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REVIEW ARTICLE

Systemic Medications and Their Effects on the Retina and Choroid: An Updated Review

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ABSTRACT

This review provides a comprehensive analysis of systemic medications and illicit substances that can lead to various forms of retinal and choroidal toxicity. Accurate diagnosis requires a detailed medication history and the identification of characteristic retinal changes using multimodal imaging techniques. The discussion includes drugs associated with retinal pigment epithelial disruption, vascular alterations, cystoid macular edema, crystalline deposits, drug-induced retinal folds, and uveitis. The ocular effects of emerging chemotherapeutic and immunotherapeutic agents are also examined. Key mechanisms of action, preventive strategies, and available treatment options are explored in detail. The focus is on medications frequently encountered in ophthalmic practice and important considerations for eye care professionals. Many drug-induced retinal toxicities are reversible with discontinuation of the medication, especially when detected early before causing significant visual impairment. However, certain agents may lead to permanent and progressive retinal damage. Close monitoring and timely intervention by ophthalmologists are essential. This review highlights the importance of early detection and proper management of medication-induced retinal and choroidal toxicity to reduce the risk of vision loss and related complications.

Keywords: crystalline maculopathy, cystoid macular edema, diffuse retinal pigment epithelium changes, retinal and choroidal toxicity, vascular damage

INTRODUCTION

Although posterior segment toxicity is uncommon, it remains a serious complication associated with certain systemic medications. This review examines commonly encountered medications in clinical practice and outlines key considerations for ophthalmologists.

We undertook a thorough PubMed search for English-language articles dating back to January 1960, targeting publications from January 1990 to April 2025. The search employed keywords including “retinal toxicity,” “choroidal toxicity,” “drug-induced retinopathy,” and the names of specific systemic medications known or suspected to affect the retina. Retinal and choroidal toxicities are classified into several main categories, including retinal pigment epithelial (RPE) disruption, maculopathy, vascular damage, crystalline deposits, uveitis, and the toxicity related to illicit substances. A clear understanding of these categories is crucial for clinicians to effectively identify, manage, and reduce the risk of medication-related ocular toxicity. A summary of common systemic medication–induced retinal and choroidal toxicities is provided in Table 1.

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Table 1 Summary of Retinal and Choroidal Toxicities Associated with Systemic Medications

Toxicity Categories	Drugs	Findings & Diagnostics	Management / Recommendations
RPE Disruption	HCQ, Chloroquine	Cornea verticillata, parafoveal or pericentral EZ loss, RPE atrophy, pigment mottling, optic atrophy, RP-like changes bull's-eye maculopathy SD-OCT, FAF, HVF 10-2/30-2, mfERG (optional). Asian patients may benefit from wide-field imaging.	Risk increases with > 5.0 mg/kg/day (HCQ), renal impairment, and tamoxifen used. Discontinue if toxicity is suspected. Damage may progress post-cessation.
	Pentosan Polysulfate Sodium	Speckled hypo/hyperautofluorescence around fovea, RPE nodules, outer retinal atrophy, thinning of ONL and choroid. OCT, FAF, NIR imaging.	Baseline and annual screening recommended after 500 g cumulative dose. Discontinue if toxicity is suspected. Damage may progress post-cessation.
	Phenothiazines: Thioridazine, Chlorpromazine	Non-specific macular pigment changes. RPE/choriocapillaris atrophy, vascular narrowing, optic atrophy, pigment plaques. ERG/EOG abnormalities in late stages.	Monitor daily and cumulative dose. Discontinue early if toxicity suspected. Some cases may stabilize or partially improve.
	Deferoxamine	Nyctalopia, visual field loss. Pigmentary retinopathy (minimal, focal, patchy, or speckled patterns), outer retinal deposits, EZ disruption. Rare: CSCR-like changes.	Maximum dose ≤ 50 mg/kg/day. Baseline and regular monitoring. Reduce dose if toxicity occurs.
	MEK inhibitors	Bilateral multifocal serous detachments, often fovea-involving. May mimic CSC but lacks leakage or choroidal thickening. Uveitis, CME, and optic neuropathy, have been reported.	Risk factors include age, impaired renal function, and preexisting eye diseases. Usually self-limited. Conservative management unless persistent. Consider stopping drug if severe.
	FGFR inhibitors	Serous subretinal fluid, pseudovitelliform lesions, EZ disruption. Often asymptomatic. Findings resemble MEK retinopathy.	Monitor with OCT. Often resolves after drug cessation. Long-term effects unknown.
Maculopathy	Nicotinic acid	CME FA typically shows no leakage. Prolonged use may lead to macular atrophy.	Discontinuation or dose reduction usually leads to resolution.
	Antimicrotubule agents	CME FA typically shows no leakage.	Discontinuation or dose reduction usually leads to resolution. Topical or systemic CAI
	Fingolimod	CME FA typically shows no leakage.	Topical anti-inflammatory agents, corticosteroids, CAI, and anti-VEGF

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Table 1 Summary of Retinal and Choroidal Toxicities Associated with Systemic Medications (cont.)

Toxicity Categories	Drugs	Findings & Diagnostics	Management / Recommendations
Vascular damage	Talc	Capillary nonperfusion, microaneurysms, cotton-wool spots, and retinal neovascularization.	Discontinue intravenous drug use, Manage ischemia or neovascularization (e.g., anti-VEGF, PRP if needed)
	OCP	May induce a hypercoagulable state, potentially leading to retinal vein/artery occlusion or ischemic optic neuropathy.	Discontinue OCP if event occurs Consider alternative contraception
	Interferon	Cotton-wool spots, hemorrhages, CME, and vascular occlusions	Retinal findings typically improve after discontinuation of the drug.
	Ergot Alkaloids	Particularly at high doses, can cause retinal vasospasm and ischemia.	Stop medication Consider vasodilator therapy if needed
Crystalline deposits	Tamoxifen	May cause dyschromatopsia, visual loss crystalline deposits, CME (dose-dependent), disruption of EZ, OCTA: right-angled vessels, deep capillary plexus changes (MacTel2-like)	Eye exam every 6 months if on > 20 mg/day > 2 yrs Consider stopping drug if symptomatic Manage CME with anti-VEGF, steroids, or oral CAIs
	Canthaxanthin	Crystalline maculopathy Often asymptomatic	Deposits resolve slowly after discontinuation
	Methoxyflurane	Crystalline retinopathy, cotton-wool spots possible	Avoid in renal impairment Discontinue if toxicity evident
Uveitis	Checkpoint inhibitors	Uveitis (anterior, posterior, panuveitis) VKH-like, Behçet-like features	Topical/local/systemic steroids as needed Continue therapy if responsive
	BRAF inhibitors	Anterior uveitis most common VKH-like posterior uveitis and panuveitis also reported	Topical/local/systemic steroids as needed Continue therapy if responsive

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CAI, carbonic anhydrase inhibitors; CME, cystoid macular edema; CSC or CSCR, central serous chorioretinopathy; EOG, electrooculography; ERG, electroretinography; EZ, ellipsoid zone; FA, fluorescein angiography; FAF, fundus autofluorescence; FGFR, fibroblast growth factor receptor; HCQ, hydroxychloroquine; HVF 10-2/30-2, Humphrey visual field 10-2 or 30-2 testing pattern; HVF, Humphrey visual field; MacTel2, macular telangiectasia type 2; MEK, mitogen-activated protein kinase/extracellular signal–regulated kinase pathway; mfERG, multifocal electroretinography; NIR, near-infrared reflectance; OCP, oral contraceptives; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; ONL, outer nuclear layer; PRP, panretinal photocoagulation; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography; VEGF, vascular endothelial growth factor; VKH, Vogt–Koyanagi–Harada syndrome

Toxicity Related to Retinal Pigment Epithelial Disruption

Chloroquine Derivatives: Chloroquine, Hydroxychloroquine

Chloroquine, a 4-aminoquinoline drug, is primarily used for malaria treatment and prevention, as well as certain inflammatory conditions.[1] Hydroxychloroquine, a related compound with better safety, is Food and Drug Administration-approved for systemic lupus erythematosus, rheumatoid arthritis, and malaria prophylaxis, and has largely replaced chloroquine. Both drugs accumulate in melanin-rich tissues, particularly the RPE and uveal tissues.[2] The mechanism of toxicity is unclear but may involve RPE lysosomal dysfunction leading to photoreceptor loss, inhibition of retinol recycling, and direct retinal toxicity.[3-5] Hydroxychloroquine toxicity is dose- and duration-dependent, with early signs including cornea verticillata and subtle macular changes that can progress to bull's-eye maculopathy, marked by a ring of depigmentation surrounding the fovea.[6] Advanced toxicity may mimic retinitis pigmentosa, with pigment mottling, vascular attenuation, optic atrophy, and bone spicule formation.[7] Hydroxychloroquine toxicity has an estimated prevalence of 7.5%, with variations influenced by daily dosage and duration of use.[8] Current recommendations limit hydroxychloroquine to ≤ 5.0 mg/kg/day and chloroquine to ≤ 2.3 mg/kg/day, based on actual body weight[7]. In individuals of shorter stature, particularly those 5 feet 2 inches (157 cm) or below, careful dosage calculation based on ideal body weight is essential to prevent excessive drug exposure. For chloroquine, toxicity is more likely above 2.3 mg/kg/day, with risk rising after cumulative doses of 100–300 g. Patients of shorter stature require careful dosing to avoid overdosing.

Spectral-domain optical coherence tomography (SD-OCT) is a key imaging modality for detecting retinal toxicity, revealing structural changes such as outer nuclear layer thinning, outer segment hyperreflectivity, and ellipsoid zone (EZ) disruption. Fundus autofluorescence (FAF) is particularly sensitive for early detection, often showing a paracentral hyperautofluorescent ring that progresses to pericentral mottled hypoautofluorescence with hyper-autofluorescent borders, and eventually to complete pericentral signal loss in advanced cases.[9] Patterns of retinal toxicity vary across ethnic groups. Asian patients may develop peripheral retinal damage **(Figure 1)**, making ultrawide-field FAF a crucial diagnostic tool. In contrast, African American, Hispanic, and European patients predominantly exhibit a parafoveal damage pattern, though African American and Hispanic individuals may have a higher likelihood of extramacular involvement.

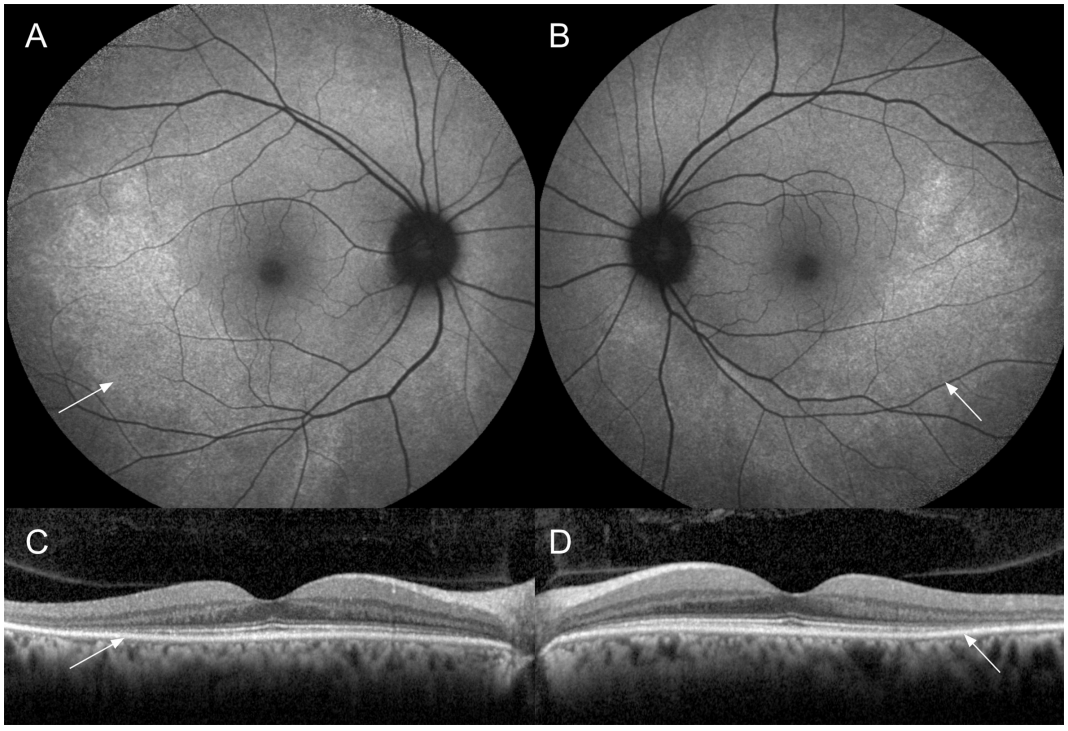

Figure 1 (A-B) Fundus autofluorescence shows perifoveal hyperautofluorescence of both eyes indicative of hydroxychloroquine toxicity in an Asian patient. (C-D) Spectral-domain optical coherence tomography reveals outer retinal thinning corresponding to the FAF abnormalities, consistent with chronic hydroxychloroquine-induced retinal damage.

The multifocal electroretinogram (mfERG) is the most sensitive test for hydroxychloroquine toxicity, detecting functional abnormalities even when fields, SD-OCT, and full-field ERG are normal.[7, 9] Abnormalities may appear as foveal, paracentral, peripheral, or generalized dysfunction. While not used for routine screening, mfERG supports multimodal imaging for reliable detection and monitoring.[9, 10]

The estimated risk of hydroxychloroquine toxicity is 1% after 5-7 years or a cumulative dose of 1000 g, rising to 20% after 20 years.[11,12] Chloroquine, due to its slow excretion, can remain in the body for years and has been linked to delayed-onset retinopathy even seven years post-cessation. In addition to dose and duration, risk factors include renal impairment, which prolongs drug clearance; concurrent tamoxifen use, which increases toxicity risk; and pre-existing retinal disease. Age, liver dysfunction, and genetic predisposition may also contribute.[7] Routine screening is vital for early detection. The 2016 American Academy of Ophthalmology (AAO) guidelines advise a baseline exam within the first year of therapy and annual screening after five years, or sooner in high-risk patients. Standard tests include SD-OCT and Humphrey Visual Field (HVF) 10-2, with HVF 24-2 or 30-2 preferred in Asian populations due to peripheral involvement. FAF and mfERG can detect subtle changes not seen with other modalities. If toxicity is suspected, prompt drug discontinuation is recommended; mild to moderate cases may stabilize, but severe disease can progress despite cessation. mfERG changes may show partial recovery. Ophthalmologists play a central role in counseling, risk assessment, and long-term monitoring. Updated AAO screening guidelines are expected in late 2025.

Pentosan Polysulfate Sodium

Pentosan Polysulfate Sodium (PPS) is commonly prescribed for the management of interstitial cystitis, a condition predominantly affecting women.[7] Early manifestations of PPS-related toxicity appear to originate in the RPE, leading to RPE thickening followed by progressive photoreceptor degeneration and RPE atrophy. This pathological progression differs from hydroxychloroquine-induced toxicity, which initially presents as pericentral EZ disruption or loss, followed by subsequent RPE damage and atrophy in later stages.[13]

The pathophysiology of PPS-associated maculopathy remains unclear, particularly whether RPE damage is primary or secondary to choroidal involvement. Recent studies suggest a potential choroidal role, with observed reductions in stromal choroidal area and increased choroidal vascular index in affected eyes.[14] Multimodal imaging is essential for detecting characteristic features of PPS toxicity. OCT findings range from early hyper-reflective RPE nodules to advanced RPE and outer retinal atrophy. FAF often shows a speckled pattern of hypo- and hyperautofluorescence radiating around the fovea **(Figure 2)**. Near-infrared reflectance (NIR) imaging can highlight punctate RPE changes and may be more sensitive than FAF in early disease.

Patients with cumulative doses exceeding 1500 g are at an increased risk of developing toxicity, though cases have been documented with doses as low as 435 g.[15] A baseline ophthalmic evaluation with OCT, FAF, and NIR is recommended at therapy initiation, with annual imaging starting at 500 g cumulative dose.[16] If toxicity is identified, PPS should be discontinued immediately, as retinal damage may be irreversible and progressive even after cessation. A prospective study of 26 eyes with PPS-associated maculopathy showed continued progression over 13 to 30 months, with a median lesion enlargement rate of 0.42 mm/year and significant thinning of the central macula, nuclear layers, and subfoveal choroid. New areas of RPE atrophy developed, and existing lesions expanded, highlighting the need for long-term follow-up after drug cessation.[17]

Phenothiazines

Phenothiazines are commonly used to treat psychotic disorders. Thioridazine, though effective, has been withdrawn in some regions due to its association with cardiac arrhythmias but remains available in certain countries.[7] Chlorpromazine, lacking the piperidyl side chain of thioridazine, has much lower retinal toxicity. Both drugs bind strongly to melanin, causing pigmentation of the skin, conjunctiva, cornea, lens, and retina, but not all phenothiazines are retinotoxic.[18] Early manifestations of thioridazine toxicity often present as non-specific pigmentary changes in the macula, which may advance to extensive nummular atrophy of the RPE and choriocapillaris[19] **(Figure 3)**. Early findings include mild field constriction or paracentral/ring scotomas, with ERG and EOG abnormalities in advanced disease.[20] Late stages show vascular narrowing, optic atrophy, and patchy depigmentation with hyperpigmented plaques.[21]

Chlorpromazine toxicity is rare but has been reported with prolonged high-dose use (e.g., 2400 mg/day for one year), presenting as pigmentary retinopathy, vessel attenuation, and optic pallor.[22] Thioridazine toxicity is dose-dependent, sometimes occurring within two weeks

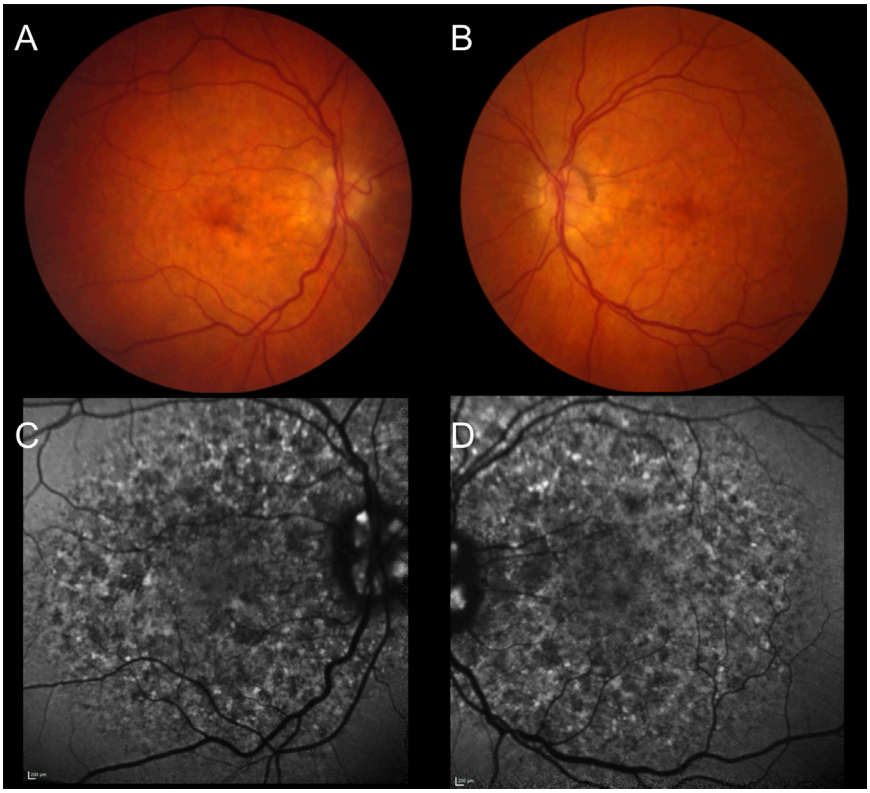

Figure 2 (A-B) Color fundus photographs and (C-D) fundus autofluorescence of both eyes show a speckled pattern of hypoautofluorescence and hyperautofluorescence corresponding to these RPE changes associated with pentosan polysulfate sodium (PPS)–related maculopathy.

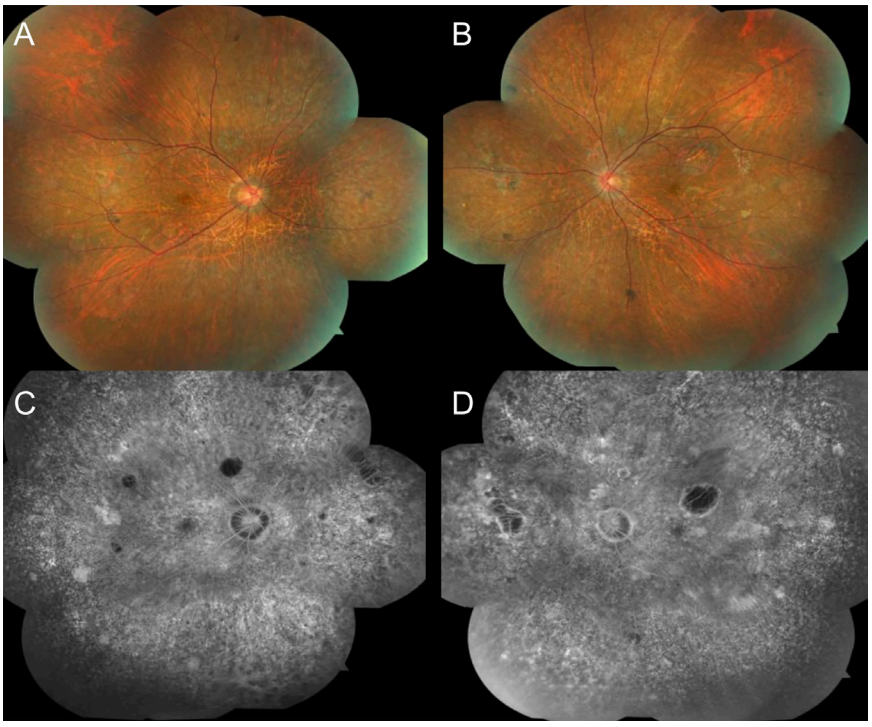

Figure 3 (A-B) Wide-angle color fundus photographs and (C-D) fluorescein angiography of both eyes showing diffuse granular pigment stippling and nummular pigment loss and choriocapillaris disruption as a thioridazine toxicity.

at high doses; risk is lower below 800 mg/day, but cumulative exposure remains important. Early drug cessation may stabilize or partly improve vision, though progression can still occur due to prior retinal injury.

Deferoxamine

Deferoxamine, an iron- and aluminum-chelating agent used in thalassemia and aplastic anemia, can rarely cause retinal toxicity, possibly via copper depletion in the RPE. Clinical signs include progressive vision loss, nyctalopia, and visual field defects, with pigmentary retinopathy as the hallmark. Early findings may show grayish macular discoloration, later progressing to diffuse pigmentary change. OCT typically reveals hyperreflective outer retinal deposits or Bruch's–RPE interface changes, leading to EZ disruption and photoreceptor thinning.[23] FAF patterns have been classified as minimal, focal, patchy, or speckled.[24] Rarely, bilateral central serous chorioretinopathy (CSC) has also been reported.[25] To reduce risk, adult dosing should not exceed 50 mg/kg/day.[26] While no formal guidelines exist, baseline and regular ophthalmic screening is recommended. If discontinuation is not feasible, dose reduction may help limit retinal damage.

Mitogen-Activated Protein Kinase Inhibitors

Mitogen-activated protein kinase (MEK) inhibitors (trametinib, cobimetinib, binimetinib) treat metastatic melanoma with BRAF mutations by blocking the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway. Retinal toxicity is dose-dependent and often reversible, even without stopping treatment. Risk factors include age, impaired renal function, and preexisting eye disease.[27] RPE dysfunction may lead to subretinal fluid via outer blood-retinal barrier disruption.[28] MEK inhibitors are most frequently associated with bilateral multifocal serous retinal detachments, with at least one detachment involving the fovea[7] **(Figure 4)**. Despite clinical evidence of retinal toxicity, some patients on MEK inhibitors remain asymptomatic.[6] Additional ocular manifestations, including uveitis, cystoid macular edema (CME), and optic neuropathy,

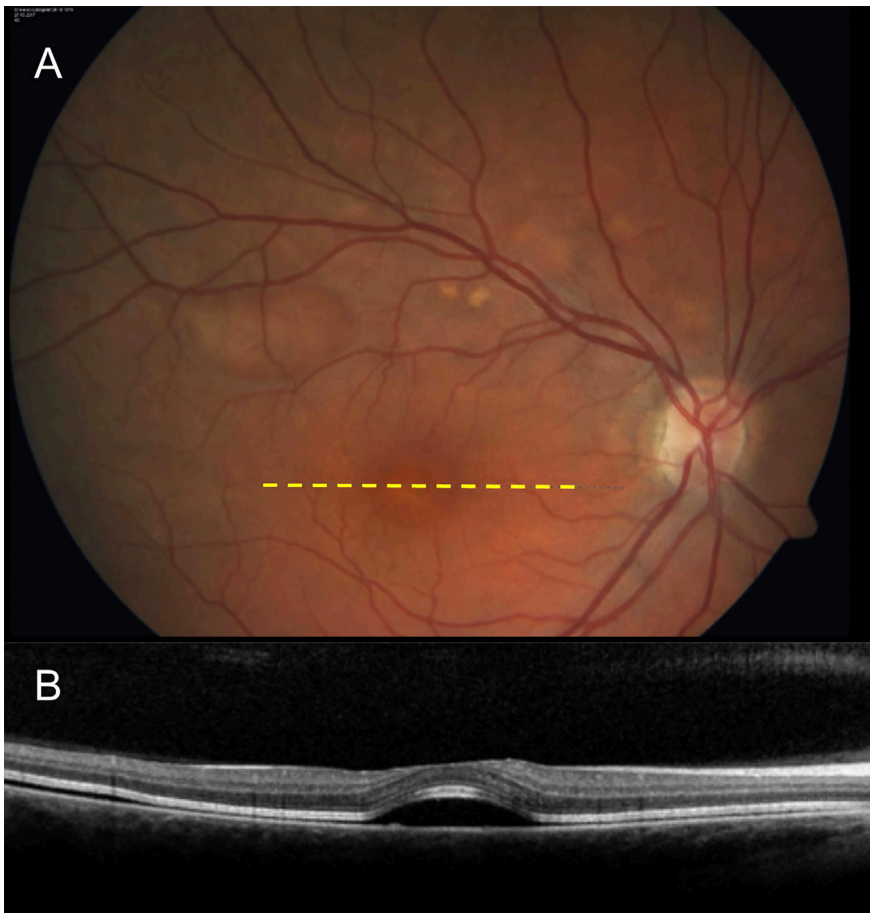

Figure 4 (A) Color fundus photographs of right eye reveal localized serous retinal detachments following initiation of MEK inhibitor therapy for metastatic melanoma. (B) Spectral-domain optical coherence tomography demonstrates shallow, loculated subretinal fluid predominantly in the subfoveal region.

have been reported. MEK inhibitor–associated serous retinal detachments may mimic CSC, but lack hallmark CSC features such as RPE defects, choroidal thickening, or leakage on FAF, fundus fluoresceine (FA), and SD-OCT. SD-OCT is the most informative modality, with four described fluid patterns: dome-shaped (most common), caterpillar-like, wavy, and splitting.[29] Management is usually conservative, as subretinal fluid often resolves spontaneously. Symptoms are typically mild and appear within days of treatment. Persistent cases may require drug discontinuation. Corticosteroids or NSAIDs can be used for associated uveitis or macular edema.[30]

Fibroblast Growth Factor Receptor Inhibitors

Fibroblast growth factor receptor (FGFR) inhibitors, approved for cholangiocarcinoma and urothelial carcinoma, include erdafitinib, pemigatinib, and infigratinib. Acting upstream of MEK, they can cause serous retinal detachments resembling MEK inhibitor–associated retinopathy. Though rare, FGFR-related retinopathy is documented: in an AZD4547 trial, subretinal fluid occurred in 22% of eyes. Reported cases with erdafitinib showed pseudovitelliform lesions, OCT changes, and bilateral serous detachments, often asymptomatic and sometimes resolving spontaneously without stopping therapy.[31] Pemigatinib has similarly been linked to multifocal serous detachments, resolving within days of drug cessation.[32] The long-term retinal effects of FGFR inhibitors remain uncertain, highlighting the need for further studies and clear monitoring guidelines.

Toxicity Related to Maculopathy

Nicotinic Acid

Niacin (nicotinic acid), used to lower lipids, can rarely cause retinal toxicity. Patients may present with blurred vision, metamorphopsia, or paracentral scotomas.[33] OCT typically shows cystoid spaces in the inner nuclear and outer plexiform layers, while FA reveals no leakage. The mechanism may involve direct Müller cell toxicity and selective blood-retinal barrier disruption. Most cases resolve after discontinuation or dose reduction,[34] but prolonged use with persistent edema can lead to macular atrophy.

Antimicrotubule Agents

Paclitaxel and docetaxel are widely used in the treatment of various malignancies, including breast, lung, and prostate cancer. Both agents have been linked to the development of CME, which typically lacks leakage on FA.[35] The proposed mechanism involves Müller cell dysfunction and subclinical extracellular fluid accumulation, like niacin-induced toxicity. Macular edema often resolves following drug discontinuation, and treatment with topical or systemic carbonic anhydrase inhibitors may also be beneficial[36, 37] **(Figure 5)**.

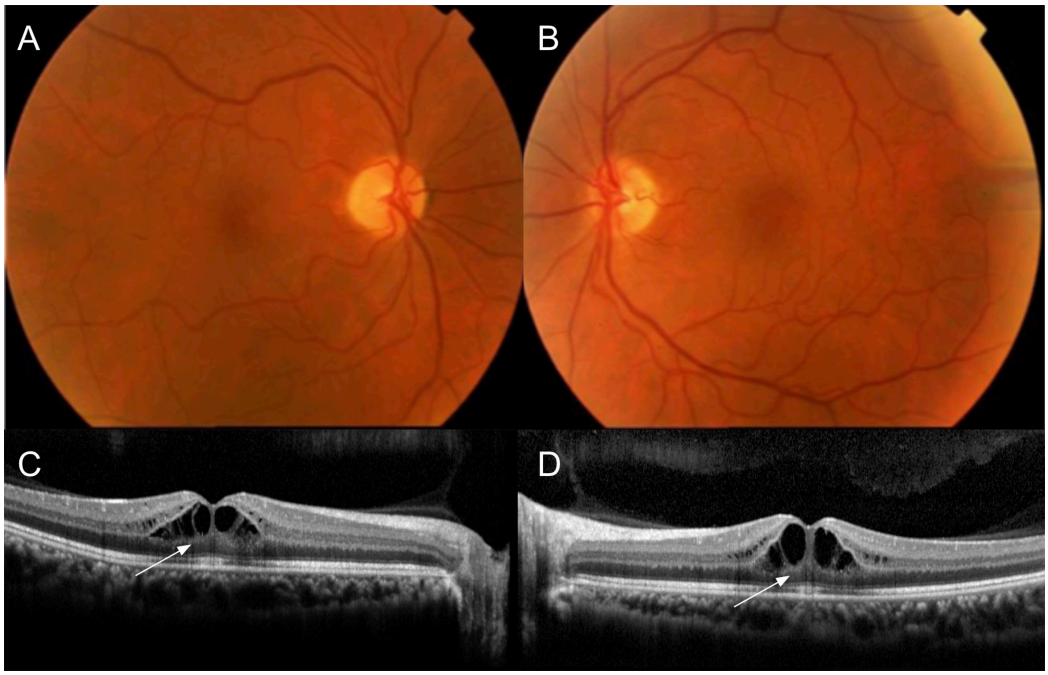

Figure 5 (A-B) Color fundus photographs and (C-D) Spectral-domain optical coherence tomography of both eyes revealing bilateral cystoid macular edema associated with paclitaxel therapy.

Fingolimod

Fingolimod, a disease-modifying agent for relapsing-remitting multiple sclerosis, acts via modulation of the sphingosine-1-phosphate receptor. A notable ocular adverse effect is fingolimod-associated macular edema (FAME), caused by blood-retinal barrier disruption, leading to protein leakage and osmotic fluid accumulation within the retina. FAME is a dose-dependent adverse effect, most reported at the standard dose of 0.5 mg daily, and generally resolves after drug discontinuation.[38] However, there is no established consensus on the optimal management approach beyond stopping the medication. Treatments that have shown potential efficacy in promoting FAME resolution include topical anti-inflammatory agents, corticosteroids, carbonic anhydrase inhibitors, and anti-vascular endothelial growth factor (VEGF) therapy.[39-42]

Toxicity Related to Vascular Damage

Talc

Talc, an inactive component of medications such as methylphenidate and methadone, can cause retinal toxicity in intravenous drug users who inject crushed tablets. Repeated injections allow talc particles to enter systemic circulation and embolize to the retina. Emboli lodge in small arterioles, producing ischemic retinopathy with capillary nonperfusion, microaneurysms, cotton-wool spots, and, in advanced stages, retinal neovascularization.[43] Management centers on patient counseling and cessation of intravenous drug use to stabilize findings and prevent progression.[44,45]

Oral Contraceptives

Contraceptive pills containing estrogen (typically ethinylestradiol at 20-40 μg per day) or progestin may induce a hypercoagulable state, with estrogen posing a higher risk. Retinal vascular occlusions have been reported in young women using these agents, particularly those on higher-dose formulations (≥ 30-40 μg).[46] Documented complications include central retinal vein occlusion, retinal and cilioretinal artery occlusion, superior ophthalmic vein thrombosis, and anterior ischemic optic neuropathy.[47-49] Although the evidence remains inconclusive, large-scale studies suggest an increased prevalence of retinal vascular abnormalities among contraceptive pill users.[50]

Interferon

Interferon alpha-2a is an antiviral and immunomodulatory agent used to treat melanoma, renal cell carcinoma, lymphoma, leukemia, and chronic hepatitis C. While generally well tolerated,[51] it has been associated with retinal vascular toxicity, often presenting as cotton-wool spots and intraretinal hemorrhages with preserved visual acuity **(Figure 6)**. In some cases, more severe complications such as vascular occlusion, CME or non-arteritic anterior ischemic optic neuropathy can occur.[52-54] The proposed mechanism involves impaired retinal microcirculation due to leukocyte adhesion and entrapment in the vasculature.[55] Patients with diabetes or hypertension are at higher risk. Retinal findings typically improve after discontinuation of the drug.[56]

Ergot Alkaloids

Ergot alkaloids, particularly ergotamine, have been associated with retinal toxicity, presenting as retinal vasculopathy, ischemia, and potential vision loss. These effects are primarily attributed to vasospasm and reduced retinal blood flow, especially when used at higher-than-recommended doses, which can lead to retinal vasoconstriction.[57]

Toxicity Related to Crystalline Deposits

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, is widely used for estrogen receptor–positive breast cancer and has been studied in other malignancies such as glioblastoma. Retinal toxicity occurs in 0.9-12% of patients on standard doses (10-20 mg/day), usually after 2-3 years, but higher daily (60-100 mg) or cumulative doses (> 100 g) may cause earlier onset.[58] Tamoxifen retinopathy is often asymptomatic but may result in vision loss or dyschromatopsia.[59] Typical findings include crystalline retinopathy with intraretinal crystals, CME, and pigmentary changes **(Figure 7)**. FAF may be normal or show mixed autofluorescence, while OCT reveals hyperreflective inner retinal deposits and disruption of the ELM, ellipsoid, and interdigitation zones. CME is dose-dependent, with lower doses more often linked to cysts than frank edema. Early OCT/ Optical Coherence Tomography Angiography features may mimic macular telangiectasia type 2 (MacTel type 2), including deep plexus alterations, right-angled vessels, and Müller cell dysfunction.

Regular ophthalmic evaluation is recommended for patients on tamoxifen, particularly those who remain asymptomatic but require continued treatment for systemic malignancies. Follow-up exams every six months are advised, particularly for patients receiving 20 mg/day of tamoxifen for two years or longer.[60] In symptomatic cases, consultation with an oncologist is necessary to assess the risk-

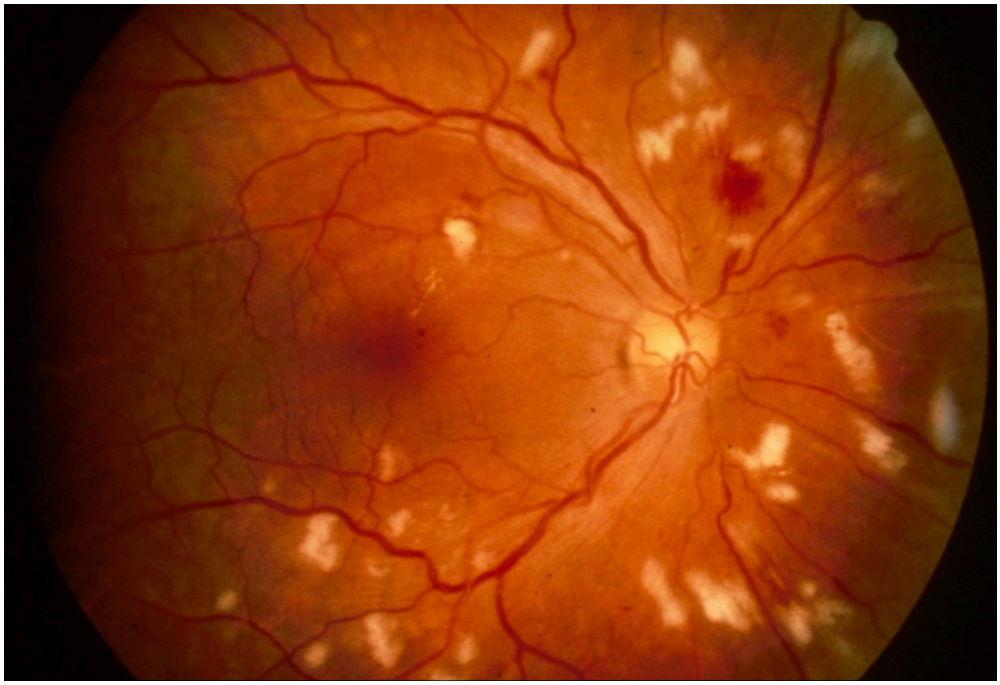

Figure 6 Color fundus photograph of right eye demonstrating cotton-wool spots and intraretinal hemorrhages associated with interferon alpha-2a toxicity.

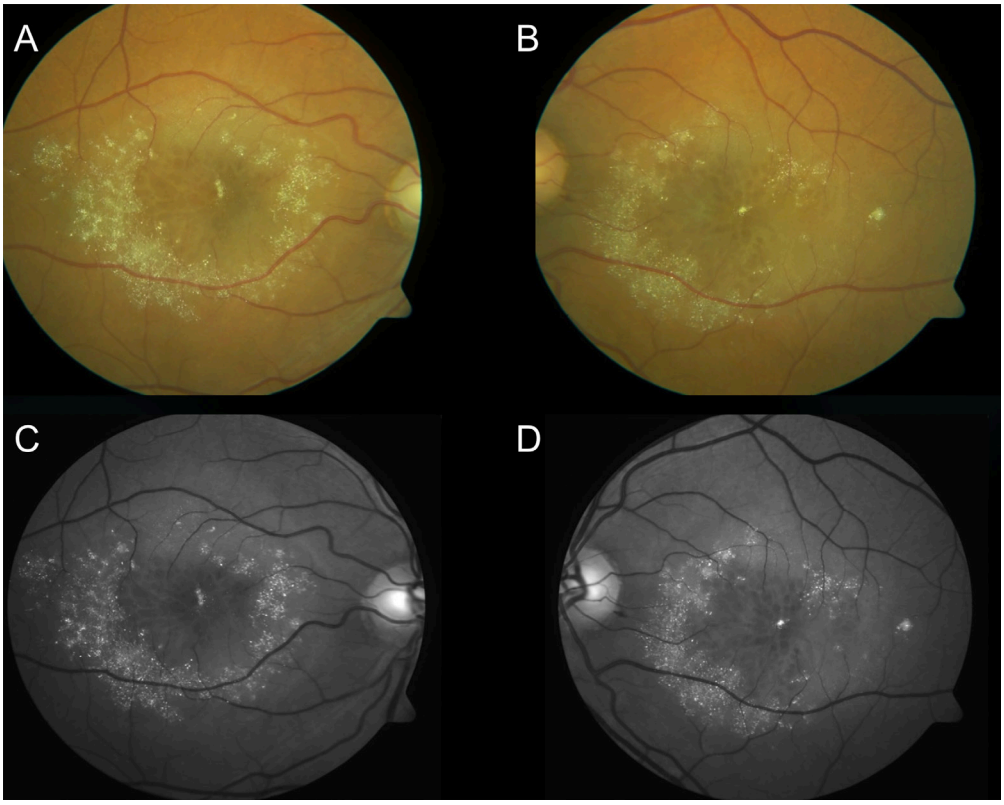

Figure 7 (A-B) Color fundus photographs of of both eyes reveal crystalline deposits at the macula. (C-D) Blue light reflectance imaging highlights punctate hyperreflective foci surrounding the macula, consistent with crystalline retinopathy secondary to tamoxifen toxicity.

benefit ratio of discontinuing the drug, as cessation often leads to improvement in visual function and resolution of edema. Management strategies for CME include intravitreal anti-VEGF therapy, intravitreal corticosteroids, and oral carbonic anhydrase inhibitors.[61, 62]

Canthaxanthine

Canthaxanthin, a carotenoid used for treating photo-sensitivity disorders and as an oral tanning agent or food additive, has been primarily associated with retinal toxicity in the context of sun-tanning use. Crystalline retinal deposits are thought to result from Müller cell atrophy and inner retinal spongy degeneration.[63] While many cases remain asymptomatic, prolonged high-dose use (total dose > 19 g generally over a 2-year timeframe) can lead to yellow-orange crystals forming a macular ring.[6] These deposits resolve slowly after discontinuation, with clearance potentially taking up to two decades. Electrophysiologic studies suggest gradual functional retinal recovery following cessation.[64]

Methoxyflurane

Methoxyflurane, a volatile anesthetic, can cause renal failure from calcium oxalate deposition, particularly in kidney impairment. Retinal involvement manifests as crystalline retinopathy with yellow-white macular or arteriolar deposits, sometimes with cotton-wool spots. Histology shows crystal accumulation in the RPE and inner retina.[65]

Toxicity Related to Uveitis

Checkpoint Inhibitors

Checkpoint inhibitors—including Programmed Cell Death protein 1 (pembrolizumab, nivolumab), Programmed Cell Death Ligand 1 (atezolizumab, avelumab, durvalumab), and Cytotoxic T-Lymphocyte Associated protein-4 (ipilimumab)—enhance antitumor immunity by blocking inhibitory pathways. Initially approved for metastatic melanoma, they are now used in multiple cancers. Their immune-modulating effects may trigger ocular autoimmunity,[66] typically within weeks to months of therapy. Reported complications include dry eye, myasthenia-like ophthalmopathy, uveitis, and syndromes resembling Vogt-Koyanagi-Harada (VKH) **(Figure 8)**, Behçet's disease, and uveal effusion.[67] Management requires coordination between oncologists and ophthalmologists. Most uveitis cases respond to topical steroids, while severe inflammation may require intraocular implants, periocular injections, or systemic therapy. Immunotherapy discontinuation is rarely necessary and reserved for severe or refractory cases.

BRAF Inhibitors

BRAF inhibitors, including vemurafenib and dabrafenib, are approved for metastatic cutaneous melanoma and are often combined with MEK inhibitors. Anterior uveitis is the most common ocular adverse effect, though VKH-like uveitis and panuveitis have also been reported.[68,69] The mechanism may involve immune responses against melanocyte-associated antigens shared by melanoma and choroidal tissue. Most cases respond well to topical, local, or systemic corticosteroids without requiring discontinuation of therapy. However, in rare cases with persistent vision loss, stopping the drug may be necessary.

Miscellaneous

Sulfa Drugs

Sulfa-containing drugs such as sulfonamides, acetazolamide, hydrochlorothiazide, and topiramate can cause ocular effects involving the ciliary body and choroid, including edema, choroidal effusion, and lens swelling. These changes may lead to transient myopia, retinal folds, shallow anterior chamber, or angle-closure glaucoma. FA typically shows no vascular leakage, suggesting that retinal folds are due to vitreous traction from axial changes rather than vascular pathology. These effects are usually reversible upon drug discontinuation.[70]

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, are used for pulmonary hypertension and erectile dysfunction by enhancing cyclic guanosine monophosphate-mediated smooth muscle relaxation. They also inhibit retinal PDE-6, disrupting phototransduction and sodium channel regulation in photoreceptors. Reported ocular effects include anterior ischemic optic neuropathy, subretinal hemorrhage, CSC, and extraocular muscle palsy. A common dose-dependent effect is bluish dyschromatopsia, typically appearing 1-2 hours post-dose. OCT in long-term or high-dose use may reveal EZ hyperreflectivity or disruption.[71] While most visual symptoms resolve within 24 hours, rare cases of persistent photoreceptor damage lasting up to a year have been described.

Alkyl Nitrites

Alkyl nitrites ("poppers") are volatile recreational drugs linked to retinal toxicity, particularly after the 2006 UK switch from isobutyl to isopropyl nitrite, though amyl

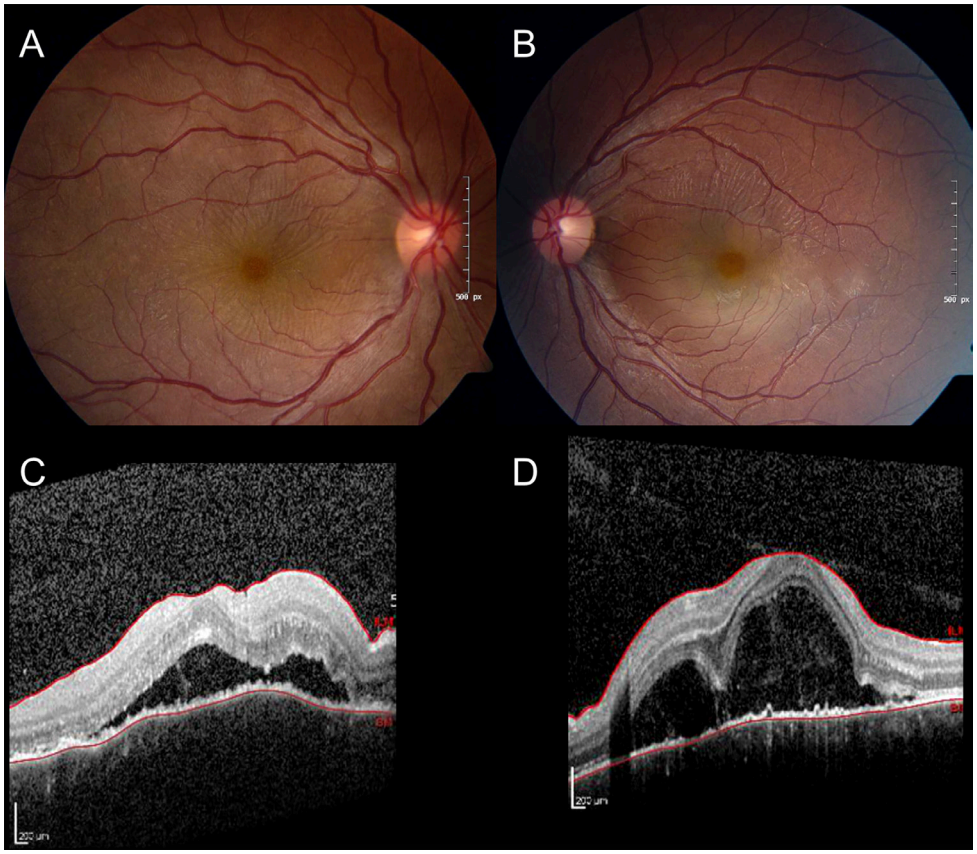

Figure 8 (A-B) Color fundus photographs of both eyes showing central macular striae and subretinal fluid. (C-D) Optical coherence tomography from another patient receiving checkpoint inhibitor therapy demonstrates subretinal fluid consistent with a Vogt-Koyanagi-Harada (VKH)-like presentation.

isobutyl nitrite has also been implicated. The proposed mechanism involves nitric oxide–mediated photoreceptor dysfunction.[72] Patients typically present with central visual disturbances (blurred vision, scotomas, metamorphopsia, phosphenes). Fundus findings range from normal to yellow foveal lesions, but OCT is most sensitive, revealing photoreceptor disruption, vitelliform-like deposits, or outer retinal microholes. As the condition may mimic photic injury, a detailed history of exposures is essential. Symptoms often improve with drug cessation, but structural retinal changes usually persist, and complete recovery is uncommon.[69]

Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase (ALK) inhibitors, including crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, and entrectinib, are targeted therapies for non-small cell lung carcinoma. The most common ocular side effect is impaired light-dark adaptation, often presenting as light trails following moving objects.[73] Other symptoms include blurred vision, photopsia, photophobia, floaters, diplopia, accommodation difficulty, and visual field defects. Structural changes such as macular edema, cataracts, and vitreous detachment have also been reported. These visual disturbances typically improve over time without requiring dose adjustment.

Illicit and Controlled Substances

Cocaine

Cocaine, derived from the Erythroxylon coca plant, exerts potent vasoconstrictive effects through benzoylmethylecgonine, a vasoactive metabolite that enhances sympathetic activity by blocking sodium channels. These physiological effects can lead to ocular complications, including retinal hemorrhages, alterations in vessel caliber, microvascular changes, and vascular occlusions **(Figure 9)**. Cocaine use has also been associated with acute macular neuroretinopathy, retinal vasculitis, posterior uveitis, and frosted branch angiitis.[74] However, differentiating these manifestations from those

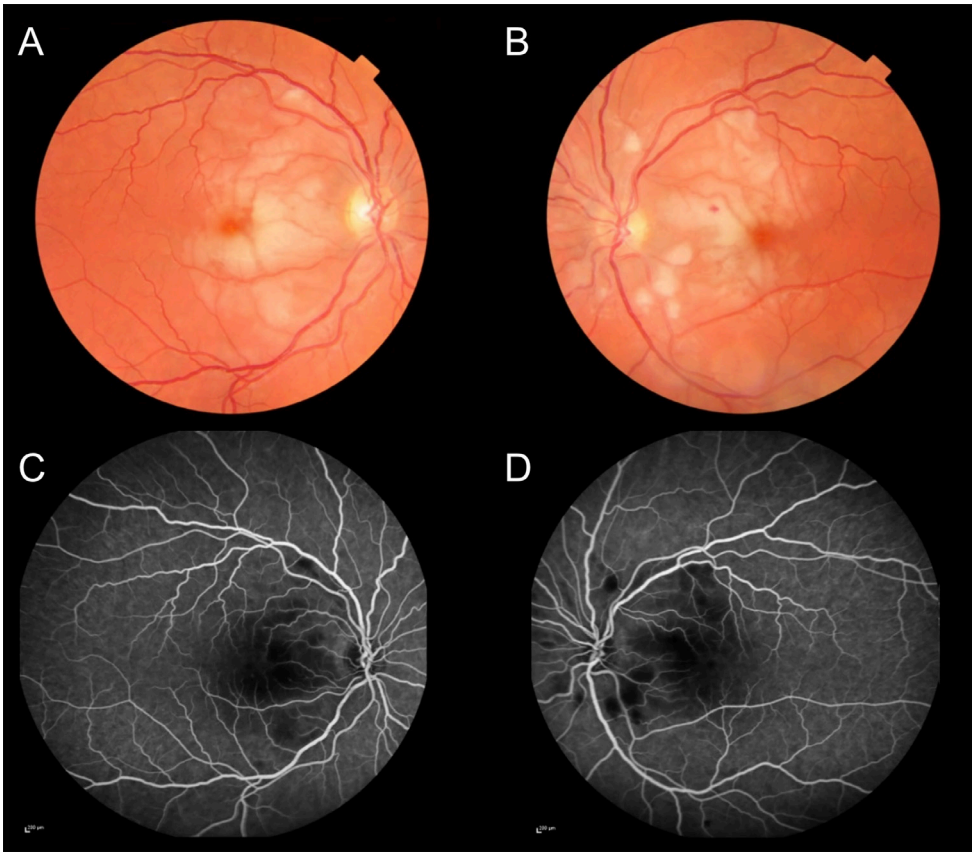

Figure 9 (A-B) Color fundus photographs and fluorescein angiography of both eyes eyes reveal multiple cotton wool spots and corresponding areas of blockage on angiography (C-D), consistent with Purtscher-like retinopathy in a patient with a history of cocaine use.

caused by other systemic conditions such as inflammation, trauma, hypotension, or eclampsia is often difficult. A detailed clinical history, including inquiry into substance use, is essential for accurate diagnosis and appropriate management.

Methamphetamine

Methamphetamine, a potent psychostimulant related to amphetamine, produces sympathomimetic effects and systemic cardiovascular and neurological complications. Ocular toxicity, reported in both humans and animal models, includes anophthalmia, microphthalmia, retinal folding, optic disc hypoplasia, scleritis, crystalline retinopathy, vascular occlusions, hemorrhages, and vasculitis.[72] These effects likely stem from oxidative stress and vascular spasm, causing vasoconstriction, ischemia, and retinal vascular injury.[75]

Cannabis and Cannabinoids

Cannabis is widely used and linked to ocular effects including eyelid tremors, ptosis, corneal opacification, reduced corneal healing, and retinal vascular changes. Mediated via CB1/CB2 receptors, it has been associated with branch retinal artery occlusion, central retinal vein occlusion, and hemorrhagic macular infarction.[73] Once considered for glaucoma therapy, it is no longer recommended due to only transient IOP reduction.[76]

CONCLUSION

A wide range of systemic medications, both prescribed and illicit, can cause retinal and choroidal toxicity. Diagnosis often depends on recognizing characteristic retinal patterns, making a thorough drug and substance use history essential. Toxicity may occur at any dose level. Illicit substances like methamphetamine, cocaine, and synthetic cannabinoids are increasingly implicated. As new agents emerge, clinicians must stay vigilant. Prompt identification and withdrawal of the offending drug are key to preserving vision. However, in some cases—such as with hydroxychloroquine and PPS—retinal toxicity may persist or even progress despite discontinuation, underscoring the need for early detection and long-term monitoring.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Author Contributions

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Data curation: TK
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