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Effects of Local and Systemic Medications on Eye Health: Adverse Reactions

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SUMMARY

Introduction: Medications can cause both local and systemic adverse effects. The field of ophthalmology involves a range of medical interventions performed within a relatively small anatomical space, often involving various medications. This presents challenges in monitoring the adverse effects of drugs, as they may produce both local and systemic side effects. Given that patients often have comorbid conditions, accurately assessing the causality of adverse effects requires a team of experienced physicians.

Topic: This paper explores three distinct avenues regarding the effects of medications on ocular health: I. Local effects of locally applied medications; II. Systemic effects of local ophthalmic medications; III. Effects of systemic medications on ocular structures.

Conclusion: Systemic side effects of eye treatment locally applied drugs are adverse effects of a medication or substance that impact the entire body or multiple organ systems, rather than being limited to the area of contact or administration. These effects occur because the substance is absorbed and distributed throughout the body via the bloodstream. Examples include fatigue, nausea, hair loss, and fluctuations in blood sugar levels.

The most common ocular adverse effect of systemic medications is dry eye, which can be caused by antidepressants, antihistamines, beta-blockers, diuretics, H2 blockers, proton pump inhibitors (PPIs), hormones (including contraceptive preparations and hormone replacement therapy), and isotretinoin (used for acne). One of the most urgent ophthalmologic condition is retinal detachment, which can be a serious adverse effect of fluoroquinolones. Ophthalmic complications of systemic drugs are typically transient and often resolve after the discontinuation of the therapy that caused them. The most serious adverse events are associated with neurotropic (neuroleptic), immunotropic, and antitumor medications (including chemotherapy). These treatments are frequently administered for severe conditions, are difficult to discontinue, and are typically long-term. Thus, when prescribing these medications, it is crucial to assess the associated risks and to monitor

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ophthalmic complications during treatment.

The list of topically applied eye medications or systemic medications that have adverse effects on eye health should not be considered exhaustive or definitive. According to Dr. Srdjan Djani Marković, in summary, reporting, monitoring and analysis of adverse drug reactions reflects the seriousness of the healthcare system.

Keywords: Side Effects in Ophtalmology, Local Side Effects, Systemic Side Effects, Eye, Ocular Toxicity, Ophtalmology

INTRODUCTION

Medications can cause both local and systemic adverse effects (AEs). These medications can be administered either locally or systemically, with the majority used in ophthalmology designed for local effects. In ophthalmology, medications primarily aim to treat and alleviate symptoms of eye diseases. They may also serve diagnostic purposes or act as adjunctive therapy during surgical interventions. The field of ophthalmology involves a range of medical interventions performed within a relatively small anatomical space, often involving various medications. This presents challenges in monitoring the adverse effects of drugs, as they may produce both local and systemic side effects. Given that patients often have comorbid conditions, accurately assessing the causality of adverse effects requires a team of experienced physicians. Typically, the monitoring of drug AEs is conducted under mild observation; however, evidence suggests that the situation may be more serious than it appears.

Local adverse effects can be severe and intense due to the eye's anatomical location, while systemic adverse effects can pose life-threatening risks. Systemic effects refer to the widespread impact a drug can have throughout the body after entering the bloodstream. In contrast, localized effects are restricted to a specific area. In the case of medications for respiratory conditions, systemic effects can influence various organ systems, providing therapeutic benefits but also potential side effects, particularly when treating conditions such as asthma and Chronic Obstructive Pulmonary Disease (COPD) [1,2].

As our esteemed colleague, Dr. Srdjan Djani Marković, noted, the reporting of adverse drug effects reflects the seriousness of a country's healthcare system and its overall efficiency in medical treatment [3,4,5].

Ophthalmology focuses on the treatment of the eye, a small yet significant organ that interacts with other organ systems. Consequently, local therapy for the eye may lead to systemic side effects, and systemic medications may also affect the eye. Given the sensitivity and importance of this organ, the authors emphasize the need for careful monitoring of both the systemic adverse effects of systemic medications on the eye and the systemic effects of locally administered medications.

The authors aim to highlight and systematically assess the severity of side effects in ophthalmotherapy and propose potential precautionary measures. When side effects occur, prompt therapeutic measures should be taken to mitigate their consequences.

METHODOLOGY

To identify ocular side effects associated with various medications, we conducted a comprehensive search of the PubMed database, meticulously sifting through case reports, clinical trials, case series, and review articles. Our focus was on the intricate relationship between ocular toxicity and a diverse array of drug classes. We employed an array of targeted keywords including „ocular toxicity" paired with terms such as „anticancer medications", „antiarrhythmic drugs", „antibiotics", „antidepressants", „antiepileptic drugs", „antihistamines", „antipsychotics", „antitubercular agents", „dermatologic medications", „hormones", „non-steroidal anti-inflammatory drugs", „antihypertensive medications", „immunotherapy drugs", „biologic medicines", and „antivirals". Each term was separately evaluated for its ocular implications. This rigorous search concluded in February 2025, culminating in an enlightening overview of ocular adverse effects associated with the most prevalent medications.

Additionally, a concerted effort was made to review the literature on ophthalmology medications. Using a combination of PubMed, Cochrane, Embase, and Scopus databases, we performed a targeted search with keywords such as „ophthalmology drugs",

„systemic drugs", „local ophthalmic agents", and „systemic treatments for local indications". This literature review was conducted exclusively in English, Russian, and Serbian, with equal consideration given to each language.

TOPIC

Types of occular adverse drug effects

The retina and optic nerve, with their remarkably high metabolic activity, underscore the critical need for careful evaluation of symptoms that ophthalmologists identify in relation to a patient's ongoing therapeutic regimen [6]. This paper explores three distinct avenues regarding the effects of medications on ocular health:

I Local effects of locally applied medications

II Systemic effects of local ophthalmic medications

III Effects of systemic medications on ocular structures

I Local Effects of Locally Applied Medications. The application of eyedrops or ointments can elicit immediate stinging or burning sensations, a temporary yet uncomfortable experience for patients. Common local side effects manifest as:

- Eye irritation, often accompanied by a persistent itch or burning sensation
- Skin rashes and hives that can mark the delicate skin surrounding the eyes
- The appearance of blisters or fever, indicative of more severe reactions
- Allergic responses, leading to redness (erythema), photophobia (increased sensitivity to light), and blurred vision
- Potential capillary damage, resulting in noticeable vascular changes in the eye
- Fluctuations in intraocular pressure (IOP), which can pose significant risks to vision

Corticosteroid therapy, particularly glucocorticoids, can introduce a host of ocular complications, notably the development of posterior subcapsular cataracts and the dangerous possibility of iatrogenic ocular hypertension and glaucoma-conditions that threaten the very essence of one's vision.

Specifically, the common side effects of naphazoline, when applied topically, include:

- Burning, stinging, dryness, or irritation in the nasal passages with the use of nasal drops
- Experiencing a burning sensation, redness, pain, or an overarching discomfort in the eyes, including pupil dilation when utilizing eye drops
- Increased tearing, often seen following the application of eye drops
- Prolonged or excessive use of nasal drops may lead to „rebound" nasal congestion, a troubling condition where nasal blockage returns or becomes exacerbated after the medication's effects subside.

Moreover, anterior and posterior segment vasculopathy associated with long-term use of tetrahydrozoline should be considered a critical adverse effect, prompting physicians to engage patients in thorough discussions about its use [7].

In light of concerning serious adverse effects, silver nitrate (Crede's drops), once a staple in clinical practice, has been withdrawn from use, highlighting the ongoing need for vigilance in medication management [8]. Fluoroquinolones are associated with a range of ocular side effects, which are localized and among the most frequently reported adverse reactions. Key issues include:

- Irritation and Discomfort: Patients may experience burning, stinging, eye pain, itching, redness, and a sensation akin to having a foreign body in the eye.
- Visual Disturbances: Symptoms such as blurred vision and diminished visual acuity are common.
- Presence of white crystalline or scale-like deposits on the corneal surface (corneal precipitates).
- Inflammation of the cornea (keratitis), which, albeit rarely, may lead to corneal perforation.
- Swelling of the eyelids, crusting along the eyelid margins, and increased light sensitivity (photophobia).

There have also been rare reports of retinal detachment; however, recent studies do not strongly support a causal link.

II Local Medications with Systemic Effects. The eye's unique blood supply makes the potential for systemic side effects from ophthalmic medications a significant consideration, despite their rarity. Pharmacodynamic and pharmacokinetic characteristics of these drugs are critical during treatment. Ophthalmic formulations are usually selective for ocular tissues and exhibit low systemic reabsorption, primarily producing local pharmacological effects.

However, systemic side effects can arise if active ingredients or excipients enter the systemic circulation via conjunctival or iris vessels, or through the nasolacrimal drainage system into the nasal mucosa [6,9]. The type of formulation affects the duration of pharmacologic action; aqueous solutions tend to have the shortest duration, whereas gel-based formulations containing highly effective agents (such as methylcellulose or polyvinyl alcohol) provide prolonged effects [10].

The potential systemic impact of topical ocular medications is often underestimated in clinical practice, leading to missed opportunities to manage adverse effects. Contemporary literature highlights serious systemic adverse effects even from localized applications, emphasizing vigilance, particularly in pediatric populations [11,12,13]. For instance, a single administration of a 1% atropine sulfate solution may induce mydriasis and cycloplegia, but in children, it can also precipitate hyperthermia and xerostomia [14].

Ophthalmic agents are designed for absorption through the cornea into ocular tissues, including the aqueous humor. Following administration, many of these drugs can exit the eye, enter systemic circulation, and be metabolized in the liver. Subsequent excretion occurs via urine or feces. Nonetheless, factors such as pathological conditions, genetic polymorphisms, and drug-drug interactions can significantly influence drug pharmacokinetics, affecting the extent of systemic side effects based on individual patient sensitivity [2,10].

Classification of local ophthalmic medications:

1. Medications for glaucoma
2. Mydriatics
3. Anti-inflammatory drugs
4. Antiallergic and decongestants
5. Anti-infective drugs (antibiotics, antifungals, antivirals)
6. Diagnostic agents and surgical preparations
7. Anti-VEGF agents: minimal number of adverse event reports
8. Lubricants: minimal number of adverse event reports

Ophthalmic drug administration may also involve injectable routes such as subconjunctival, parabulbar, and retrobulbar injections, with direct intraocular administration (anterior chamber or intravitreally) in specific cases. The volume used in these injections typically does not exceed 0.5–1.0 ml, allowing for significantly higher therapeutic concentrations than traditional drops. For example, a single subconjunctival injection can equate the effect of administering multiple eye drops at intervals [10].

Adverse reactions to ophthalmic medications may arise from active pharmaceutical ingredients or excipients (e.g., solvents, buffers, preservatives). These reactions may be classified as either allergic or specific, depending on their association with the drug's pharmacological characteristics. A notable illustration of systemic adverse effects following localized application includes cyclopentolate, which may induce reversible cycloplegia and, in infants, has been correlated with paralytic ileus [11,12,15]. Instances of psychotic reactions following its application in refractive surgery preparations have also been documented [13].

In clinical practice, it is critical to navigate the use of these medications while considering both local effectiveness and potential systemic repercussions for each glaucoma patient, tailored approach.

1. *Systemic Adverse Effects of Medications for Glaucoma*

Agents Enhancing Aqueous Humor Outflow

Among the M-cholinomimetics, pilocarpine remains a cornerstone in the treatment of glaucoma. The hypotensive effect post-instillation typically lasts 4–6 hours, necessitating 4–6 daily applications with commonly used concentrations of 1% and 2%. Notably, increasing the concentration does not significantly enhance the hypotensive effect but substantially elevates the risk of adverse reactions, which include:

- Headache (temporal or periorbital)
- Rhinorrhea
- Bronchospasm
- Hypersalivation
- Nausea and vomiting
- Diarrhea
- Fluctuations in blood pressure (both elevation and reduction)
- Allergic reactions

To mitigate systemic absorption, patients should perform punctal occlusion by applying pressure to the inner canthus over the lacrimal sac for 1–2 minutes post-instillation

[16,17,18].

Agents Inhibiting Aqueous Humor Production

Selective Sympathomimetics: Brimonidine and clonidine, classified as selective α2-adrenergic agonists, exhibit common systemic adverse effects, including:
- Drowsiness
- Slowed cognitive and motor responses
- Constipation
- Decreased gastric acid secretion
- Clonidine eye drops may also lead to hypotensive events.

Beta-blockers, predominantly utilized as first-line agents for glaucoma management, can demonstrate synergistic effects when used both locally and systemically (e.g., Glaumol® and Inderal®, both β1,2-adrenergic blockers). Non-selective beta-blockers like timolol (timolol maleate) are noteworthy for potential systemic side effects, which may include:
- Dizziness
- Headache
- Arrhythmias
- Bradycardia
- Bronchospasm
- Nausea and vomiting

Selective β1-blockers, such as betaxolol, bear similar respiratory implications. Non-selective α,β-adrenergic blockers may induce bradycardia, arterial hypotension, and bronchospasm in predisposed individuals (17,18,19]. Local use of beta blokers (e.g. thimolol maleat) in hypersensitive individuals can cause arterial COLAPSE [20]. Notably, the use of topical beta-blockers does not correlate with an elevated risk of cardiovascular or respiratory conditions in glaucoma patients [21].

Carbonic Anhydrase Inhibitors: brinzolamide and dorzolamide are contraindicated in patients with hypersensitivity to any component. Systemic adverse reactions may manifest as:
- Headache
- Nausea
- Asthenia
- Urolithiasis
- Eruptions
- Altered taste perception [17]

M-cholinomimetics, pilocarpine is commonly used to treat glaucoma. The duration of its hypotensive effect after a single pilocarpine solution instillation varies among individuals and typically lasts 4 to 6 hours. Therefore, aqueous solutions should be administered 4 to 6 times daily, with the most frequently used concentrations being 1% and 2%. Increasing the concentration beyond this range does not significantly enhance the hypotensive effect, but it substantially increases the risk of adverse reactions, which may include [22]:
- Headache (temporal or periorbital)
- Rhinorrhea
- Bronchospasm
- Hypersalivation
- Nausea and vomiting
- Diarrhea
- Blood pressure changes (either increased or decreased)
- Allergic reactions

To reduce systemic absorption, punctal occlusion is recommended. The patient should press the inner corner of the eye (over the lacrimal sac) for 1 to 2 minutes immediately after instillation [22].

2. Mydriatics

M-anticholinergics, such as tropicamide and atropine, are used in eye drops to dilate the pupil. They differ mainly in their duration and strength. Tropicamide acts quickly and is short-acting, making it ideal for quick eye examinations. Atropine is not recommended for patients with severe urinary disorders caused by prostate adenoma and should be prescribed with caution in children under 3 months of age, as well as in patients with severe cardiovascular diseases. Serious side effects of ophthalmic atropine may include a fast, pounding, or irregular heartbeat. When treating with atropine, the risk of systemic adverse effects can be minimized by compressing the lacrimal duct at the inner corner of the eye for 1 to 2 minutes.

3. Anti-inflammatory Medications Glucocorticosteroids (GCS) and nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammatory eye diseases. With the exception of hydrocortisone, glucocorticosteroids readily penetrate most ocular tissues, including the lens, whether applied topically or admin-

istered systemically. Prolonged use of these steroid medications may slow wound healing and could lead to secondary infections, corneal fungal infections, and non-healing ulcers. An example of a steroid eye drop is Oftalmol® (prednisolone), which contains 5 mg/mL and is in suspension [23]. NSAIDs used in ophthalmology include 0.1% diclofenac sodium solution, indomethacin, and 0.09% bromfenac solution. Physicians should check whether patients have a history of intolerance, aspirin-induced asthma, or rhinitis before prescribing these medications [16,24].

4. Antiallergic Drugs and Decongestants Among this group, chromoglicic acid is the most frequently used medication. It is not recommended for patients with hypersensitivity to the compound, pregnant or breastfeeding women, or children younger than 4 years of age. Antihistamines, such as Polinadim® (diphenhydramine and naphazoline), are used to treat allergic eye diseases, either as single-component or combination medications. Their use is not advised during pregnancy and breastfeeding, nor for children under 4 years of age. Systemic adverse reactions are rare, especially when the recommended dosage is followed and may include [25]:
- Headache
- Dizziness
- Nausea
- Increased blood pressure (particularly in individuals predisposed to hypertension)
- Rapid heartbeat (tachycardia)
- Anxiety, nervousness, sleep disturbances
- Pale skin
- Increased sweating

Decongestants, which contain vasoconstrictors, may be used to alleviate allergic symptoms. Single-component and combination medications containing α-adrenergic agonists, such as tetrahydrozoline (Visine®, Octilia®), are common. These medications are not recommended for individuals with drug hypersensitivity, angle-closure glaucoma, severe cardiovascular diseases (such as coronary artery disease, arterial hypertension, pheochromocytoma), or metabolic disorders (like hyperthyroidism and diabetes mellitus), nor for children younger than 5 years of age.

Possible systemic adverse effects from this group of medications may include [10,26]:
- Tachycardia
- Headache
- Increased fatigue and sweating
- Elevated blood pressure
- Hyperglycemia

Occasionally, an adverse effect of corticosteroids, such as dexamethasone sodium phosphate, hydrocortisone acetate, or prednisolone acetate, may become a beneficial therapeutic effect. For instance, long-term use of corticosteroid eye drops may delay the spontaneous remission of pulmonary sarcoidosis [27].

5. Anti-infective Drugs Anti-infective medications used in ophthalmology include antiseptics, sulfonamides, antibiotics, antifungal agents, and antiviral drugs. Standard contraindications for most topical anti-infective medications include hypersensitivity and age under 1 year. All drugs used in anti-infective ophthalmic therapy (ointments, drops, gels) can cause severe allergic reactions and should be managed like any other systemic allergic reaction. Common antiseptics include boric acid, chlorhexidine digluconate, polyhexanide, povidone-iodine, and silver nitrate (Credé's drops) [28]. Anti-infective drugs may show the following adverse effects:
- Heart Rhythm Changes:There is a potential prolongation of the QT interval, which can lead to a potentially fatal irregular heart rhythm. Although this risk is very rare, it increases when combined with other medications that also affect heart rhythm.
- Heart Valve Issues: A slight increase in the risk of heart valve regurgitation has been observed. It is advisable to conduct a careful risk-benefit assessment for patients who may be at risk.
- Allergic Reactions: Patients may experience hives, rashes, swelling of the face, throat, or tongue, and difficulty breathing.
- Hypoglycemia/Hyperglycemia: Disturbances in blood sugar levels may occur, particularly in diabetic patients.
- Photosensitivity: Some individuals may experience an exaggerated sunburn reaction after exposure to sunlight.
- Unpleasant Taste: Patients might experience a bad or metallic taste in their mouth due to the drops draining into the nasopharynx.

6. Diagnostic Agents and Surgical Preparations Sodium fluorescein is used systemically for fluorescein angiography of the retinal vessels, optic nerve, and anterior segment of the

eye, as well as for detecting corneal epithelial defects. However, its use is contraindicated in patients with kidney disease or hypersensitivity to any of its components. When fluorescein is administered, possible adverse effects may include nausea, vomiting, brief fainting, and allergic reactions (e.g., urticaria, itching). Most of these reactions resolve on their own. In cases of severe allergic reactions, desensitization therapy may be necessary. After fluorescein administration, transient yellow discoloration of the skin and mucous membranes may occur within 6–12 hours, and urine discoloration may occur within 24–36 hours [29].

III Systemic drug adverse effects on the eye. The eye's sensitivity to medications, even those not targeted at the visual system, can be attributed to several factors. The visual apparatus comprises tissues from different origins, has a relatively small mass, and is characterized by rich vascularization [6]. Tissues such as the retina and optic nerve exhibit very high metabolic activity. These factors underscore the importance of evaluating ophthalmologists' reported symptoms in relation to the medications the patient has received [6,30,31,32,33].

Some drug reactions present with ocular symptoms typical of allergic responses, including redness, itching, scleral injection/hyperemia, and lacrimation. Though any drug can cause such reactions, they are more frequently associated with known allergens, such as penicillin antibiotics, vitamins, and nonsteroidal anti-inflammatory drugs (NSAIDs). Individuals with an atopic constitution are more prone to these reactions, which may occur alongside seasonal allergy symptoms. Patients often recognize the source of their allergic reactions [34,35,36,37].

Another type of reaction involves nonspecific systemic effects of medications, where the eye may become a locus minoris resistance, resulting in pronounced manifestations in ocular structures [32 ,33,38]. Such reactions may include dry eyes, blurred or double vision, excessive tearing, or photophobia [6,29,39,40,41]. In cases of acute onset of these symptoms, it is important to assess whether the patient is taking any of the following medications:

1. Contraceptives: Some contraceptives with antimineralocorticoid activity can cause dry eyes. Hence, this potential side effect should be considered for women of reproductive age when evaluating oral contraceptive use [30].
2. Antihistamines: First-generation antihistamines may lead to dry eyes, redness, burning, blurred vision, light sensitivity, and, in some cases, excessive tearing in susceptible individuals. Similar symptoms can arise from vasoconstrictive cold medications like phenylephrine, often found in combination products [37].
3. Antihypertensive Drugs: Dry eyes are commonly reported with many antihypertensive agents, particularly beta-blockers and diuretics. This side effect is especially prevalent among elderly patients undergoing antihypertensive therapy who already have existing ocular conditions. As discontinuation of such treatment is generally not an option, artificial tears may be used to alleviate symptoms. Additionally, color perception changes, myopia, and blurred vision can occur during diuretic therapy [35].
4. Antibiotics and Antimicrobial Agents: Adverse effects in this category may include visual disturbances, burning sensations in the eyes, and sometimes increased light sensitivity. Typically, these symptoms resolve after completing the course of antibiotics. If photophobia arises, patients are advised to wear high-quality sunglasses and avoid excessive visual strain. For instance, ethambutol, an antituberculosis medication, may increase light sensitivity due to functional changes in the optic nerve; however, these changes are usually reversible [30,37].

Certain medications are known to induce significant ocular adverse effects (Table 1). For example, aminoquinolines can cause a characteristic bull's-eye maculopathy. Phenothiazines can bind to melanin granules, leading to severe phototoxic retinopathy. Tamoxifen use may result in crystalline deposits in the inner retina. Patients on long-term retinoid therapy may experience decreased night vision and abnormal dark adaptation. Long-term use of linezolid may lead to optic neuropathy, presenting as a swollen or pale optic disc, symmetric painless decrease in visual acuity and color vision, and bilateral visual field defects. There is a probable association between amiodarone and a type of bilateral optic neuropathy similar to nonarteritic ischemic optic neuropathy (NAION) [42].

The most common adverse effects of cGMP-specific phosphodiesterase type 5 inhibitors (erectile dysfunction medications) include changes in color perception, blurred vision, and increased light sensitivity; these drugs have also been implicated in the development of NAION. A bilateral, retrobulbar optic neuropathy, characterized by loss of visual acuity, color vision deficits, and visual field defects, has been associated with ethambutol use. A wide variety of medications can cause similar ocular adverse reactions, and conversely, a single medication can affect multiple ocular structures, resulting in various clinically recognizable disorders. Clinicians should remain vigilant for drug-induced ocular disorders, whether or not they are listed in product package inserts, and consult an ophthalmologist if any uncertainties arise [43].

5. Antiarrhythmics: Certain medications, such as amiodarone, may cause microdeposits on the anterior surface of the cornea. While this usually does not affect vision, rare cases may result in blurred vision or colored halos around light sources. These adverse effects typically resolve after discontinuing the medication; however, their occurrence necessitates medical evaluation [36,42].

6. Pain Medications (NSAIDs): In rare instances, frequent use of NSAIDs, such as those containing acetylsalicylic acid, diclofenac, or ibuprofen, may lead to blurred or double vision. Additionally, some analgesics can induce pupillary constriction, potentially worsening night vision. In such cases, switching to an alternative medication may be beneficial [30,33,44].

7. Vaccines : Reports of ocular adverse effects have also emerged in connection with the COVID-19 pandemic For the Sputnik V vaccine, photophobia has been reported in the product information [45].

Certain medications can have specific effects on ocular structures. When such drugs are administered-especially over prolonged periods-regular ophthalmologic monitoring is essential. Long-term use of corticosteroid-containing drugs can lead to several ocular changes, including increased intraocular pressure, which may worsen or result in the development of glaucoma, and subsequent optic nerve damage. These drugs can also heighten the risk of cataract formation [6]. Amiodarone may cause blurred vision and has been associated with ischemic optic neuropathy. Patients have reported experiencing halos around lights or decreased vision following amiodarone use [42].

Doxazosin can commonly cause impaired color perception, and on rare occasions, atonic iris syndrome has been reported. Terazosin often results in reduced visual acuity, impaired color perception, and, less frequently, conjunctivitis. When tamsulosin is used during cataract or glaucoma surgery, intraoperative iris instability (intraoperative floppy iris syndrome, IFIS) has been reported. Thus, it is crucial to clarify the use of these medications when planning ophthalmologic surgery for men [46].

Typical neuroleptics have a broad range of ocular impacts due to their neurotropic effects. The most common ocular side effects associated with chlorpromazine include epithelial keratopathy, pigmentation of the eyelids and interpalpebral conjunctiva, corneal and lens opacities, retinopathy, and reduced accommodation. The incidence of these adverse effects increases with higher doses and prolonged use (greater than 300 mg/day for periods longer than 3 years) [39,47]. Generally, these changes do not lead to vision reduction and tend to resolve completely or partially after discontinuation of the drug. A rarer and more severe complication of chlorpromazine therapy, noted in individual clinical case reports, is secondary corneal edema caused by phototoxic lysis of corneal endothelial cells. In such cases, vision may not be restored, making the timely discontinuation of the drug essential. Thioridazine, when used at high doses for extended periods, can often cause lens opacities (cataracts) and retinopathy, with retinal toxicity typically occurring at doses of 800 mg/day or higher [48,49].

Among atypical neuroleptics, the ocular side effects of clozapine have been most extensively studied. Its use can lead to dry eye symptoms and other ocular complications [47].

Common complications associated with the anticholinergic effects of tricyclic antidepressants (TCAs) include mydriasis (pupil dilation), cycloplegia (loss of accommodation), reduced tear production, and photophobia (sensitivity to light). These complications may resolve spontaneously over time. If symptoms persist, a 0.5% pilocarpine solution may be prescribed. Additionally, wearing tinted or photochromic lenses can help alleviate patient discomfort. TCAs can trigger acute closed-angle glaucoma (CAG) in individuals who are predisposed to this condition. Therefore, it is important to consider CAG risk factors when prescribing these medications. Risk factors include Mongoloid race, narrow anterior chamber angle, shallow anterior chamber depth, nanophthalmos, previous angle closure in the fellow eye, advanced age, family history, and female sex [39,47].

Selective serotonin reuptake inhibitors (SSRIs) are usually preferred over older antidepressants because they have fewer adverse effects while maintaining similar efficacy. The most common ocular adverse effect associated with SSRIs is mydriasis. This can lead to vision-threatening complications, such as acute angle-closure glaucoma (CAG), in predisposed individuals. Additional ophthalmological evaluation is recommended for patients taking SSRIs who have risk factors for CAG [39,47].

Immunotherapy and Anticancer Drugs: This category of drugs is used to treat autoimmune diseases and includes monoclonal antibodies, cytokine inhibitors, and antitumor agents. The range of potential adverse effects is related to their impact on metabolism and rreparative processes. If retinal or ocular adnexal damage or uveitis develops in patients undergoing treatment for immunological or malignant conditions, the cause may be the ongoing therapy. Biologic therapy can induce a wide spectrum of ocular adverse effects, ranging from dry eye symptoms to severe complications that can lead to ocular morbidity and vision loss, such as uveitis, central retinal artery occlusion (CRAO), and branch retinal vein occlusion (BRVO) [50,51].

All patients receiving biologic therapy should have an ophthalmologic examination before starting treatment, followed by monitoring every 4 to 6 months during therapy and a final evaluation at the end of treatment. Patients on biologic therapy who experience ocular complaints should be urgently referred for ophthalmologic consultation to enable early identification and potential treatment. In such cases, symptomatic therapy may be prescribed, such as artificial tears or autologous tears. Ongoing ophthalmological observation is recommended, alongside a collaborative clinical management plan developed with a clinical pharmacologist and a clinical transfusiologist [50,51,52,53,54].

Ocular changes can also be caused by antiepileptic drugs. For example, vigabatrin may lead to vision loss [55]. Topiramate (Topamax®) can cause angle-closure glaucoma shortly after treatment begins. In these cases, the medication should be discontinued promptly, as continued use may result in permanent vision loss [56].

Of serious clinical aspect are to keep in mind to serious adverse invents (Table 1):

Retinal Detachment

One of the most urgent ophthalmologic conditions is retinal detachment, which can be a serious adverse effect of fluoroquinolones. Fluoroquinolones interfere with collagen synthesis and the extracellular matrix, a mechanism that could potentially affect the connective tissues in the eye, increasing the risk of retinal detachment [57,58].

Cataract Development

Certain antidepressants, such as amitriptyline, may contribute to the development of cataracts, considered a serious ocular adverse effect. Several mechanisms may explain the positive association between antidepressant use and cataract risk. In animal models, serotonin has been shown to play a crucial role in lens transparency. Elevated serotonin levels have been linked to lens opacity in rats. Furthermore, cataract and glaucoma patients also exhibited increased serotonin levels in their aqueous humor. It has been reported that serotonin receptors (5-HT1A, 5-HT2A/2C, and 5-HT7) are present in the crystalline lens and participate in the regulation of intraocular pressure (IOP) homeostasis. Increased IOP can contribute to glaucoma, a known risk factor for cataract formation. The use of tricyclic antidepressants (TCAs) is associated with photosensitivity to ultraviolet or sunlight, which has been suggested to relate to cortical cataracts. Additionally, TCAs inhibit norepinephrine uptake, which may also have cataractogenic properties [59,60].

Ophthalmic adverse effects of Herbal Medications

Herbal medications represent a $60 billion industry worldwide, with the United States accounting for $20 billion of that. „Essentially, half of the population uses some form of nutritional supplement or herbal medicine, and among those, many don't inform their doctors because they believe it's not relevant", explains

Side effect	Drugs
Retinal detachment	Antibiotics (Fluoroquinolones)
Uveitis	Checkpoint inhibitors, BRAF inhibitors, Rifabutin, Cidofour, Latanoprost (prostaglandin analog), Bisphosphonates (Fosamax)
Crystaline retinopathy	Talc, Ritonavir, Tamoxifen, Canthaxanthine, Methoxyflurane, Nitrofurantoin, Fludarabine
Cystoid Macular Edema	Epinephrin, Nicotin acid, antimicrotubule agent, Fingolimod, Imatinib, Glitazones, Trastuzumab
Papillaredema	Tetracycline (Minocycline)
Ischemic optic neuropathy	Sildenafil citrate (Viagra) and tadalafil (Cialis)
Vascular demage	Alkylating agents, talk, oral contraceptives, aminoglycosides (intraocular), Vankomycin (intraocular), interferon, tacrolimus, Gemcitabin, Metamphetamine, Cocain, Ergot alkaloides, Phenylpropanolamine
Disruption of the retina and retinal pigment epithelium	Chloroquine derivates, Phenotiazines, Pentosan polysulfate sodium, MEK inhibitors, FGFR inhibitors, Quinine sulfate, Clofazimine, Dedeoxylnosine (DDI) Deferoxamine, Ritonavir, Alilating agents, Cortikosteroides, Potasium or Sodium iodate, Denileuken diftitiox
Scleritis	Bisphosphonates (Fosamax)
Blindness	Antiepileptic (Phenytoin)
Dry eye	Antibiotics (synthetic penicillins, isotretinoin), anticancer drugs, immunotherapy, antidepressants (amitriptyline, SSRIs), antipsychotics (lithium), antihistamines, beta-blockers (metoprolol), diuretics, H2 blockers, proton pump inhibitors (PPIs), hormones (contraceptive preparations, hormone replacement therapy), antivirals (ganciclovir), NSAIDs (ibuprofen)
Night blidness	Antipsychotics (thioridazine, chlorpromazine)
Cataract	Antidepressives (amitriptilin), antiviral drugs (ganciklovir), corticosteroidi (prednisolon)
Pseudotumor cerebri in children	Hormones (levothyroxine)
Intraoperative floppy iris syndrome	Alpha-1 Blockers (Tamsulosin)
MIscelaneous	Sulfa Derivatives, Cardiac Glycosides, Methanol, Phosphodiesterase-5 (PDE5) Inhibitors, Alkyl nitrites, ALK inhibitors

Table 1. Ophthalmic Side Effects Associated with Various Drugs

Dr. Fraunfelder. „However, these medications can indeed be relevant, as they may interact with prescription medications that the patient is already taking. For example, ginkgo biloba can prolong bleeding time, which increases the risk of bleeding in individuals on blood thinners". Dr. Fraunfelder also mentions that black licorice can have ocular side effects, leading to migraine headaches and visual disturbances, such as scintillating scotomas. Additionally, canthaxanthin, which is often taken orally as a tanning agent and used as a coloring in certain foods, can deposit small crystals in the retina, affecting electroretinogram readings [61].

CONCLUSION

The reporting and monitoring of adverse events reflect the seriousness of a healthcare system.

A characteristic feature of the pharmacodynamics of ophthalmic dosage forms is the selectivity of their action on the visual organ and their low systemic reabsorption. It is essential for ophthalmologists to be aware of the potential systemic effects and contraindications of ophthalmic agents to minimize complications. The list of medications provided should not be considered exhaustive or conclusive.

Systemic side effects are adverse effects of a medication or substance that impact the entire body or multiple organ systems, rather than being limited to the area of contact or administration. These effects occur because the substance is absorbed and distributed throughout the body via the bloodstream. Examples include fatigue, nausea, hair loss, and fluctuations in blood sugar levels.

The most common ocular adverse effect of systemic medications is dry eye, which can be caused by antidepressants, antihistamines, beta-blockers, diuretics, H2 blockers, proton pump inhibitors (PPIs), hormones (including contraceptive preparations and hormone replacement therapy), and isotretinoin (used for acne). One of the most urgent ophthalmologic conditions is retinal detachment, which can be a serious adverse effect of fluoroquinolones.

Ophthalmic complications are typically transient and often resolve after the discontinuation of the therapy that caused them. The most serious adverse events are associated with neurotropic (neuroleptic), immunotropic, and antitumor medications (including chemotherapy). These treatments are frequently administered for severe conditions, are difficult to discontinue, and are typically long-term. Thus, when prescribing these medications, it is crucial to assess the associated risks and to monitor ophthalmic complications during treatment. All ophthalmic manifestations should be evaluated, taking into account the patient's medication history.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Neželjeni efekti lokalnih i sistemskih lekova na zdravlje oka

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KRATAK SADRŽAJ

Uvod: Lekovi mogu izazvati i lokalne i sistemske neželjene efekte. Oblast oftalmologije obuhvata niz medicinskih intervencija koje se izvode u relativno malom anatomskom prostoru, često uključujući više lekova. Ovo predstavlja izazove u praćenju neželjenih efekata lekova, jer oni mogu izazvati i lokalne i sistemske neželjene efekte. S obzirom na to da pacijenti često imaju komorbiditete, tačna procena uzročnosti neželjenih efekata zahteva tim iskusnih lekara.
Tema: Ovaj rad istražuje tri različita puta povezana sa efektima lekova na zdravlje oka: I. Lokalni efekti lokalno primenjenih lekova; II. Sistemski efekti lokalnih oftalmoloških lekova; III. Efekti sistemskih lekova na očne strukture. U skladu sa ovom podelom, rad navodi i analizira neželjene efekte lekova u okviru oftalmologije.
Zaključak: Sistemski neželjeni efekti lokalnih očnih lekova su neželjeni efekti leka ili supstance koji utiču na celo telo ili više organskih sistema, a ne da su ograničeni na područje kontakta ili primene. Ovi efekti se javljaju zato što se supstanca apsorbuje i distribuira po celom telu putem krvotoka. Primeri uključuju umor, mučninu, gubitak kose i fluktuacije nivoa šećera u krvi.

Najčešći očni neželjeni efekat sistemskih lekova je suvoća očiju, koju mogu izazvati antidepresivi, antihistaminici, beta-blokatori, diuretici, H2 blokatori, inhibitori protonske pumpe, hormoni (uključujući kontraceptive i hormonsku substitucionu terapiju) i izotretinoin (koristi se za akne). Jedno od najhitnijih oftalmoloških stanja je ablacija mrežnjače, što može biti ozbiljan neželjeni efekat fluorokinolona. Oftalmološke komplikacije sistemskih lekova su obično prolazne i često se povlače nakon prekida terapije koja ih je izazvala. Najozbiljniji neželjeni efekti povezani su sa neurotropnim (neuroleptičkim), imunotropnim i antitumorskim lekovima (uključujući hemoterapiju). Ove terapije se koriste za ozbiljna medicinska stanja, rizično ih je prekinuti i obično su dugotrajni. Stoga je prilikom propisivanja ovih lekova neophodno proceniti rizik I dobit i pratiti oftalmološke komplikacije tokom lečenja.

Spisak lokalno primenjenih lekova za oči ili sistemskih lekova koji imaju negativne efekte na zdravlje očiju ne treba smatrati iscrpnim ili konačnim. Prema rečima dr Srđana Đanija Markovića, ukratko, izveštavanje, praćenje i analiza neželjenih reakcija na lekove odražava ozbiljnost zdravstvenog sistema.

Ključne reči: neželjena dejstva u oftalmologiji, lokalna neželjena dejstva, sistemska neželjena dejstva, oko, toksičnost za oko, oftalmologija

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