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Exploring the Impact of Caffeine, Alcohol, and Opioids on Intraocular Pressure: A Comprehensive Analysis of Short-Term and Long-Term Effects on Vision

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Exploring the Impact of Caffeine, Alcohol, and Opioids on Intraocular Pressure: A Comprehensive Analysis of Short-Term and Long-Term Effects on Vision

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Abstract

Coffee, alcohol, and opioids are addictive drugs commonly used in modern society, yet their impact on ocular health remains ambiguous. This systematic review aims to elucidate this ambiguity by examining their effects on intraocular pressure (IOP). Utilizing IOP as a metric, both short-term and long-term effects are evaluated across individuals with irregular IOP levels and healthy subjects. Furthermore, the study analyzes choroidal thickness as an additional measure to reinforce or challenge the findings regarding IOP, leveraging the inverse relationship between the two metrics concerning elevated IOP-related illnesses, such as open-angle glaucoma (OAG).

A comprehensive literature search was performed through Google Scholar to find articles relating to the subject. Once found, 18 sources (including two meta-analyses with additional sources) were analyzed to find a consensus in data on the effects of IOP tested on each of the three drugs. An IOP increase of 1 mmHG was considered a statistically significant change caused by the injection of the drug. For choroidal thickness, a measurement of 20 microns (μm) or higher fluctuations affected by the drug in either direction showed the drug affected the choroid.

In short-term studies, caffeine was found to significantly increase intraocular pressure (IOP) in individuals with genetic predisposition to or existing abnormal IOP levels, but not in healthy subjects. Conversely, habitual alcohol consumption was associated with increased IOP in patients with and without open-angle glaucoma (OAG), while moderate or light ethanol intake showed no significant effect on either population. Studies on opioids revealed a decrease in IOP

for both patient groups. Notably, opioids administered directly into the eye resulted in a reduction of IOP by over 10 mmHg within a single day for individuals with elevated IOP levels.

Long-term studies have not identified any significant effects of alcohol or caffeine on intraocular pressure (IOP) or ocular diseases. However, due to limited data in this category, these findings should be viewed as preliminary rather than conclusive. Additional research across all these domains would enhance confidence in the conclusions drawn from this study. Current scientific evidence suggests that excessive alcohol and caffeine consumption may diminish ocular health, while opioid use, particularly when induced in the eye, may have positive effects. This study underscores the importance of moderation in alcohol and caffeine intake and highlights the potential benefits of opioids in maintaining ocular health.

Introduction

The usage of drugs that impact the body has been ingrained in human cultures throughout civilization. From discovering Opium (Lachryma papaveris) within poppy seeds in 5900 B.C, fermenting crops into alcohol, to mixing crushed coffee beans into water for energy, the role body-altering chemicals have played in shaping the actions of the human species is evident.[1] Due to the impact each drug had on the human body, these ancient innovations were experienced and replicated, leading to their growing popularity throughout time. Through trade and time, drugs have only further interwoven themselves within the fabric of virtually all global societies, making their presence in modernity commonplace.

As with all substances humans ingest, each has unique advantages and disadvantages. The stimulating effects of caffeine, the inebriating effects of alcohol, and the relieving effects of opioids are commonly recognized. These have widely been the rationale for each drug's daily use by millions of people across the globe. In parallel, the academic community began to research how such ubiquitous elements in our lives impact other facets of health. The scrutiny of research has removed many drugs, such as quaaludes and tobacco, from being considered health-conscious choices. This fate is possible for other medications as well, especially considering recent developments, such as the opioid epidemic facing many areas of the United States.

Analyzing the specific effects of several drugs commonly used in society, this work seeks to explore the role of caffeine, alcohol, and opioids on eye health. Each drug's health impact on the human body is often explored in a less holistic way, generally omitting the role these drugs play in ophthalmological health. As such, this work uses a compilation of research studies that pertain to these individual drug effects on eye health. Beyond an overview of each individual drug, this systematic review will specifically investigate the effects these drugs have on intraocular pressure (IOP) to provide consensus over the impact of substances on a devastating condition. A secondary approach to corroborate the accuracy of the IOP findings, given through the inverse relationship found with choroidal thickness. Ultimately, the purpose of this study is to observe the direct effect of caffeine, alcohol, and opioid ingestion on optic damage, explain the potential reason and provide steps for researchers who aim to address this problem potential ways of experimentation.

Relevant Topics

Prior to investigating the individual effects of caffeine, alcohol, and opioids on the eye, it is vital to establish a framework for analyzing ocular health. This reference section will outline the specific methods and metrics employed to assess the impact of these substances on the eye. Though this list is not a complete collection of all the topics that will be mentioned, it provides essential context that will be referenced throughout the study.

Intraocular pressure (IOP)

The anatomy of the eye is highly intricate, with a myriad of specific components that enable its function. Simplified for brevity, the eye has two sections of liquid which are separated by three chambers: the vitreous chamber and the grouped anterior/posterior chambers. Both the anterior and posterior chambers are filled with a liquid known as aqueous humor, which supplies nutrients to the cornea. As it performs this task, aqueous humor flows around the iris to eventually be filtered through the trabecular meshwork and pass the canal of Schlemm to be reabsorbed into the body. When the flow of aqueous humor through the trabecular meshwork is restrained, intraocular pressure is created, which is generally calculated by the amount of resistance.[2] This process is easier to understand, ***Figure 1*** shows the location of the aqueous humor, its location in the eye, and the exit point (canal of Schlemm).[3] As normal intraocular pressure is between 10 to 21 mmHg, any increase or decrease beyond this range can severely damage the eye.[2]

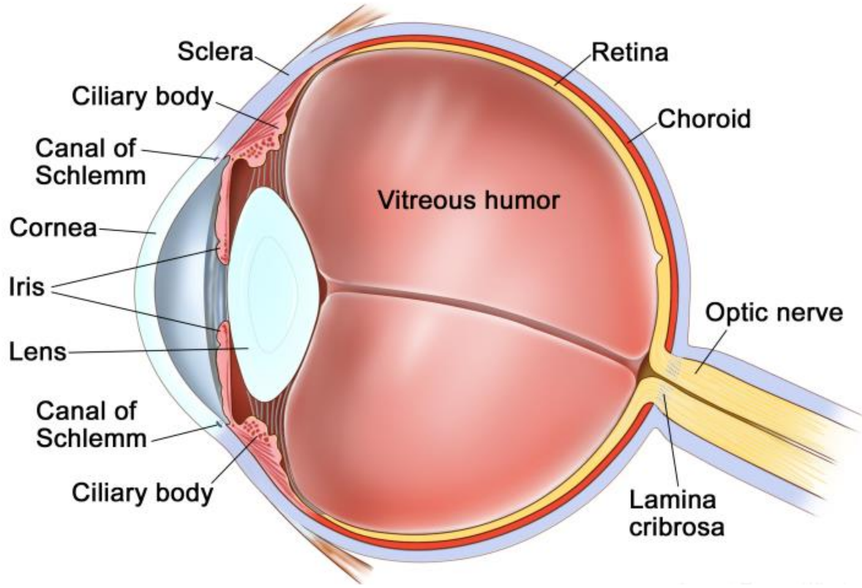

Figure 1: Anatomical Diagram of a human eye.[3]

Open-Angle Glaucoma (OAG)

Open-Angle Glaucoma, or OAG, often refers to progressive and irreversible damage to the optic nerve, onset by an increase in intraocular pressure beyond the normal range. When intraocular pressure is between 10 to 21 mmHg, eye function is maintained by low resistance in the trabecular meshwork. However, with OAG, the resistance in the trabecular meshwork is gradually increased, leading to consistently higher pressure over time. When this pressure buildup occurs, the optic cup (inside the optic disc) increases beyond its normal size in a gradual process known as “cupping.” When the optic cup grows to half the size of the disk, this pressure buildup creates an irreparable problem in one's eye, causing open-angle glaucoma. Open-angle glaucoma can be measured at an optometrist clinic by taking a tonometry test to find intraocular pressure and or ophthalmoscopy to scan the back of the eye to see the size of the optic disk, cup, and nerve.[4]

Choroidal Thickness (CT)

The choroid, a vascular layer nestled between the sclera and retina, plays a vital role in vision. It functions as the circulatory supply for the outer retina, delivering essential nutrients and oxygen for optimal function. Furthermore, the choroid facilitates the removal of waste products from this region is seen in ***Figure 1*** above.[3] Choroidal thickness, measured as the distance between its inner and outer borders, is a crucial parameter in assessing ocular health. Optical coherence tomography (OCT) is a primary non-invasive method for quantifying this parameter. OCT utilizes light waves to generate high-resolution cross-sectional images of the eye's structures, including the choroid. Changes in choroidal thickness have been linked to various eye diseases, including glaucoma, age-related macular degeneration (AMD), and myopia (nearsightedness).[5] This highlights the potential of choroidal thickness measurement as a valuable tool for investigating ocular health and potential disease risk.

Materials and Methods

When analyzing the effects of a specific substance or activity on an organ as complex as the eye, one must establish a standardized methodology for assessing ocular health. In this context, the primary objective of this paper is to delineate a comprehensive guideline by focusing on two key metrics: the measurement of intraocular pressure (IOP), and choroidal thickness. With most of this data representing the findings on IOP levels, choroidal thickness was chosen as a second metric to further support conclusions found by the first metric. As there is limited research on many drugs' effects on intraocular pressure, further examination of the drug's effect on IOP can be seen in choroidal thickness due to the two variables having an inverse relationship. The scientific community widely agrees that there is an inverse relationship between choroidal thickness and IOP.[6] This fundamental assumption leads to the paper having additional support in determining the effect caffeine or alcohol on IOP. Given this relationship, if IOP were to decrease without increasing choroidal thickness, there would be a potential inaccuracy with the conclusions found from the IOP data.

For IOP measurement, this paper analyzed the effects of the independent variables, such as caffeine and alcohol on healthy participants with genetically predisposed elevated levels of IOP. To see whether a drug affects intraocular pressure for a participant group, the validity of data will be questioned through the consensus of scientific articles in the IOP movement. Reading meta-analyses were prioritized due to the plethora of sources used to support their findings, followed by studies that were re-creatable given proper materials. Analyzing intraocular pressure data first, the baseline of health patients had to start within 10-21 mm Hg (millimeters of mercury), which is a health range.[2] As such, participants within each study with an IOP outside of this range were deemed to be unhealthy. In terms of understanding the magnitude of shifts in IOP, studies suggest each millimeter of mercury change in IOP during follow-up corresponded to a 10% change in the risk of progression for OAG.[7] This was typically seen in a shift between 1 mm Hg change in IOP as this measurement for IOP is standard. This standardization facilitates the comparability of results obtained from diverse datasets and investigations. This paper's evaluation of the significance of intraocular pressure (IOP) relies both on using the standard measurement of 1 mm Hg and the metrics used within each individual study on how they found their results to be statistically significant.

The second criterion employed for evaluating the impact of the drugs under investigation is the alteration in choroidal thickness. By measuring choroidal thickness at multiple points, particularly at the fovea, this method enables a detailed analysis of the effects induced by each drug. Typically this number is measured in µm (microns), with the average adult in the range between 250 µm to 350 µm.[8] In this study, any shift in the baseline to post-consumption choroidal thickness was analyzed and deemed statistically significant if it was over 20 µm in either direction.

Considering the inverse relationship between choroidal thickness and intraocular pressure (IOP), examining the ratio difference between these two factors for each specific drug may further yield valuable insights into each metric’s long-term implications. As data for long-term studies on this subject were seldom, one on alcohol and coffee was found, however none on opioids. The two studies provide additional commentary on the two measured drugs' effect on ocular health through IOP but also provide a starting point for improving this data in the discussion portion of the paper.

Caffeine

Since the discovery of the liquid extracted through the roasted seeds of Coffea species, coffee has been widely consumed worldwide for its rich flavor and stimulating effects. Beyond its role as a morning ritual or social lubricant, coffee usage has many implications for human health, spanning from its effects on cognition and metabolism to its potential impact on ocular physiology. The main compound found within the beverage, the methylxanthine alkaloid caffeine ($C_8H_{10}N_4O_2$), is known for its stimulatory properties specifically on the Central Nervous System (CNS). However, similar to other consumed drugs, coffee comprises a plethora of diverse compounds that exert various other effects on its consumers. A few notable examples of these compounds include chlorogenic acids, trigonelline, and antioxidants.[9] Though these are present in smaller concentrations, each also significantly contributes to the overall composition and physiological impacts of the beverage.

Considering these chemicals as coffee usage continues to grow worldwide, it becomes increasingly imperative to explore the drug's potential influence on ocular health.[10] This section aims to delve into the existing literature to illuminate the relationship between coffee consumption and intraocular pressure for individuals who are healthy and at risk of open-angle glaucoma in the short and long term. In addition, to contextualize our results further, studies on coffee's effect on choroidal thickness will also be compared through the inverse correlation between the two measurements.

Effects of Coffee on Intraocular Pressure

Analyzing a meta-analysis published by five doctors from the Department of Ophthalmology and Vision Science at Shanghai Medical School, their research highlights the significant result of coffee increasing the IOP levels in patients with glaucoma. Six studies were analyzed to fit their short-term measured criterion intervals, ranging from half an hour to an hour and a half, to analyze the effect of ingestion of caffeine ranging from 30 mg to 300 mg. The doctors found that IOP increased in patients with a known track record of ocular pressure problems, with a significant margin of 2 mmHG throughout the duration of all the time intervals. Specific fluctuations in intraocular pressure can be seen in ***figure 2*** as the increase of IOP is measured with the mean of test subjects in this category as 0.347 mmHG to 2.395 mmHG in the span of 0.5 hours.[11] In terms of patients with a healthy IOP prior to the testing, the same figure shows the average IOP only decreasing, then increasing by -0.742 mmHG to 0.522 mmHG in the next hour, respectively.[11] As the shift in IOP for those with elevated rates of IOP justified by the study as statistically significant, the paper recommended that these patients should not regularly drink coffee. While having no additional recommendations for other patients.

Time point of measurement	Group	Reference	Test of heterogeneity			Combined effect		Publication bias test		
			Q	*P*-value	I^2	Pooled WMD	95% CI	*P*-value	Begg's *P*	Egger's *P*
0.5 h	overall	3–5, 8	4.77	0.312	16.1%	0.326	0.070-0.582	0.013	1.000	0.174
	healthy	4, 8	0.28	0.597	0	-0.740	−2.454–0.974	0.397	1.000	N.A.
	glaucoma	3, 5	2.87	0.238	30.3%	0.347	0.078–0.616	0.011	0.602	0.603
1 h	overall	3–8	19.27	0.004	68.9%	1.734	0.951–2.517	<0.001	0.548	0.060
	healthy	4, 6–8	1.48	0.686	0	0.522	−0.568–1.613	0.348	0.734	0.534
	glaucoma	3, 5	5.84	0.054	65.8%	2.395	1.741–3.049	<0.001	1.000	0.684
1.5 h	overall	3–5, 8	6.21	0.184	35.6%	1.847	1.255–2.439	<0.001	0.221	0.273
	healthy	4, 8	1.5	0.221	33.4%	0.580	−1.524–2.684	0.589	1.000	N.A.
	glaucoma	3, 5	2.49	0.288	19.7%	1.998	1.522–2.474	<0.001	1.000	0.967

Figure 2: Meta-analysis data suggest that while intraocular pressure (IOP) remained largely unchanged in healthy individuals following caffeine ingestion (Weighted Mean Difference (WMD) with 95% CIs were −0.740 (−2.454, 0.974), 0.522 (−0.568, 1.613) and 0.580 (−1.524, 2.684) for 0.5 h, 1 h, and 1.5 h), while individuals with glaucoma

or ocular hypertension experienced significant increases in IOP at various measurement points post-intervention (WMD and 95% CIs being of 0.347 (0.078, 0.616), 2.395 (1.741, 3.049) and 1.998 (1.522, 2.474)).[11]

Additionally, other international studies such as "The Blue Mountains Eye Study" and "UK Biobank" from Australia and England have congruent data regarding the effect of caffeine risk patients for glaucoma.[12,13] Despite many of these studies seen to be throughout the world, as the effects of the drug on individuals IOP were seen as constant, this underscores the significance of this claim. The number of studies used to support the understanding of, in the short term, a a positive correlation between caffeine and furthering IOP abnormalities for patients who are predisposed to IOP imbalance, like open-angle glaucoma, is a testament to this claim's validity.

The effect of caffeine on intraocular pressure (IOP) in healthy individuals broadly remains a topic of debate within the scientific community, as evidenced by conflicting study findings. Articles previously stated that which also measured the caffeine's effect on healthy patients found that there was no statistical significance to coffee affecting the IOP of a patient, however, a group of studies refute this claim. For instance, a study conducted in Nigeria observed an increase in IOP by approximately 1.39 to 3.94 mmHg within 30 to 90 minutes after ingestion of caffeinated coffee among healthy adults aged 20 to 27.[14] This magnitude of increase significantly surpasses the widely accepted statistical significance metric of 1 mm Hg, raising concerns about the legitimacy of the findings.

Several factors may contribute to potential inaccuracies in the study's results, including the demographic characteristics of the participants, such as being males and of African descent, which are considered by many studies as known risk factors for primary open-angle glaucoma

(POAG).[15] Furthermore, the study lacked background checks on participants, potentially overlooking familial predispositions to abnormal intraocular pressure, and failed to determine if individuals are genetically predisposed. These inaccuracies are also addressed in the action statement provided in the article stating “glaucoma screenings and proper patient education” as an issue. Due to these factors, although more testing should be conducted, currently relying on the Nigerian study’s conclusion that caffeine causes a statistically significant rise of IOP in healthy individuals is less likely to be accurate then conclusion supported by many other different studies.

In the context of the long-term effects of coffee consumption on intraocular pressure (IOP), a notable research gap exists that warrants further investigation. Nonetheless, a comprehensive study conducted from 1980 to 2004 sought to explore caffeine consumption's impact on open-angle glaucoma (OAG). This large-scale study encompassed a sample size of 79,120 women and 42,052 men, with data collection facilitated through meticulously updated and validated follow-up questionnaires, complemented by the confirmation of patient medical history through hospital health records. The analysis revealed intriguing findings: while high caffeine intake (600 mg) exhibited a positive association with the risk of open-angle glaucoma (OAG) for patients with predisposed higher IOP, a negative correlation was observed between coffee consumption and OAG incidence among healthy individuals.[16] Moreover, analogous conclusions were drawn from other short-term studies, demonstrating that caffeine consumption heightened the risk of high-tension POAG in individuals with a history of glaucoma. Notwithstanding the evident need for further research in this realm, this statistical evidence underscores the necessity of considering familial predispositions before consuming caffeine.

Effects of Coffee on Choroidal Thickness

The second measure in determining ocular health in the study is seen through the drug effect on choroidal thickness. In the case of caffeine, there are currently mixed results. Analyzing five different research papers, an 80% majority found a significant decrease in thickness, while one did not.[17,18,19,20,21] The primary research found after the ingestion in the range between 57 to 200 mg of caffeine, depending on the study, the majority found that thickness decreased by 20 µm in a three-hour period.[17,18,19,20] One example of this is seen in a Turkish study which found after drinking one cup of coffee participants choroidal thickness would on average decrease by 51 µm in two hours before rising back to a normal amount by six hours seen in ***figure 3***.[20] With these experiments being tested and run worldwide, similar results are one indication that this conclusion is widely accepted in the scientific community. Additionally, the one paper that analyzed no effect on choroidal thickness due to caffeine intake primarily focused on measuring another ocular phenomenon: Ocular Pulse Amplitude (OPA).[21] Due to the overarching support of evidence in the scientific community that has measured the effects of caffeine on choroidal thickness, this paper draws upon the conclusion that caffeine thins the choroidal layer in the short term.

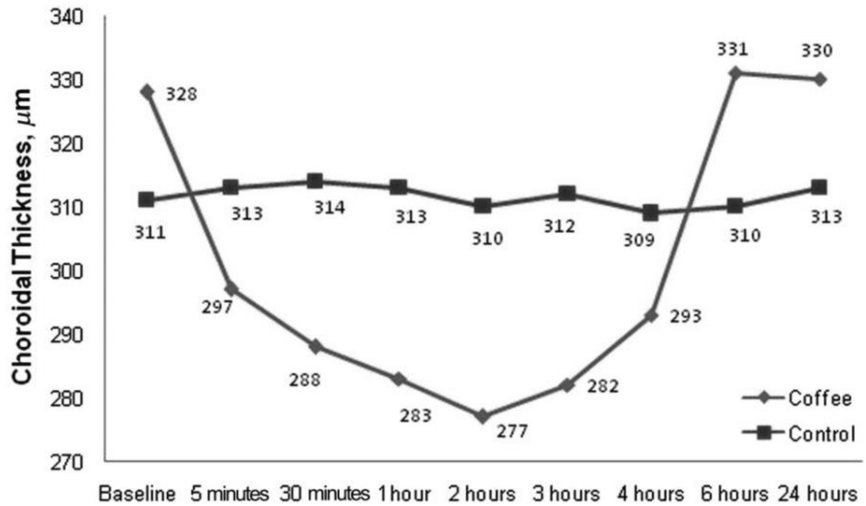

Figure 3: Graph showing the mean CT before and after a cup of coffee drinking in the study group and at correspondence times in the control group preformed by Research Ophthalmology Department of Kanuni Sultan Suleyman Research and Education Hospital.[20]

Physiological Rationale

As caffeine's effects on intraocular pressure depend on whether a patient has healthy IOP or a predisposition to OAG, a justification for this result is pondered. Potentially, the rationale behind this can be seen through blood flow. Caffeine has vasoconstriction, which prohibits macular and ocular blood flow to the eye. Due to the already compromised blood flow within an OAG patient's ocular system, further reduction in this category could increase IOP compared to patients with healthy IOP levels. As healthy patient ocular regulatory systems are in place, they could mitigate the caffeine effect. A statistically insignificant increase in IOP in these patients is a further suggestion.

Alcohol

When baker's yeast is added to glucose, the process of fermentation creates two products: carbon dioxide and ethanol.[22] The ethanol found in alcohol enables the drug to have physiological effects such as intoxication, the slowing of the central nervous system, and causing dehydration. Discovered thousands of years ago, this innovation sparked the proliferation of a wide array of beverages enjoyed by many societies throughout history. In a contemporary context, the consumption of alcohol remains high, even after several discoveries pertaining to the negative effects of this drug. This work aims to analyze the optic effects of this depressant, aiming further to understand the impact of the commonly used substance on human eye health.

Effects of Alcohol on Intraocular Pressure

A preponderance of evidence from global in-vivo studies suggests a dose-dependent relationship between alcohol consumption and intraocular pressure (IOP). Studies report that moderate alcohol intake in healthy individuals is associated with short reductions in IOP, whereas chronic heavy consumption leads to elevated IOP. Observed in a meta-analysis on alcohol intraocular pressure and open-angle glaucoma, 34 individual studies were investigated for their association between elevated intraocular pressure (IOP) and high alcohol consumption patterns. Out of those studies, ten state that habitual alcohol (consumtion once a day) use is associated with not only a higher IOP but also a prevalence of ocular hypertension.[23] Within the data found in this study, there is a general consensus that when alcohol is consumed habitualy, IOP increases and this increase has an association with OAG. Likewise, in a Korean experiment studying this phenomena, healthy men who consumed alcohol daily had a higher IOP; given the average intraocular pressure of a person increased by a range between 0.33 - 1.32 mmHg.[24] As the study determined alcohol to have a statistical signifacnt effect on intraocular pressure, this raw data reinforced the findings examined in the meta-analysis regarding everyday drinking.

The Korean study not only supported the conclusion of the meta-analysis and other research on the effects of habitual drinking on IOP, but also identified another effect on IOP associated with lower alcohol consumption rates. Particularly evident with patients that less frequently consumed alcohol, this source emphasized that light drinking decreased the patient's intraocular pressure by as much as 1 mmHg. Concluding that light and moderate drinking habits inversely affect raising IOP, this data suggests potential acceptance of occasional alcohol consumption for patients predisposed to high IOP as seen in ***figure 4***.[24] Further supported by a collaboration between the UK Biobank Eye and Vision Consortium and the International Glaucoma Genetics Consortium, moderate alcohol consumption is observed to have no perceived negative effect on intraocular pressure.[25]

Variables	Total (n = 6504)		p Value	Non-Glaucoma (n = 6216, 96.1%)		p Value	Glaucoma (n = 288, 3.9%)		p Value
	IOP ≥ 18 mmHg (n = 730, 11.3%)	IOP < 18 mmHg (n = 5774, 88.7%)		IOP ≥ 18 mmHg (n = 683; 11.1%)	IOP < 18 mmHg (n = 5533, 88.9%)		IOP ≥ 18 mmHg (n = 47, 16.9%)	IOP < 18 mmHg (n = 241, 83.1%)	
Age, years	41.8 (0.6)	41.4 (0.3)	0.523	41.2 (0.6)	41.1 (0.3)	0.905	51.8 (2.3)	48.6 (1.3)	0.236
Male, %	59.1 (2.2)	51.9 (0.75)	0.004	58.6 (2.3)	51.5 (0.76)	0.056	67.6 (8.46)	63.5 (3.64)	0.665
Current smoker, %	35.1 (2.43)	29.4 (0.82)	0.021	34.6 (2.56)	29.5 (0.82)	0.044	43.3 (9.12)	29 (3.7)	0.13
Drinker, %	73.7 (2.05)	67.3 (0.8)	0.005	73.3 (2.15)	67.4 (0.81)	0.011	79.6 (7.23)	66.7 (3.55)	0.14
BMI, kg/m^2	24.3 (0.2)	23.6 (0.1)	0.002	24.3 (0.2)	23.6 (0.1)	0.002	24.1 (0.6)	23.8 (0.3)	0.592
Waist circumference, cm	82.7 (0.5)	80.8 (0.2)	0.001	82.6 (0.5)	80.8 (0.2)	0.001	84.6 (2.3)	81.8 (0.7)	0.226
Systolic blood pressure, mmHg	120 (0.7)	116.1 (0.3)	<0.001	119.6 (0.7)	115.9 (0.3)	<0.001	126.9 (3.6)	121.9 (1.3)	0.181
Diastolic blood pressure, mmHg	78.9 (0.5)	76.5 (0.2)	<0.001	78.7 (0.5)	76.4 (0.2)	<0.001	82.5 (2.5)	79.6 (0.8)	0.267
Serum glucose, mg/dL	97.3 (1.2)	94.8 (0.3)	0.052	97.4 (1.3)	94.6 (0.3)	0.033	95.7 (3.7)	100.8 (2.2)	0.249
Total cholesterol, mg/dL	191.4 (1.6)	186.6 (0.6)	0.004	191.4 (1.7)	186.6 (0.6)	0.007	192.5 (7.2)	187.8 (3.7)	0.552
HDL-C, mg/dL	52.4 (0.6)	53.3 (0.2)	0.138	52.4 (0.6)	53.4 (0.2)	0.1	52.5 (2.1)	50.7 (1.1)	0.417
LDL-C, mg/dL	120.1 (2.2)	110.8 (0.8)	<0.001	120.8 (2.3)	110.9 (0.8)	<0.001	111.7 (6.7)	109.7 (5.3)	0.806
Triglycerides, mg/dL	143.4 (5.4)	131.7 (2.1)	0.049	142.8 (5.7)	130.8 (2)	0.056	152.5 (18.2)	154.2 (17)	0.945
Diabetic, %	25.9 (2.05)	21.7 (0.76)	0.038	25.7 (2.18)	21.3 (0.77)	0.04	29.3 (7.7)	31.5 (3.71)	0.811
Hypertension, %	53.1 (2.14)	41.4 (0.95)	<0.001	52.1 (2.21)	40.8 (0.98)	<0.001	70.2 (8.38)	56.5 (3.94)	0.151
IOP (mmHg)	18.7 (0.04)	13.4 (0.1)	<0.001	18.7 (0.04)	13.4 (0.1)	<0.001	18.6 (0.2)	13.6 (0.2)	<0.001

Data are presented as mean (SE) for continuous variables and as percentage (SE) for categorical variables. BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IOP, intraocular pressure; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

Figure 4: Differential in Intraocular Pressure (IOP) exceeding 18 mmHg among alcohol drinkers and non-drinkers from the Korea National Health and Nutrition Examination Survey 2010 to 2011 (In IOP ≥ 18, 73.7% Drinkers).[24]

In terms of the long-term effects of alcohol on ocular health, there is currently not nearly as much research done relative to its short-term effects. As of now, there is currently one study that measures this effect. In this prospective study spanning 16 years, it was found that the consumption of one daily alcoholic drink did increase the possibility of developing open-angle glaucoma.[25] Although this study supports the hypothesis found in many short-term alcohol experiments, finding that habitual drinking raises IOP, it is in no means definitive. One factor that the study states could be also attributed to this is the underlying genetic reasons which were too expansive to understand fully with the 174,000 plus participants in the study.[26] Due to the lack of comparable data and accuracy found in surveys (the method of this study), this data should be analyzed more as a start in examining the long-term effects of alcohol rather than a confirmed conclusion. It is essential to perform more research, specifically long research studies.

Effects of Alcohol on Choroidal Thickness

From analyzing the effects of alcohol on IOP, the second measurement of this paper's criteria for ocular health is choroidal thickness. As of now the scientific community is generally in agreement about alcohol's impact on choroidal thickness. One study that expresses these findings was conducted by doctors from the Yonsei University College of Medicine. In their research, four 30-minute increments of 1 mg of ethanol consumption led to the discovery of clear statistical significance in an increase of cordial thickness over a short period. The data revealed a mean increase of 20 µm at its peak, occurring 60 minutes post-baseline, followed by a subsequent decrease after the 90-minute mark.[27] As IOP is linked to choroidal thickness, their results suggest that the patient's IOP would potentially decrease. This data is consistent with the previous section’s findings on low frequency alcohol consumption for ocular health.

Physiological Rationale

By analyzing the data, there are several potential physiological explanations for the IOP fluctuations considering the consumption of alcohol. The first explanation could be seen considering blood vessels. Drinking large quantities of alcohol could have moderate vasodilatory effects, leading to relaxation of blood vessels, increasing blood flow and elevating intraocular pressure in the short term. Additionally, another factor that could explain the physical effect is dehydration caused by alcohol. Dehydration could further cause a decrease in blood volume and lead to a compensatory mechanism to increase IOP.

Secondly, intraocular pressure decreases with moderate alcohol consumption to be seen due to a potential stress reduction provided by the drug. Relaxation could reduce pressure through the smooth vessels surrounding trabecular meshwork, leading to a better outflow of aqueous humor. Additionally, a lowered systematic blood pressure possibly limits the amount of pressure to the eye, thus preventing buildup.

Opioids

Today there is a widespread use of opioid medications for pain management in the United States, evidenced by 5.7% of adults who self-reported using them between 2015 and 2018 alone.[28] A substance known for its addictive nature through the activation of dopamine in tandem with numbing pain, its effects on optic vision have been considered more of an afterthought, with much less research done on the topic. Unfortunately, as experimentation on opioids effect on choroidal thickness is limited this aspect of verification of IOP results is not present for this substance. This section investigates the impact of opium, specifically on IOP, exploring potential mechanisms to gain a fuller understanding of ocular health.

Effects of Opioids on Intraocular Pressure

From an ethical standpoint, it is a complex issue to clear the human testing of a drug such as opiates due to the risk of creating a life-threatening addiction. As such, the breadth of research on this topic, especially for the ocular health of individuals actively taking opioids, is highly limited. As of now, there is a single study that measured the effect opioids have on IOP being reviewed: "Effects of opiates and opioids on intraocular pressure of rabbits and humans."[29] This paper's particular review is focused solely on the study's affected human participants; among the four experiments highlighted in the research article, only experiments 3 and 4 will be analyzed.

In experiment 3, heroin-addicted and morphine-addicted patients were tested to see how their IOP was affected relative to a presumably normal IOP. The test results found significantly lower levels of intraocular pressure in those addicted to opioids. A significantly larger difference when analyzing the control of healthy participants to those injected with opioids. The decrease in intraocular pressure (IOP) for individuals receiving opiates exceeded 4 mmHg between the initial injection and the 6-hour mark, demonstrating a substantial impact of the drug on participants' IOP.[28] This reduction surpassed the standard measurement of 1 mmHg by 4 times, indicating a significant effect opioids have on ocular health. Further support for these findings was observed in the fourth experiment. The fourth experiment tested the injection of a saline solution with diluted morphine dropped in the eyes of opioid-addicted patients with open-angle glaucoma to see the effect of the drug on IOP. In the patients diagnosed prior with OAG, when added morphine drops were in their eyes, a difference of 11.4 - 4.9 mmHG decreased since the start of the experiment. Each day shows this impact as incrementally decreasing. As depicted in the table below, opioids successfully reduced the intraocular pressure (IOP) in individuals with open-angle glaucoma (OAG), decreasing their IOP by 29.29%. This reduction effectively brought their IOP within a healthy range, as 19mmHG falls between 10 - 21 mmHG, the standard healthy IOP range.[29]

Days of treatment	Morning				Afternoon			
	Before		After		Before		After	
	mean	s.e.m.	mean	s.e.m.	mean	s.e.m.	mean	s.e.m.
1	29.7	3.5	18.5*	1.4	28.9	2.6	19.5*	1.2
2	28.5	3.0	19.0*	1.6	27.8	2.5	19.3*	1.2
3	26.5	2.6	18.9*	0.8	26.4	1.8	18.4*	0.9
4	24.4	1.9	19.0*	1.2	24.3	0.8	18.3*	0.7
5	24.0	1.7	18.6*	1.4	23.4	0.9	18.5*	0.6

* Significantly different from the value obtained before treatment.

Figure 5: IOP Response 30 Minutes After Morphine Instillation (2 drops of 10 mg/ml solution) in 12 Patients with Chronic Open-Angle Glaucoma.[29]

This experiment's results show the short-term effect of opioids on intraocular pressure on both healthy patients and those suffering from OAG. The effect of opioids on IOP in the short term for test subjects who have a healthy IOP range is a significant decrease, Although these results are noteworthy, the conclusion made with individuals suffering from OAG injecting morphine through eye drops is potentially revolutionary. Having the ability to decrease the starting IOP for patients with chronic OAG within five days by over 5 mmHG provides a case to be made for allowing opioids to be a treatment for the illness. Analyzing ***figure 5***, with two times of day and consistent post-drug intraocular pressures found at 18.3 - 19.6 mmHG, a sense of stability that can be provided by the drug can be seen.[29]

With the significant decrease in IOP due to the effects of opioids due to opiate injection in the eyes, this data shows not only a potential correlation with the drug healing individuals with IOP but additionally a potential method for taking any drug or medication to fluctuate an IOP range seen through diluted contact in the eye.

One important distinction to point out when incorporating this data is the variability in the injection site. Comparing the results seen in opiates to alcohol or caffeine, the method of delivery in proximity to the eye is different, as the administration of the drug directly into the eye had the most prominent statistical effect. To compare the information on the OAG patients to the results from studies of the other drugs, without further testing by administering the opioids in the atypical way the substance is used, the comparison of results to the other drugs in this paper will not be equal and thus accurate. However, the largest issue with the implications of this research is the limited data source restricts it. While this source fulfills the specific criteria for opioid analysis employed within this research, the lack of comparable data from the broader scientific community hinders the generalizability and conclusiveness of the findings. Thus, replicating the observed effects through additional studies is crucial to establishing the validity of the reported statistics and, more importantly, a more profound knowledge of the drugs' effect on ocular health.

Physiological Rationale

As opioids are found to have a significant effect in decreasing intraocular pressure, this could be because receptors found throughout the eye have many receptors, including opioid receptors, which are found to be present in the trabecular meshwork by binding to the sites and could potentially influence aqueous humor to exit the eye faster. This makes logical sense to the conclusion found prior; due to the injection of morphine into the level of IOP decrease was more significant than that of a typical injection of the drug. Additionally, as blood flow affects IOP, opioids might affect blood flow, leading to vasodilation, which would directly decrease IOP. Due to these factors, opioids could decrease intraocular pressure significantly.

Discussion

Based on the variations in intraocular pressure (IOP) across the testing of the three drugs, the differences in millimeters of mercury (mmHg) were significant indicators for results. In terms of alcohol and caffeine one similarity in these drugs is a shown increase IOP levels for people currently or predisposed to eye issues such as glaucoma. However, in terms of research, the distinguishing factors between what studies have found to affect IOP in alcohol and those of coffee are different. As the effect of ethanol on intraocular health dependent on the frequency of days drinking, caffeine's effect on IOP is based on the patients' current IOP health. In the short run, caffeine experiments with 30 to 300 mg of OAG participants affecting their intraocular pressure by 2 mmHG were shown to be similar to the effect of habitual alcohol use, showing both drugs have some form of cause to increase IOP.

Both caffeine and alcohol ingestion show an increase in intraocular pressures (IOPs), likely due to their affect the regulation of aqueous humor outflow from the eye. Like the differences in the effect of the drug based off of the patient the effect on the regulations is different as well. In healthy participants, caffeine is not believed to affect IOP, indicating that any increase in IOP from caffeine may be offset by a functioning regulatory system. However, when issues arise in regulating the flow of aqueous humor out of the eye, coffee may exacerbate ocular health problems for patients suffering from IOP issues. Conversely, regardless of whether the patient has a pre-existing intraocular pressure condition, alcohol consistently increases IOP, suggesting a direct effect on the regulation of aqueous humor outflow from the eye. Based on the data, daily alcohol consumption may have detrimental effects on eyesight, potentially contributing to ocular health degradation in any patient, while caffeine may only worsen this damage in those with pre-existing IOP issues.

Choroidal thickness data on coffee and alcohol also suggest further differences. As CT decreases with the consumption of coffee, this result indicates a negative correlation between coffee and ocular health, as IOP inherently increases. The increase in intraocular pressure (IOP) with caffeine aligns with decreased choroidal thickness, suggesting short-term harm to optic health. However, as choroidal thickness returns to average levels without sustained injury to IOP regulation, the long-term effects of coffee on healthy individuals' ocular health are unclear. In terms of alcohol, the opposite effect was observed as the CT decreased by a similar margin of 20 um to that of caffeine. Initially, this observation may seem inconsistent, as an increase in choroidal thickness inherently implies a decrease in intraocular pressure, an effect seen to be disassociated with daily alcohol consumption. However, the finding is consistent with the impact of light and moderate alcohol intake, where IOP remained stable or exhibited insignificant decreases. The data on choroidal thickness suggests a potentially stronger association between light alcohol consumption and decreased IOP; however, further research is required to substantiate this hypothesis.

In contrast to alcohol and coffee, opioids have shown a significant ability to decrease intraocular pressure (IOP), particularly observed at the site of entry into the eye. This promising result suggests a potential treatment avenue for conditions characterized by high IOP, such as open-angle glaucoma (OAG). Moreover, the sustained reduction in IOP observed in patients with elevated levels further underscores the potential of opioids as a therapeutic option for OAG.

However, the lack of extensive research on opioid effects on ocular health introduces doubt regarding the accuracy of these findings. Despite this limitation, the effective and theoretically replicable nature of the research warrants cautious optimism for further analysis and exploration in this area.

The designs for each of the studies on all three drugs differed greatly, potentially leading to different results. Starting with caffeine, most studies used in this analysis tested subjects' daily caffeine use within a short period. In terms of the studies found on alcohol's effect on IOP, they relied on survey results of alcohol use per individual and based on their self-reported alcohol use, which their IOP was tested. As the data on alcohol conducted surveys a larger group of individuals were tested compared to the experiments conducted in the majority of research in the caffeine section. One of the negative of surveys are the lack of specifics, such as the amount of alcohol drank per day which was not prevalent in the vast majority of studies. In terms of the testing done in the one research article found for opioids, it was an experiment through set quantities of the drug injected to patients in the short-term period. However, an additional element that the opioids study implements is not found with the other substances seen in addition to the drug straight into the eye. Opiates are easier to inject into the eye through saline drops; this was another form of injection into a patient's body to potentially foster a more significant effect. This is not to say that caffeine or alcohol injection through eye drops are not possible, as it is feasible and could be replicated and tested in future IOP experimentation. An aspect of opioid testing is significantly lacking any survey results as this may be due to lack of asking and a social stigma to answer truthfully about opioid use, two potential incorrect data for a survey result.

Application of Analysis

Touching on this point throughout the paper, understanding the improvements for research in measuring intraocular pressure is essential. As long-term papers are few and far between, all the valuable insights available in the current scientific community lack substantial answers relating to longevity. Questions such as how chronic substance use affects participant IOPs over time are vital to understanding the solutions to these issues. Only having research that tests participants for a week cannot provide statistical data on whether or not consistent increases or decreases in intraocular pressure caused by drugs over time will eventually decrease homeostasis IOP. As opioids in this study have been proven to lower IOP for patients with significantly, understanding this phenomenon is essential to potentially treat ocular diseases.

By grasping the effects of habitual drinking alcohol, and drinking caffeine with an elevated IOP; this information can be used to create a public safety program. Providing awareness of intraocular diseases, such as open-angle glaucoma, the systematic review conducted could be used to provide information on how to go about dealing with drugs for those patients. Creating a resource such as an online pamphlet or promoting the results of this paper through social media accounts could potentially help individuals who suffer irregular IOPs. From genetic predisposition to increasing blurriness due to forming OAG, a resource made to inform these patients would be the first of its kind in this space. As most education information produced analyzes the effects of caffeine, alcohol, or opioids more holistically, this resource can be vital for individuals who suffer from specific ocular diseases. Providing specialized instructions for healthy ways to limit intraocular pressure could help the typical American to make more informed decisions.

As seen in the analysis of the research done in drug testing on IOP, different statistical results could be attributed to factors such as higher dosage, different injection sights, and different methods of measuring IOP. With one study of opioids being the only scientific literature on the drug in this context, a potentially higher dosage could be one of the reasons why opiates showed a higher fluctuation in IOP then than caffeine or alcohol. This could not be analyzed based on the lack of replication done in the study. Another factor that this testing may have affected the specifics of alcohol is the lack of experiments done to test the effect rather than relying on surveys. Technically, more accurate data could be collected through a more in-depth experiment than a large survey. This technique may be the reason behind some of the differences between alcohol and coffee's effect on IOP. Lastly, the method of testing IOP seemed shrouded throughout many papers. Many studies mention different methods on how the intraocular pressure was found, such as using a Schiotz tonometer vs. a Ocular Response Analyzer.[29] This leads to the question of potential errors due to a difference in finding subjects' intraocular pressure. Looking at these differences leads this analysis to formulate additional ways to mitigate such differences for future experimentation to have the most accurate results.

Experimental Methodology Exploration

Two potential ways to accurately compare the direct effect of the three drugs could be seen with creating a survey and an experiment. The first method should be conducted in a nation that permit the use of all these drugs to provide accurate answer from participants, not being afraid of answering the question truthfully. Naturally, anonymity will be provided in the survey. However, people's fear of punishment may lead to potential lying; definitely, in a nation where the use of any of these three drugs could be severely frowned upon, a nation with little punishment at all for using these drugs would be ideal for testing in. From there, the survey would ask individuals first to fill out basic demographics, such as ethnicity and age, before asking if they use a drug and what is the estimated quantity per use and frequency per week of substance use. Once a survey is completed, the individual would be paid a small amount to have the opportunity to get a free scan of their IOP. Among the many different ways to calculate intraocular pressure, the clinic should use an Ocular Response Analyzer (ORA). As compared to other methods of IOP calculation, this test is one that is known to have the ability to be replicated.[30] With this test, research will be able to be done on the IOP, comparing the standard based on what individuals said throughout the three groups.

The second study perhaps could have a group of individuals with both healthy IOP and elevated levels of IOP compared to the normal to spend time researching the effects of alcohol and coffee at the same time. Individuals would be split up into placebo, alcohol, and caffeine groups to have different results with a control to further substantiate the validity of the study. From their specified groups, the test subjects would ingest the substance at the same time with the equivalent of one standard drink size (14g of alcohol and 100mg of caffeine).[31,32] Additionally, with another set of test subjects with both healthy and raised IOP, the drugs would be in an eye drop form to see further fluctuations. In terms of the quantity of drug in each drop, this paper recommends further research based on the safety of the patient and to find a standardizable quantity of drug per eye drop. Being from a similar population and testing a baseline amount of caffeine and alcohol, respectively, in a short span of time, the short-term effects of the drug would be more accurate. Using the same ORA, the patient's IOPs could be compared by making the only independent variable, the consumed drug. Although adding opioid users to the same study would be much more difficult, this hypothetically could be done through an ethical program mentioned in the ethics section of the discussion.

Ethical Implications

With an action statement of providing more research on a topic related to human clinical trials, ethics plays a significant role. This section will explain the ethical dilemma over conducting further research in the field, with two factors: access to resources and consistent/prolonged exposure to a drug. With the first two reliably consistent for all the drugs analyzed in this study, the damming health effects of igniting addiction are primarily centered toward the adverse effects of opioid use.

In the conclusion of the Nigerian study, its comparative weakness stemmed from resource limitations, impacting the research outcomes differently than other studies. Developing countries often lack the economic resources necessary to compete in research with developed nations, resulting in less frequent data statistics from economically disadvantaged populations. Limited resources and additional challenges faced by researchers increase the likelihood of errors. For instance, in the Nigerian study, an incomplete understanding of patients' medical histories exemplifies this issue, particularly concerning intraocular pressure (IOP) assessments. Perceived to have less credibility in a study topic, individuals who spend their resources on the subject will be deterred as their money and time are discounted. This would lead to neglecting research in specific field, such as IOP of drugs in populations of developing nations. A potential way to stop this ethical dilemma is by providing aid to countries for public health research grants, which can bolster academic research specifically in ocular health, by earmarking funds for a specific purpose. This could potentially allow further studies on ocular health to be conducted and examined, leading to more beneficial knowledge in the field.

The second issue is the ethical concern of continuing research to ultimately better understand ocular health in multiple consistent long-term research projects. Among many issues in providing a project would be prolonged exposure to caffeine, alcohol, or opioids which, in theory, can be dangerous. Providing either monetary or social incentives to individuals to have decades-spanning consistency to a substance they have no control over could have psychological and physiological effects on those studied. As seen in the other studies, research is typically done through surveys with their own set of issues. An ethical way to conduct this type of research is through a much smaller population size who actively commits to being a part of the research for a smaller long-term period of time, such as one year, which can be stopped at any time by the participant's desire. Although producing ethically accurate data is hard in order to understand the full breadth and gravity of alcohol, opioids, and coffee in an individual, it is imperative to analyze effects longer than the span of a week.

The most ethically concerning implication of conducting further research is seen with opioids. It is a moral conundrum to conduct human tests with this drug. Despite opioids being highly prevalent in pain reduction for hospitals in the United States, testing for this drug is astonishingly complex. As a highly addictive substance with known consequences, an ethical researcher would not subject any participant to the potential of that fate. Understanding the full effects that opioids could have, not only in other physiological settings but in the optic specialty, is important. It is a disservice to individuals prescribed these drugs, whether they have an increased risk of angle glaucoma or a healthy IOP.

The ethical implications of utilizing individuals with active opioid dependence as research subjects remain a contentious issue, as exemplified by the study conducted by researchers from the University of Catania Medical School's Department of Ophthalmology and Psychiatry. An alternative approach might involve adapting the harm reduction model implemented by Switzerland. These centers provide comprehensive rehabilitation programs encompassing social support, meals, structured activities, and shelter while also allowing controlled access to opioids.[33] Research programs could potentially adopt a similar framework, integrating a research component within these existing harm reduction structures. While replicating this model entirely within a research setting might incur significant financial costs compared to traditional studies, ethical research could be achieved by offering controlled doses of opioids to consenting participants with appropriate compensation. This strategy would facilitate the investigation of the drug's effects on humans in a morally sound manner, potentially contributing to a reduction in opioid-related deaths while simultaneously advancing our understanding of ocular physiology.

Conclusion

To conclude, by analyzing data on intraocular pressure (primarily in the short run), supported by choroidal thickness research, this study aim is to provide a measure to test the effect of three drugs on ocular health. Seen in the increase of intraocular pressure for caffeine specifically, with those already suffering from diseases with IOP imbalance such as glaucoma, caffeine is a drug that should be avoided by this demographic or people with genetic predispositions to IOP issues. With alcohol, it’s important for individuals to drink substances in moderation; statistically, intraocular pressure has mainly increased with daily alcohol consumption. Lastly, as opioids are found to increase intraocular pressure, ocular health degradation adds to the long list of ailments due to this addictive analgesic. Although extensive additions to research must occur, the importance of moderation of caffeine and alcohol has positively impacted ocular health. This is seen by preventing an increase in intraocular pressure in the short run. Furthermore, as both the choroidal thickness data for caffeine and alcohol have shown a inverse relationship with IOP level, this information furthers the accuracy of the results found in IOP data. As preventing anyone from ending their consumption of caffeine, alcohol, or even opioids is unlikely, this culmination of research aims to inform the general public of the known research on their effects on ocular vision to make informed decisions. Additionally, for opioids, this study highlights both the adverse effects and a lack of knowledge in dealing with opioids, aiming to deter patients from taking the substance if at all possible. Understanding the importance of substance use in moderation, despite further research, which can be concluded with the implementation of proposed research initiatives, this paper provides a framework for analyzing ocular health and preventive measures for vision issues.

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