

# Possible Ocular Side Effects of Phosphodiesterase Enzyme 5 Inhibitors in Intermittent Low Doses

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## Karaarslan: Physiological Effects of Phosphodiesterase Enzyme 5 Inhibitors

**This study aimed to identify the potential adverse physiological effects of sexual performance-enhancing medication. Phosphodiesterase enzyme 5 inhibitors are the most common medications used for the treatment of male erectile dysfunction. In this study, nine cases were administered 5 g tadalafil per orally for 2 d in a week with 3 d intervals over 1 y. In addition to routine ophthalmological examinations, macular optical coherence tomography, electrooculography, and electroretinography test results of all participants were evaluated. Bilateral central serous retinopathy with pathological changes on electrooculography and macular optical coherence tomography was found in one patient with blurred central vision. In another patient with bluish-colored vision, light sensitivity, abnormal electrooculography and electroretinography patterns, and increased thickening of the retinal pigment epithelial layer were observed. This study indicates that phosphodiesterase enzyme 5 inhibitor may cause mild-to-moderate transient ocular adverse effects and visual disturbances, even at intermittent low doses, and these changes often tend to return to normal upon prompt discontinuation of medication.**

**Key words:** Erectile dysfunction, phosphodiesterase enzyme 5 inhibitors, retina, macula

Human relations have deteriorated in many ways owing to social isolation and unfavorable restrictions during and after the recent pandemic. The fear of death due to a mysterious infection and its uncertain vital complications has led to a lack of self-confidence, anxiety in social or sexual affairs, and even misanthropy in some people. Normal male sexual activity depends on consecutive psychosomatic events to ensure sufficient penile erectile function. Erectile Dysfunction (ED) is an inadequate or an impotent form of penile erection. Some physical or emotional etiological factors can cause male ED issues. Phosphodiesterase Enzyme (PDE)-5 inhibitors, such as sildenafil, vardenafil, and tadalafil are widely used for the treatment of ED, besides benign prostatic hyperplasia, and pulmonary arterial hypertension. Although these drugs are generally well-tolerated, they can cause ocular side effects owing to their mechanisms of action<sup>[1,2]</sup>. The use of PDE5 inhibitors, increases cyclic Guanosine Monophosphate (cGMP) levels and leads to vasodilation. They also weakly inhibit PDE6, an enzyme finding at high concentrations in the retinal rod and cone photoreceptor cells. Partial inhibition of PDE6 can result in visual disturbances such as

impaired color vision, blurred vision, and increased light sensitivity<sup>[3,4]</sup>. In addition to these transient visual effects, some studies have linked PDE5 inhibitor use to more serious ocular conditions, such as serious retinal detachment, retinal vascular occlusion, and ischemic optic neuropathy. While the risk of these events appears low, patients who regularly use PDE5 inhibitors should be aware of potential ocular adverse effects and promptly report any visual changes to their healthcare providers<sup>[5,6]</sup>. Ongoing research and careful ophthalmologic monitoring are important to better understand the ocular safety profile of PDE5 inhibitors and manage potential complications<sup>[7,8]</sup>. Nine healthy adult male participants, aged 39 y-54 y old were included in this study. Informed consent was obtained from all the participants. This study was initiated in March 2023 and ended in February 2024. The participants received a 5 mg p.o PDE-5 inhibitor tablet, and after an interval of 3 d, one more tablet. Therefore, they had two pills per week at 3 d intervals during the study period. This medication schedule was recommended by a special family sexual therapy center, and ocular examinations of the patients were conducted by the same physician at the beginning,

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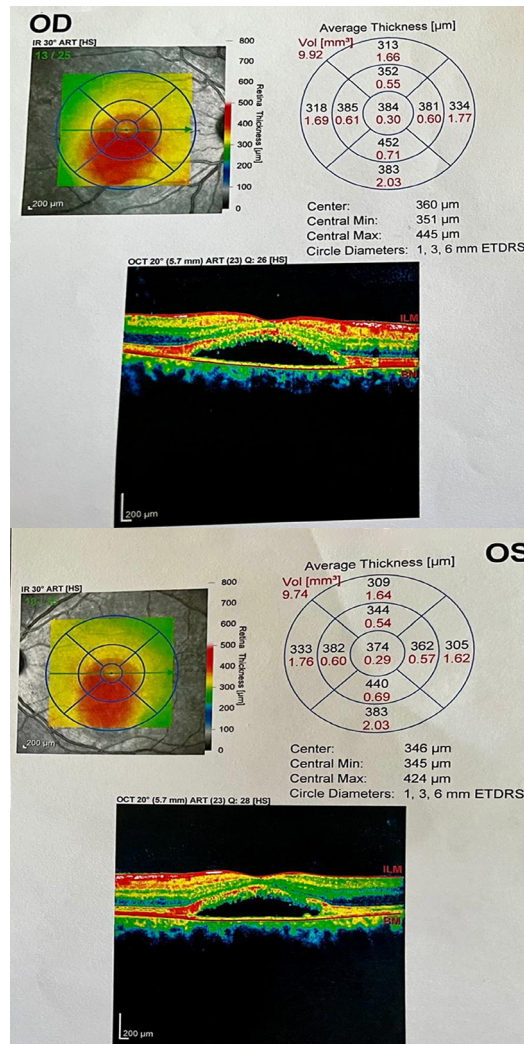
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and consequently at the end of the 1<sup>st</sup> mo, 3<sup>rd</sup> mo, 6<sup>th</sup> mo, and 1<sup>st</sup> y. In this study, in addition to routine ophthalmological examination, Optical Coherence Tomography (OCT), Electrooculography (EOG), and Electroretinography (ERG) were performed to observe the electrophysiological changes caused by PDE5-Is. These tests can be briefly explained; provides a cross-sectional view of the retina, potential electrical differences between anterior (cornea) and posterior (retinal pigment epithelium) eye segments, and potential electrical activity of retinal photoreceptor cells (rods and cones) under flashing light and dark conditions<sup>[9]</sup>. Nine adult males with good ocular and general health conditions were included in this study. Three of them used near-vision glasses and there were no other refractive errors among the patients. The mean age of the patients in this study was 46.5 y old and all participants were eager to avoid sexual performance anxiety. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for the study was granted by the Adana Branch of the World Eye Foundation. Besides a careful eye examination OCT Macula, EOG and ERG tests were conducted to all patients while they were taking per oral tadalafil for two times in a week due to 72 h long efficiency of the pill. This treatment schedule was recommended by a physician at a special sexual counseling center. The sexual performances of the participants were evaluated by International Index of Erectile Function (IIEF) questionnaires. The mean IIEF score of nine patients was  $8.81 \pm 1.6$  (indicates moderate ED) before using the PDE-5 inhibitor medication, and after 3 mo of use of the medication, it was reported as  $21.16 \pm 1.2$ . These findings showed that medication was useful because there was no longer ED anxiety or ED among the patients, and the difference was statistically significant ( $p < 0.05$ ). During the study, all participants were routinely examined by the same ophthalmologist at the end of the 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup>, and 12<sup>th</sup> mo. At the end of the 1<sup>st</sup>, one patient reported significantly blurred central vision in both eyes. Bilateral central serous retinopathy was diagnosed in this patient with the OCT macula (fig. 1). Fortunately, his visual complaints and OCT findings spontaneously returned to normal in both eyes 3 w after the PDE 5 inhibitor treatment was discontinued (fig. 2). During the edematous stage, a significant disruption was seen in his EOG trace, and this pathological EOG scene returned to normal pattern 3 w after the recovery of

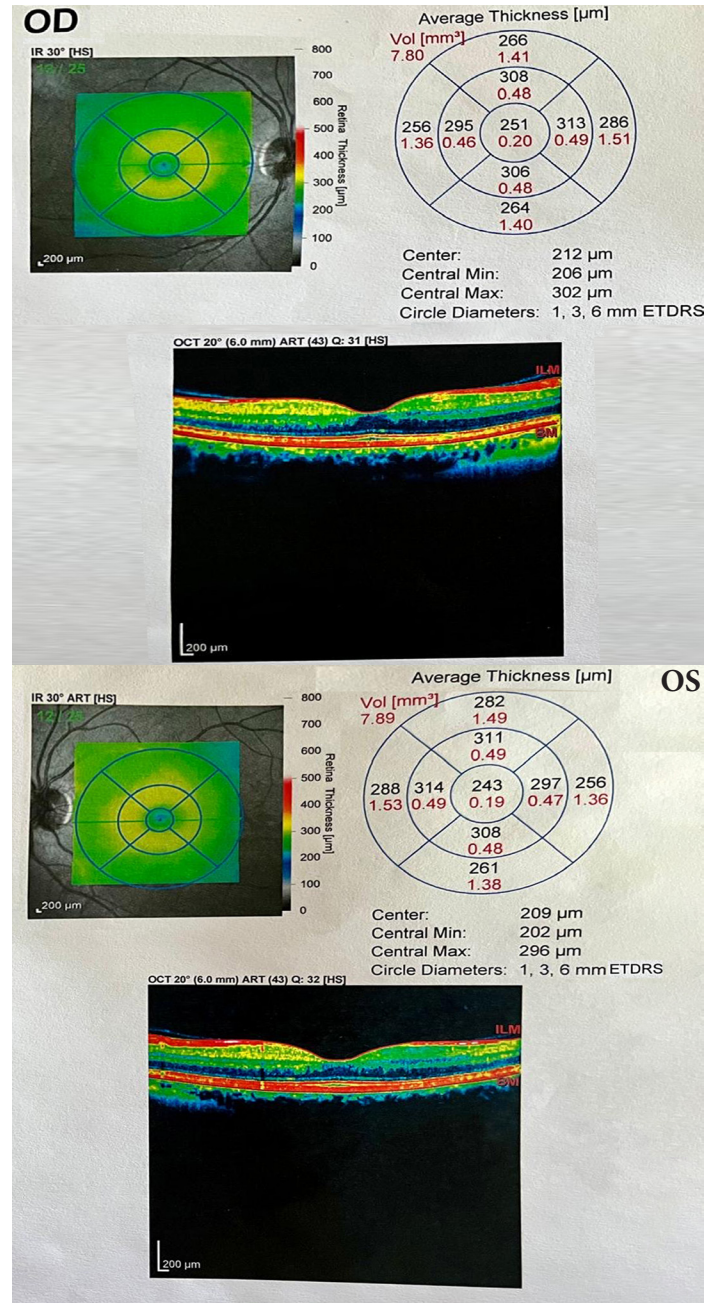
the OCT findings. Another patient with bluish-colored vision showed some EOG and ERG changes by the end of the 3<sup>rd</sup> mo. Due to this and his increased intra ocular pressures he was excluded from the study and medication at the end of the 3<sup>rd</sup> mo, while his automated perimeter findings and Intraocular Pressure (IOP) measurements were normal. His EOG and ERG findings also returned to normal after 10 d of cessation of medication. ED is a common and heterogeneous disorder originating from physiological and psychological factors. The main problem in the ED is the impossibility of normal sexual intercourse and sperm ejaculation due to insufficient penile erection. Even so, ED may occur in any age group of adult males, it seems more common in older adults and recurrent ED can lead to persistent sexual and emotional disorder. Although ED is not a rare condition, approximately 2 % of the patients visit a physician. As a multidimensional phenomenon, there are four phases of healthy male sexual activity. These are the arousal, erectile, ejaculative, and latent (post-ejaculation) periods. ED can be observed in any phase and by any hormonal, neurological, vascular, or emotional reasons. Oral PDE5 inhibitors may be the first-choice treatment for ED<sup>[10]</sup>. Avanafil, tadalafil and sildenafil are prominent examples of PDE5-Is, and are recommended by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the United States of America (USA). The desired effect of these mentioned medications occurs in (15-60) min while the patient takes one pill in each day for 2 d in a week with a 3 d interval, he does not need waiting time to be ready to engage in sexual activity, as he is already sexually active for approximately 4 h-72 h<sup>[11]</sup>. The PDE-5 plays an important role in regulating the blood flow through the specialized capillaries and erectile tissue in cavernous corpus of penis. Imbalanced release of PDE-5 can cause unstable penile erection and sexual impotence<sup>[12,13]</sup>. The central serous retinopathy of one patient at the end of the 1<sup>st</sup> mo and increased retinal thickness in another patient at the end of the 3<sup>rd</sup> mo were thought to be linked to choroidal vascular leakage through the retinal pigment epithelial microspores and increased blood flow during the PDE-5 medication. For the patient who had abnormal ERG pattern at the end of the 3<sup>rd</sup> mo of the study, it was thought that it could be related to the affected photoreceptor cell activity. His complaints, such as bluish vision and increased photosensitivity, could also be related to the

thickened retinal pigment epithelium, detected by macular OCT. His additional Retinal Nerve Fiber Layer (RNFL) OCT and automated perimeter tests were within normal limits. So, it is evaluated that the retinal ganglion cells are not affected by PDE-5 inhibitor using. During the study period, mild and transient increase in the IOP was observed in some patients. However, these changes were not been found as statistically or clinically significant. To reveal the underlying cause of visual disturbance and colored vision in bright light, OCT RNFL and automated perimeter tests were added to one patient who had these problems. Due to his normal findings in automated perimeter and OCT\_RNFL tests, the retinal nerve fiber layer cells were thought to be intact. Delayed and extended maximum wave on EOG and increased thickness of the pigment epithelium on macular OCT were evaluated as consistent findings. PDE5-inhibitors prevent the backflow of blood from escaping capillaries and may elevate intra-capillary pressure. Increased blood flow

through the ocular ciliary body may cause headaches and eye aches in some cases<sup>[14]</sup>. It is widely accepted that these issues are unrelated to glaucoma or permanent damage of optic nerve. However, according to the American National Health and Nutrition Examination Survey (NHANES), glaucoma patients are not good candidates for long-term use of Sildenafil or other PDE-5 inhibitors because of their potential worsening effects on optic nerve damage. PDE-5 inhibitors are not recommended for glaucoma patients, especially who were suffering from optic nerve damage<sup>[15]</sup>. The PDE-5 inhibitors can cause some ocular adverse effects due to retinal thickening resulting from excessive blood perfusion pressure through the choroidal capillary plexus and most probably these effects are going to be transient. Despite the small sample size and limited options for electrophysiological ocular tests, these potential issues should be considered when using the PDE5 inhibitors.



**Fig. 1: Bilateral central serous retinopathy at the end of the 1<sup>st</sup> mo**



**Fig. 2: Bilateral recovery in both eyes after the discontinuation of the medication**

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The authors declared no conflict of interests.

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