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A Review of the Influence of Psychoactive Substances on the Visual Apparatus

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Abstract

This review explores the visual and cognitive impacts of opioids, cannabinoids and synthetic drugs. Key studies using Optical Coherence Tomography (OCT), eye-tracking, and visual evoked potentials (VEPs) were reviewed. Results show that opioids cause pupil constriction, impaired low-light vision, and slower saccadic eye movements. Cannabinoids, particularly THC, act on CB1 receptors, leading to retinal thinning, impaired accommodation, and delayed visual processing. Synthetic drugs, such as synthetic cannabinoids and stimulants, increase risks of retinal apoptosis, reduced color vision, and slower visual response due to neurotoxicity. The review underscores the need for targeted visual assessments: OCT for cannabis users, IOP and saccadic evaluations for opioid users, visual assessments for synthetic drug-dependent individuals. Future longitudinal research is critical to understanding these impacts and refining preventive care.
Keywords: opioids, cannabinoids, synthetic drugs, visual apparatus, neurotoxicity, cognitive impairments

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Обзор влияния психоактивных веществ на зрительный аппарат

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Резюме

В обзоре рассматриваются визуальные и когнитивные эффекты опиоидов, каннабиноидов и синтетических наркотиков. Проанализированы ключевые исследования с использованием оптической когерентной томографии, отслеживания глаз и вызванных зрительных потенциалов. Результаты показывают, что опиоиды вызывают сужение зрачков, нарушение зрения при слабом освещении и замедление саккадических движений глаз. Каннабиноиды, особенно тетрагидроканнабинол, действуют на рецепторы CB1, что приводит к истончению сетчатки, нарушению аккомодации и задержке визуальной обработки. Синтетические наркотики, такие как синтетические каннабиноиды и стимуляторы, повышают риск апоптоза сетчатки, ухудшения цветового зрения и замедления зрительной реакции из-за нейротоксичности. В обзоре подчеркивается необходимость целевых визуальных оценок: оптической когерентной томографии для потребителей каннабиса, оценки ВГД и саккадических движений для потребителей опиоидов, визуальные оценки для лиц, зависимых от синтетических наркотиков. Будущие исследования имеют решающее значение для понимания этих эффектов и совершенствования профилактической помощи.
Ключевые слова: опиоиды, каннабиноиды, синтетические наркотики, зрительный аппарат, нейротоксичность, когнитивные нарушения

■ INTRODUCTION

The visual system, comprising the retina, optic nerve, and cortical visual centers, plays a critical role in interpreting sensory input and is highly susceptible to disruption by psychoactive substances. With the increasing global prevalence of substance use, understanding the impacts of psychoactive agents – such as opioids, cannabinoids and synthetic drugs – on visual function has become a pressing area of study in public health and neurobiology [1]. The implications of these substances extend beyond cognitive and behavioral effects, directly affecting vision-related parameters like intraocular pressure (IOP), retinal integrity, and the efficiency of visual processing pathways. These effects carry

significant consequences for individuals' day-to-day activities, including tasks requiring visual precision and quick cognitive responses, such as driving and work-related activities.

The rise in substance use worldwide is stark. According to the World Health Organization (WHO), the prevalence of opioid, cannabis, and synthetic drug use has significantly increased over the past decade [2]. In particular, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated that around 18 million people in Europe aged 15 to 34, representing 15% of this demographic, used cannabis in 2019 alone [3]. The widespread consumption of these substances, combined with their varying legal statuses, underscores the need for rigorous study into their physiological and neurotoxic effects on the body, especially their less understood impacts on the visual system.

The primary psychoactive compounds in cannabis, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with cannabinoid (CB) receptors throughout the central nervous system (CNS), including visual pathways. This interaction affects visual functions such as accommodation, pupil response, and retinal integrity, with THC notably disrupting autonomic regulation, leading to potential visual disturbances like impaired focus and reading difficulties [4, 5].

Opioids, particularly short-acting types like remifentanil, are used in anesthesia to manage intraocular pressure (IOP) increases during surgery, a benefit linked to CNS-mediated muscle relaxation [6]. Although useful in controlled environments, the chronic use of opioids poses risks for visual and cognitive impairments, with limited research on long-term effects.

Synthetic drugs, including potent synthetic cannabinoids and stimulants like amphetamines, impact visual pathways through intense neurotoxic effects. Synthetic cannabinoids have been linked to retinal damage and ganglion cell dysfunction due to strong CB1 receptor binding, while amphetamines may cause oxidative stress and neurovascular changes in the retina and optic nerve [7–9].

These findings highlight the neurotoxic risks that psychoactive substances pose to the visual system, emphasizing the need for clinical monitoring and public health measures tailored to mitigate visual and cognitive impairments associated with substance use. This review aims to consolidate findings on the impacts of opioids, cannabinoids and synthetic drugs on visual structure and function. By synthesizing evidence from studies employing advanced techniques such as eye-tracking, OCT, and PERG, this review highlights the neurotoxic, vascular, and cognitive changes that arise from substance use. The ultimate goal is to provide a comprehensive understanding of how these substances affect ocular health, thereby informing clinical, public health, and research perspectives on mitigating and preventing substance-related visual impairments.

■ MATERIALS AND METHODS

Study search and selection

The databases PubMed, Scopus, and Cochrane were searched for studies using keywords such as "opioids", "cannabinoids", "synthetic drugs" and "visual system". Studies employing Optical Coherence Tomography (OCT), pattern electroretinography (PERG), and eye-tracking techniques were included.

Inclusion and exclusion criteria

Inclusion criteria:

1. Randomized controlled trials (RCTs), systematic reviews, and observational studies assessing the impact of the mentioned substances on IOP, the retina, or visual functions.
2. Studies with available data on cognitive effects of these substances on vision.

Exclusion criteria: publications with limited data on visual effects or animal studies without human confirmation.

■ RESULTS

Impact of opioids on intraocular pressure and visual functions

Opioid use, especially among addicted individuals, is marked by changes in pupil dynamics, primarily through miosis (constriction). Miosis can hinder visual adaptability in low-light conditions, a significant finding noted by Christie and colleagues in 2008, which showed that users experienced impaired visual clarity due to limited light entry [10]. Additionally, Elsaadany and peers found that opioids disrupt saccadic eye movements, leading to reduced saccadic velocity and visual focus accuracy, a problem especially pronounced in high opioid doses or with long-term use [11].

Cognitive functions essential to visual perception, such as memory, attention, and processing speed, are negatively affected by chronic opioid use. Some researchers reported increased errors in visual recognition tasks among opioid-dependent individuals, suggesting that opioids reduce accuracy and response efficiency in visual tasks [12]. This finding is supported by Walhovd et al. (2015), which documented neurodegenerative changes in the thalamus and frontal cortex, areas essential for visual cognition [13].

Studies utilizing visual evoked potentials (VEPs) provide further insight into the impaired visual processing pathways in opioid users. Elsaadany et al. (2021) found that opioid-dependent individuals showed delayed VEPs, indicating slower neural transmission within visual pathways. This delay suggests a possible neurotoxic impact of opioids on the CNS that extends into visual processing domains.

Research by Courtney et al. (2016) indicates that chronic opioid use affects visual memory and reaction time, with opioid users showing diminished speed and efficiency in processing visual information [14]. Christie et al. (2008) also demonstrated that these individuals struggle with tasks requiring sustained visual attention, with errors commonly noted during prolonged visual searches. The cognitive dysfunction associated with long-term opioid use is collectively termed "opioid-induced cognitive dysfunction" and includes deficits in attention and working memory critical to visual tasks.

Long-term exposure to opioids appears to contribute to neurodegenerative effects within the CNS that impact both retinal structure and function. The neurotoxicity of opioids was evidenced in a study [15], which demonstrated that opioid-dependent individuals exhibited significant thinning of the retinal nerve fiber layer (RNFL), an indicator of neural degradation. This thinning compromises visual signal transmission to the brain, which may exacerbate difficulties in visual processing and contribute to longer response times, as noted in [16, 17].

Walhovd and colleagues further highlighted that opioid use affects the neural circuitry involved in both visual perception and higher-order cognitive functions, including attention, suggesting that chronic opioid use may lead to lasting impairments in visual processing abilities due to neural changes. The visual deficits observed in opioid-dependent

individuals carry significant clinical implications, particularly for activities requiring precise visual coordination, such as driving. Researchers recommended that chronic opioid users undergo regular eye exams, with particular focus on saccadic eye movement and pupil response assessments, to identify early signs of visual impairment.

Given the neurotoxic effects of opioids, several studies have proposed neuroprotective strategies to mitigate their impact on the CNS. Courtney et al. (2016) and Evans and Cahill (2016) both suggested the use of antioxidants and anti-inflammatory agents as potential interventions to protect retinal and CNS pathways involved in visual processing. These interventions could help reduce oxidative stress and inflammation in visual processing areas, which are exacerbated by chronic opioid exposure.

Influence of cannabinoids on visual aspects

Cannabinoids, particularly THC, act on CB1 receptors located in the retina and optic nerve, resulting in altered neural signal transmission. Studies indicate that chronic cannabis use affects the N95 component of PERG, reflecting delayed signal transmission in the retinal ganglion cells, indicating potential neurotoxic effects [18]. OCT studies also reveal reduced retinal nerve fiber layer (RNFL) thickness, suggestive of neurodegeneration [19].

Cannabis's psychoactive effects are primarily due to THC, with CBD recognized for its non-psychoactive properties [20]. Smoked cannabis quickly activates CB receptors in various CNS regions, including critical visual system structures like the lateral geniculate nucleus and superior colliculus, as well as the retina and ciliary muscle responsible for accommodation [21, 22]. Studies confirm that cannabis can impair accommodation, resulting in visual discomfort and reading difficulties due to interference with the autonomic nervous system [23]. These impairments in accommodation have been linked to the cognitive effects of cannabis on memory and attention [24], which disrupts the eye's ability to adjust focus. Evidence form [25], [26] suggests that this accommodation disruption is closely tied to broader cognitive deficits linked to cannabis use, including impairments in memory and attention. However, other studies report minimal effects on sustained attention among chronic users, indicating that cannabis impacts may vary with frequency of use and cognitive load [27].

One area of significant interest is the effect of cannabis on retinal ganglion cells, as these cells represent the final retinal relay in visual processing before signals are transmitted to the brain. Studies using pattern electroretinogram (PERG) measurements have shown that regular cannabis users exhibit delays in the N95 component of the PERG, which reflects slowed neural transmission within the retinal ganglion cells [28]. Specifically, Schwitzer et al. demonstrated that the N95 implicit time is significantly increased in cannabis users, indicating slower visual signal processing from the retina to the visual cortex, which could be neurotoxic over the long term. This slowing suggests a direct effect of exogenous cannabinoids on retinal glutamatergic transmission, as cannabinoids influence neurotransmission by modulating the release of glutamate, a major excitatory neurotransmitter in the CNS [29].

Further research has explored how long-term cannabis use, particularly when initiated at an early age, affects visual processing and eye movement behavior. Studies indicate that chronic cannabis users with an onset of use during adolescence exhibit distinctive deficits in visual scanning tasks. For example, Huestegge et al. (2021) conducted a study

in which cannabis users were asked to search for targets in a visual matrix while their eye movements were tracked. The cannabis users showed less efficient search behaviors, including longer response times, more frequent fixations, and increased re-inspection of previously viewed areas. These findings highlight two specific areas of impairment: a reduction in visual short-term memory and less effective, top-down controlled visual processing, which impacts the efficiency and accuracy of visual scanning [30].

This impairment in visual processing, particularly in tasks involving visual search, has also been linked to early onset of cannabis use. Ehrenreich et al. (1999) found that early-onset cannabis users performed significantly worse on visual scanning tasks compared to later-onset users and controls. Their analysis suggested that early initiation of cannabis use was a better predictor of impaired visual processing than either acute intoxication or cumulative lifetime dose. This association between early onset and visual processing deficits underscores the possibility of a lasting impact of adolescent cannabis use on visual and cognitive function [21].

Eye movement research further corroborates these findings by showing that cannabis users exhibit atypical patterns in tasks requiring visual search. Eye tracking reveals that cannabis users, particularly those with a history of early use, display more conservative scanning patterns, often characterized by shorter saccades and longer fixation durations. These patterns suggest that cannabis users may rely more on local, bottom-up processing rather than global, strategic search strategies [32–34]. This shift in visual search behavior likely reflects the impact of cannabis on higher-order cognitive functions, including the planning and control of eye movements necessary for efficient search.

The effectiveness of extrafoveal processing, a critical factor in visual search performance, also appears to be compromised in cannabis users. Research od Scott and peers has shown that the ability to process visual information in peripheral areas, a skill essential for efficient scanning, is often reduced in chronic cannabis users. Given that extrafoveal processing allows individuals to identify objects outside of their direct line of sight, deficits in this area suggest that cannabis users may struggle with broader aspects of visual perception, which could have implications for tasks requiring rapid situational awareness, such as driving [35].

In addition to changes in eye movement behavior, studies on visual memory have revealed significant deficits among cannabis users. For instance, Horowitz and Wolfe (1998) posited that visual search in cannabis users may follow a "memory-less" model, where items are reinspected rather than systematically ruled out [36]. Supporting this, Peterson et al. observed that cannabis users returned to previously fixated items more frequently than expected by chance, indicating potential difficulties in visual working memory and inhibitory control [37]. This suggests that the impairment in visual memory among cannabis users may extend to difficulties with strategic search and object identification, factors critical to efficient visual processing.

Optical Coherence Tomography (OCT) studies further demonstrate the neurodegenerative impact of cannabis on the retina. For example, OCT imaging has revealed significant thinning in the retinal nerve fiber layer (RNFL) among regular cannabis users, particularly in the temporal quadrant. This thinning is indicative of neurodegeneration within the retinal layers, potentially due to the chronic neurotoxic effects of THC on retinal ganglion cells. As the RNFL comprises axons that transmit visual information to the brain, degeneration in this layer suggests a compromised visual

pathway, which could account for the delayed response times and reduced accuracy observed in visual tasks among cannabis users.

Effects of synthetic drugs on visual function

Synthetic drugs, including amphetamines and synthetic cannabinoids, exert a substantial impact on vision. Studies report that synthetic cannabinoids induce retinal damage, impairing light response due to CB1 receptor effects [38].

Synthetic drugs, including synthetic cannabinoids (e.g., "Spice" and "K2") and stimulants such as methamphetamine and MDMA (ecstasy), have marked effects on the central nervous system (CNS) and are known to impair cognitive functions, memory, and attention. These substances can disrupt visual function, affecting the retina, optic nerve, and cognitive processes tied to visual perception. Research shows that synthetic cannabinoids, for example, impact the visual system through CB1 receptors, which are also involved in retinal processing, while stimulants like methamphetamine exert neurotoxic effects, potentially leading to long-term vision and cognitive impairments [39].

Synthetic cannabinoids are designed to mimic the effects of THC, the psychoactive component in cannabis, but they often produce more intense and prolonged effects due to their high affinity for CB1 receptors. These receptors are highly expressed in the retina and visual processing areas of the brain, making them susceptible to synthetic cannabinoids' effects. Studies have shown that synthetic cannabinoids can disrupt retinal ganglion cell function and cause neurotoxic damage, impairing light sensitivity and visual processing. Gerak in 2019 reported that synthetic cannabinoids induced significant disruptions in retinal cell signaling, particularly in pathways linked to visual attention and image processing [40].

Due to their potent effect on CB1 receptors, synthetic cannabinoids can also increase the risk of retinal cell apoptosis, as excessive activation of these receptors has been linked to cell death in the visual system. This damage, when accumulated, could lead to permanent visual impairments, including decreased contrast sensitivity and color vision deficits. Synthetic cannabinoids have been shown to affect visual processing speed and accuracy, which may result in difficulties in visual tasks that require quick decision-making, such as driving.

Methamphetamine and MDMA are powerful CNS stimulants that alter dopamine, serotonin, and norepinephrine levels, contributing to their effects on mood, cognition, and sensory perception. Methamphetamine, in particular, has neurotoxic properties that can damage dopaminergic and serotonergic pathways, which are essential for normal visual processing. Studies have shown that methamphetamine use can lead to oxidative stress and inflammation in the brain, which may damage the optic nerve and visual cortex. These effects are associated with impairments in visual acuity, reduced ability to process visual information accurately, and slower reaction times to visual stimuli [41].

MDMA, although less neurotoxic than methamphetamine, also influences visual perception. It affects serotonergic pathways, which are essential for regulating light sensitivity and retinal function. Chronic use of MDMA has been linked to visual disturbances, including increased sensitivity to bright lights, visual distortions, and issues with visual memory. These alterations are thought to result from MDMA's effect on serotonin receptors within the retina and cortical areas responsible for visual perception. Long-term use may exacerbate these visual issues, with some studies suggesting that

MDMA users may experience permanent changes in visual processing speed and accuracy even after discontinuation [42].

Synthetic drugs not only affect the physical structures of the visual system but also disrupt cognitive processes tied to visual function. Methamphetamine and MDMA, for instance, are associated with impairments in visual scanning and saccadic eye movement control. These effects are especially pronounced in long-term users, who often demonstrate slower and more erratic eye movements during visual search tasks. Research indicates that stimulant use is linked to an increase in fixation duration and reduced saccade velocity, suggesting impaired attentional control over eye movements. Users may also experience difficulty tracking moving objects or shifting focus quickly, as synthetic drugs can hinder the integration of visual and motor responses [43].

■ DISCUSSION

Comparison of mechanisms across substances

Each substance-opioids, cannabinoids, synthetic drugs – exerts unique yet overlapping impacts on the visual system through distinct neurophysiological mechanisms. Opioids primarily affect intraocular pressure (IOP) and pupil dynamics by acting on the autonomic nervous system, which can impair visual clarity in low-light environments due to constricted pupils (Christie et al., 2008). Additionally, opioids' neurotoxicity has been linked to cognitive deficits in visual tasks that demand sustained attention and memory (Yassin et al., 2020; Courtney et al., 2016).

Cannabinoids, especially THC, act on CB1 receptors in the retina and visual pathways, leading to neurodegenerative effects such as retinal nerve fiber layer (RNFL) thinning, visual scanning inefficiency, and accommodation issues (Schwitzer et al., 2017; Dayi et al., 2020). Synthetic cannabinoids, designed to mimic THC but often with heightened potency, increase risks for retinal cell apoptosis, further reducing contrast sensitivity and color discrimination (Gerak et al., 2019). Stimulants like methamphetamine and MDMA disrupt dopaminergic and serotonergic pathways, potentially damaging the optic nerve and visual cortex and impairing visual processing speed (Manning et al., 2017). Below there is provided a table that compares primary visual effects, mechanisms and clinical implications associated with addiction to different substances.

This comparison table embraces the primary visual effects, mechanisms, and suggested clinical strategies for managing visual impairments associated with each substance. The table offers a concise reference for clinicians to anticipate and address the distinct visual challenges in substance-dependent populations.

Comparison of visual impact affected by different substances

Substance	Primary visual effects	Mechanism	Clinical implications
Opioids	Miosis, impaired low-light vision, slower saccades	CNS suppression, reduced IOP	Regular IOP checks, neuroprotective agents
Cannabinoids	RNFL thinning, delayed N95 (PERG), accommodation issues	CB1 receptor impact in retina, autonomic disruption	OCT monitoring, neuroprotection in long-term users
Synthetic Drugs	Retinal cell apoptosis, slow visual processing, color vision loss	Neurotoxicity, oxidative stress in visual pathways	Visual assessments, neuroimaging, early interventions
Source: made by authors			

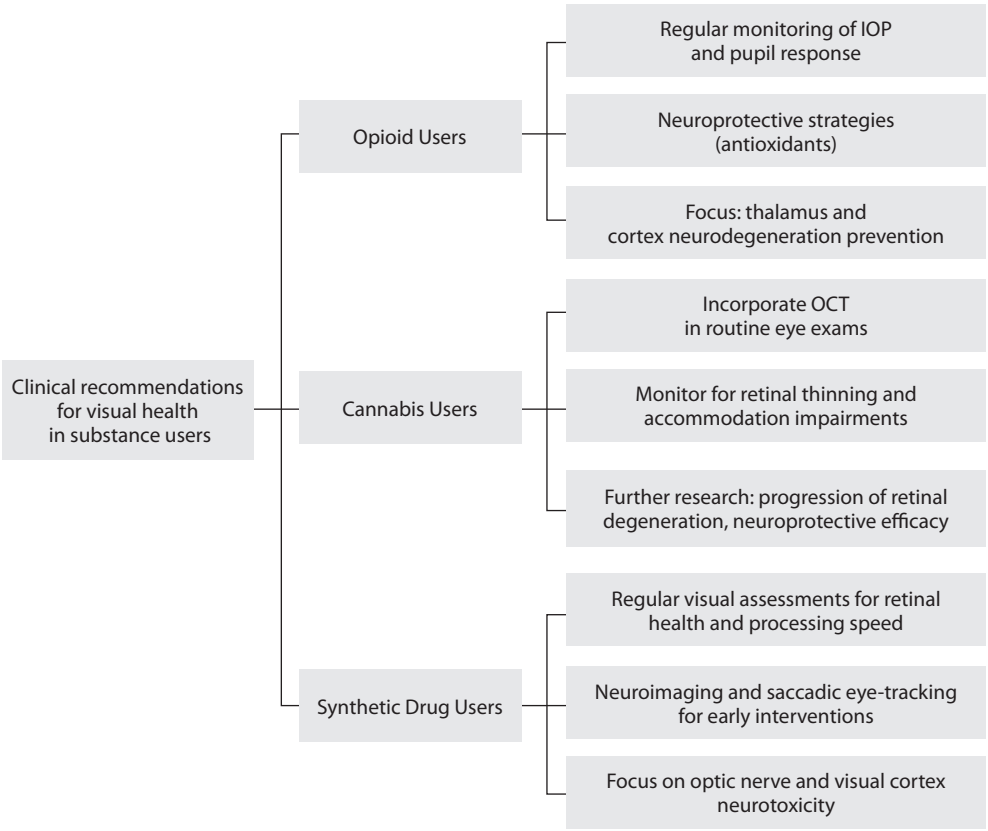
Clinical implications and research directions

The visual impairments associated with these substances highlight the need for specialized ophthalmologic assessments and neuroprotective strategies, particularly for populations with long-term substance dependence. The authors developed a set of recommendations based on the references provided earlier in this research (see Fig.). To note, for each substance, early identification, intervention, and individualized care may enhance visual health outcomes and mitigate long-term impacts.

Limitations and future perspectives

While this review provides an overview of the visual impacts of psychoactive substances, it is limited by the variation in methodologies and study designs across the cited research. Many studies rely on small sample sizes and cross-sectional designs, limiting generalizability. There is also a need for standardized metrics to evaluate visual and cognitive impairments, particularly for eye-tracking and OCT parameters, to enable more consistent comparison across studies.

Future research should address the differential impact of these substances on specific visual and cognitive tasks, including long-term follow-ups to assess potential recovery



Clinical recommendations for visual health improvement

or progression of impairments. Randomized controlled trials examining neuroprotective strategies, such as antioxidants or neurocognitive rehabilitation programs, may also provide valuable insights into preventing or mitigating neurodegeneration and visual dysfunction in substance users. Expanding research to include gender-specific and age-related differences could offer further personalized approaches to managing and preventing substance-related visual impairments.

■ CONCLUSION

This review synthesizes the primary visual and cognitive impacts associated with opioids, cannabinoids and synthetic drugs use, highlighting how each substance exerts unique but overlapping effects on the visual system. Opioids, through CNS modulation, affect intraocular pressure and pupil dynamics, reducing visual clarity, particularly in low-light environments. Chronic opioid users display neurodegenerative changes, impacting both visual and cognitive processing. Cannabinoids, especially THC, disrupt CB1 receptors in the retina and optic pathways, leading to retinal thinning, impaired accommodation, and slower visual signal transmission, which collectively diminish visual accuracy. Synthetic drugs, such as synthetic cannabinoids and stimulants, pose risks of retinal cell apoptosis, decreased color vision, and slowed visual processing due to oxidative stress and neurotoxic effects, contributing to long-term retinal damage.

These findings underscore the need for targeted ophthalmologic evaluations, neuroprotective interventions, and visual monitoring strategies tailored to the visual health risks of substance-dependent populations. Clinical recommendations such as OCT monitoring for cannabinoid users, IOP assessments for opioid users can improve early detection and treatment of substance-related visual impairments. Moving forward, more standardized and longitudinal research is essential to fully understand the chronic impacts of substance use on the visual system and to guide effective preventive and rehabilitative measures.

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