDF) measures the blood flow in the capillary beds with the laser directed at areas between the larger vessels [8]. Grunwald et al. [51] examined the effects of sildenafil on blood flow in the optic nerve head and the foveal avascular region, where choroidal measurements were limited to the foveal avascular region of the retina. They investigated and concluded that there were no changes in the CBF and optic nerve blood flow parameters after sildenafil, which is inconsistent with other studies. It is possible that limiting assessment of the choroidal vasculature to the macular avascular window may not be representative of the overall CBF, thus accounting for this inconsistency. The absence of changes in the optic nerve head blood flow may be interpreted as no change in the retinal hemodynamics, which agrees with Paris et al. [84].

Likewise, Metelitsina et al. [75] found no change in the CBF, despite a decrease in the systemic BP after administration of sildenafil. Those authors concluded that PDE5 inhibitors do not alter daytime ocular autoregulation. However, the same group later detected a significant increase in venous diameter up to 300 min after administering PDE5 inhibitors, using a more sensitive vessel measurement technique, the Vessel Map analysis program (IMEDOS GmbH, Weimar Germany) [74].

Polak et al. [86] also examined the effects of sildenafil on the retinal hemodynamics using laser Doppler flowmetry, the Retinal Vessel Analyzer (RVA) (Carl Zeiss Meditech, Dublin, CA) and response to flicker stimulation. The study showed a significant (15.7%) increase in RBF after 100 mg of sildenafil citrate and did not find flicker-induced retinal vasodilation.

Pache et al. [83] measured retinal arterial and venous diameters using the RVA after administration of 50 mg of sildenafil and reported increased vessel diameters, followed by a gradual decline toward baseline values during the following 90 min, suggesting an increase in RBF.

These data conflict with the findings of Paris et al. [84] and Grunwald et al. [51] and could have resulted because the latter studies were performed at the retinal capillary level, where the amount of increase in vessel diameter could have resulted in an undetectable increase in the blood flow level. Besides, the increase in vascular diameter could not be accompanied by a decrease in the retinal blood velocity, resulting in no change in the volumetric blood flow that could occur with increased CBF.

Polak et al. [86] also reported a 4.7% increase in retinal venous diameter using the RVA. As explained previously, this study used the results of both measures—diameter and velocity—to calculate the blood flow. These findings, combined with those of previous studies, suggest that sildenafil may have a slight effect on the retinal vasculature.

Using digitized fundus photographs, Grunwald et al. [49] examined the effect of sildenafil on retinal artery and vein diameters in a static way. Unlike the study of Pache et al. [83], no significant difference from baseline or placebo was detected in any vessel diameter, possibly because the RVA in the study of Pache et al. used a series of frames in a video that allowed for better resolution and details.

Diameter measurements, as with the RVA, achieves high resolution by performing numerous analyses at the frame rate of 25 Hz, meaning 25 images per second. As mentioned previously, Metelitsina et al. [74] improved their methods of analysis and increased the sensitivity of the technique to detect increased venous diameter compared to previous studies.

Swept-mode high-frequency digital ultrasound is a modification of the standard B-mode acquisition process that allows time-domain (as opposed to Doppler) assessment of flow by speckle tracking, as previously described [62, 93]. Speckle tracking is advantageous in maintaining high spatial resolution compared to color-flow Doppler. Kim et al. [60] used this technique and reported increased choroidal perfusion in 11 of 12 eyes, after the use of systemic sildenafil citrate.

Using a videomicroscopy technique, Yuan et al. [113] isolated, cannulated, and pressurized cadaveric porcine retinal arterioles without flow and reported that sildenafil caused modest arterial dilation in a dose-dependent manner. The authors emphasized that clinical doses of sildenafil did not cause substantial vasodilation and that the threshold concentration for sildenafil to dilate retinal arterioles was 10 ng/mL. The authors also found that the highest concentration (1 µg/mL) produced up to 30% maximal dilation, which has a notable impact on local retinal perfusion.

**Implications of PDE5 inhibitors on chorioretinal diseases CSC**

Serous detachment of the neurosensory retina can occur due to any process that disrupts the outer blood-ocular barrier controlled by the RPE [109]. The finding of focal leaks in the RPE together with impaired fluid reabsorption is characteristic of idiopathic CSC [112]. This subretinal leakage occurs due to altered choroidal vascular perfusion that leads to localized vascular congestion and impaired circulation, resulting in ischemia and facilitating choroidal exudation through a focally hyperpermeable choroid. Accordingly, the integrity of the choroidal vasculature has an important impact on subretinal fluid
accumulation and plays a paramount role in normal retinal adhesion [19].

As demonstrated previously, PDE5 inhibitors increase the CBF and choroidal thickness [104], and as a result of engorgement of the choroidal vasculature, some patients may have leakage across the RPE and accumulated subretinal fluid [89]. The consequence is distortion or loss of central vision, decreased color perception, and relative scotoma [100].

Information about CSC has emerged during the use of sildenafil citrate for from 1 day to 2 years, so it is impossible to ascertain which dose of sildenafil citrate causes CSC at a specific time [25].

Murata et al. [79] was the first to report a unilateral case of CSC in a 33-year-old man taking sildenafil. The condition resolved within days when sildenafil was stopped (positive dechallenge) and recurred when he used sildenafil again a year later (positive rechallenge). After that case, many other unilateral and bilateral case have been described, in which some had a positive dechallenge with discontinuation of PDE5 inhibitors [1, 3, 4, 21, 38, 45, 80, 89, 90, 103], and some a positive rechallenge with PDE5 inhibitors [38, 89], proving that cessation of therapy was not associated with improved CSC in every case. Another important consideration is that CSC can resolve spontaneously, and the positive dechallenge may simply represent this possible outcome [38].

However, in a study of 43 prospective patients using sildenafil citrate, Damar et al. [25] did not identify one case of CSC. In 2010, French and Margo [40] reported that patients with decreased choroidal perfusion and thickness increase in response to systemic sildenafil [60]. While it is intuitively obvious that the choroidal thickness alone does not guarantee better choriocapillaris oxygenation, this could be a reasonable step toward ameliorating ischemia in dry AMD. Systemic treatment using a PDE5 and PDE6 inhibitor (sildenafil) is suggested as a means of increasing choroidal perfusion. Based on the hypothesis of increasing choroidal perfusion as a means of elevating NO (a messenger molecule) transfer across Bruch’s membrane by PDE5 as well as the increase in photoreceptor regeneration caused by a decrease in Warburg glycolysis by PDE6, some studies treated a series of patients with AMD with systemic sildenafil [20].

In a double-blinded phase II study, Birch et al. [12] examined the acute effect of sildenafil administration in patients with early AMD and showed no significant or clinically relevant changes in visual acuity, Humphrey perimetry, D15 color discrimination, photo-stress tests, and the Amsler grid. Furthermore, sildenafil did not cause significant changes in the foveolar choroidal circulation of patients with AMD [75] and showed similar vasodilatation of the major retinal veins as in normal subjects [74].

Coleman et al. [20] conducted a 2-year trial to evaluate the effect of sildenafil measured by spectral-domain OCT, color fundus photography, EDI, and best-corrected visual acuity. The group concluded that sildenafil is a safe treatment for AMD or vitelliform macular degeneration and suggested that a thickened Bruch’s membrane reduced the beneficial effect of the perfusion increase, but all eyes appeared to benefit from PDE6. The authors emphasized that the maintenance or improvement of the photoreceptor layer might have been the most significant result of sildenafil and that it was consistent with PDE6 inhibition. Thus, sildenafil treatment of macular degeneration offered significant potential for vision retention and recovery.

Nevertheless, given the lack of current evidence for the benefit and known cardiovascular and ocular risks of sildenafil, such as NAION, the use of PDE inhibitors as therapy for AMD should await further evaluation [111].

In conclusion, to date, PDE5 inhibitors have shown numerous effects on the choroid related to blood flow, such as clinical consequences in CSC and AMD. Based on their physiologic effects, PDE5 inhibitors could affect other diseases whose pathophysiology involves increased choroidal thickness. The treatment of other diseases with
PDE5 inhibitors deserves further study. Thus, it is important to emphasize the importance of careful ophthalmologic follow-up in patients on this medication, so that possible consequences can be managed over time.

Abbreviations
AMD: Age-related Macular Degeneration; BP: Blood Pressure; CBF: Choroidal Blood Flow; cGMP: Cyclic Guanosine Monophosphate; CRA: Central retinal artery; CSC: Central Serous Chorioretinopathy; DChI: Color Doppler image; ED: Erectile Dysfunction; EDI-OCT: Enhanced-Depth Imaging-Optical Coherence Tomography; EDV: End Diastolic Velocity; FDA: Food and Drug Administration; HRF: Heidelberg Retina Flowmetry; LDF: Laser Doppler Flowmetry; NAION: Nonarteritic Anterior Ischemic Optic Neuropathy; NO: Nitric Oxide; OA: Ophthalmic artery; PDE5: Phosphodiesterase type 5; PDE6: Phosphodiesterase type 6; POBF: Pulsatile Ocular Blood Flow; PSV: Peak Systolic Velocity; RBF: Retinal Blood Flow; RPE: Retinal Pigment Epithelium; RVA: Retinal Vessel Analyzer; SPCA: Short Posterior Ciliary Artery.

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Competing interests
The authors declare that they have no competing interests.

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