# RATIONAL USE OF OPHTHALMIC MEDICATIONS IN PRIMARY CARE: AN APPROACH FOR GENERAL PRACTITIONERS ON PHARMACOKINETICS, IATROGENESIS, AND PRESCRIPTIVE SAFETY

# USO RACIONAL DE MEDICAMENTOS OFTÁLMICOS NA ATENÇÃO PRIMÁRIA: UMA ABORDAGEM PARA O MÉDICO GENERALISTA SOBRE FARMACOCINÉTICA, IATROGENIA E SEGURANÇA PRESCRITIVA

# USO RACIONAL DE MEDICAMENTOS OFTÁLMICOS EN LA ATENCIÓN PRIMARIA: UN ENFOQUE PARA EL MÉDICO GENERALISTA SOBRE FARMACOCINÉTICA, IATROGENIA Y SEGURIDAD PRESCRIPTIVA

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## ABSTRACT

**Introduction:** Self-medication in Brazil represents an endemic public health problem, within which topical ophthalmic medications (eye drops) occupy a critical position. Frequently underestimated as mere visual hygiene solutions and widely marketed as over-the-counter products, eye drops are highly potent medications. Their route of administration allows rapid bypass of first-pass hepatic metabolism through nasolacrimal drainage, resulting in systemic bioavailability capable of inducing clinically relevant cardiovascular and respiratory effects in susceptible patients.

**Objective:** This chapter aims to deconstruct the fallacy of the harmlessness of eye drops and to equip the general practitioner, the principal gatekeeper of the healthcare system, for the prevention, identification, and management of ocular and systemic iatrogenic events resulting from the irrational use of these formulations. It also seeks to enable recognition of patients undergoing advanced ophthalmologic treatments (intravitreal injections, sustained-release implants, and prescribed therapies for dry eye disease) who may present to primary care with complications.

**Development:** The chapter details the pharmacokinetics of the ocular surface and examines the main therapeutic classes. It discusses the deleterious potential of indiscriminate corticosteroid use (inducing steroid-induced glaucoma and cataracts), topical vasoconstrictors, and empirical antibiotics. At the systemic level, it explores the inadvertent toxicity of ophthalmic beta-blockers. It further addresses in depth the toxicity of benzalkonium chloride (BAK) and the transition toward preservative-free formulations, while dedicating a specific section to patients undergoing highly complex ophthalmologic treatments and how the general practitioner should approach them.

**Final Considerations:** Mitigating morbidity associated with ophthalmic medications requires the general practitioner to adopt an active approach: rigorous inclusion of ophthalmic


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formulations in medication reconciliation, patient health literacy initiatives (including punctal occlusion technique), recognition of warning signs requiring immediate ophthalmologic referral, and pharmacovigilance reporting of detected systemic adverse reactions.

**Keywords:** Self-medication. Ophthalmic Preparations. Rational Use of Medicines. Pharmacokinetics. Primary Health Care. Glaucoma. Iatrogenic Disease.

**RESUMO**

**Introdução:** A automedicação no Brasil é um problema endêmico de saúde pública, cenário no qual os medicamentos oftálmicos tópicos (colírios) ocupam uma posição crítica. Frequentemente subestimados como meras soluções de higiene visual e amplamente comercializados isentos de prescrição, os colírios são fármacos de alta potência. Sua via de administração permite rápida evasão do metabolismo de primeira passagem hepática através da drenagem nasolacrimal, com biodisponibilidade sistêmica capaz de induzir efeitos cardiovasculares e respiratórios clinicamente relevantes em pacientes susceptíveis. **Objetivo:** Este capítulo visa desconstruir a falácia da inocuidade dos colírios e instrumentalizar o médico generalista, principal gatekeeper do sistema de saúde, para a prevenção, identificação e manejo de iatrogenias oculares e sistêmicas decorrentes do uso irracional dessas formulações, bem como para reconhecer os pacientes em uso de tratamentos oftalmológicos avançados (injeções intravítreas, implantes de liberação prolongada, terapias para olho seco prescritas) que possam apresentar-se na atenção primária com complicações.

**Desenvolvimento:** A obra detalha a farmacocinética da superfície ocular e destrincha as principais classes terapêuticas. Discute o potencial deletério do uso indiscriminado de corticosteroides (indutores de glaucoma cortisônico e catarata), vasoconstritores tópicos e antibióticos empíricos. Em nível sistêmico, explora a toxicidade inadvertida de betabloqueadores oftálmicos. Aborda em profundidade a toxicidade do cloreto de benzalcônio (BAK) e a transição para formulações sem conservantes, e dedica seção própria ao paciente que faz tratamentos oftalmológicos de alta complexidade e como o generalista deve abordá-lo.

**Considerações finais:** A mitigação da morbidade associada aos medicamentos oftálmicos exige que o generalista adote postura ativa: inclusão rigorosa de formulações oftálmicas na reconciliação medicamentosa, letramento em saúde do paciente (técnica de oclusão do ponto lacrimal), reconhecimento de sinais de alarme para referenciamento oftalmológico imediato, e notificação farmacovigilante de reações adversas sistêmicas detectadas.

**Palavras-chave:** Automedicação. Preparações Oftálmicas. Uso Racional de Medicamentos. Farmacocinética. Atenção Primária à Saúde. Glaucoma. Doença Iatrogênica.

**RESUMEN**

**Introducción:** La automedicación en Brasil constituye un problema endémico de salud pública, escenario en el cual los medicamentos oftálmicos tópicos (colirios) ocupan una posición crítica. Frecuentemente subestimados como meras soluciones de higiene visual y ampliamente comercializados sin prescripción médica, los colirios son fármacos de alta potencia. Su vía de administración permite una rápida evasión del metabolismo hepático de primer paso a través del drenaje nasolagrimal, con una biodisponibilidad sistémica capaz de inducir efectos cardiovasculares y respiratorios clínicamente relevantes en pacientes susceptibles.

**Objetivo:** Este capítulo tiene como finalidad deconstruir la falacia de la inocuidad de los colirios y capacitar al médico generalista, principal gatekeeper del sistema de salud, para la prevención, identificación y manejo de iatrogenias oculares y sistémicas derivadas del uso irracional de estas formulaciones. Asimismo, busca reconocer a los pacientes en tratamiento oftalmológico avanzado (inyecciones intravítreas, implantes de liberación prolongada y terapias prescritas para ojo seco) que puedan presentarse en la atención primaria con complicaciones.

**Desarrollo:** La obra detalla la farmacocinética de la superficie ocular y analiza las principales clases terapéuticas. Se discute el potencial deletéreo del uso indiscriminado de corticosteroides (inductores de glaucoma cortisónico y cataratas), vasoconstrictores tópicos y antibióticos empíricos. A nivel sistémico, se explora la toxicidad inadvertida de los betabloqueadores oftálmicos. También se aborda en profundidad la toxicidad del cloruro de benzalconio (BAK) y la transición hacia formulaciones sin conservantes, dedicando además una sección específica al paciente sometido a tratamientos oftalmológicos de alta complejidad y a la manera en que el médico generalista debe abordarlo.

**Consideraciones finales:** La mitigación de la morbilidad asociada a los medicamentos oftálmicos exige que el médico generalista adopte una postura activa: inclusión rigurosa de las formulaciones oftálmicas en la conciliación medicamentosa, alfabetización en salud del paciente (técnica de oclusión del punto lagrimal), reconocimiento de signos de alarma para derivación oftalmológica inmediata y notificación farmacovigilante de reacciones adversas sistémicas detectadas.

**Palabras clave:** Automedicación. Preparaciones Oftálmicas. Uso Racional de Medicamentos. Farmacocinética. Atención Primaria de Salud. Glaucoma. Enfermedad Iatrogénica.

## 1 INTRODUCTION

Self-medication is a complex behavioral phenomenon and a public health challenge on a global scale, finding in Brazil a sociodemographic and regulatory ecosystem that catalyzes it. Data from the population-based survey of the National Survey on Access, Use and Promotion of the Rational Use of Medicines (PNAUM), as well as extensive systematic reviews, demonstrate the wide dissemination of this practice in the Brazilian adult population, especially for the management of acute diseases[1, 2]. Although self-care is encouraged by the World Health Organization (WHO) when restricted to over-the-counter drugs (OTC) that are duly indicated, the national reality is marked by lack of control. The ease of access at the pharmacy counter, the scarcity of health literacy, aggressive advertising, and the asymmetry in access to primary and specialized care transform this practice into a silent generator of morbidity and mortality[2, 3].

Within this vast and problematic panorama, topical ophthalmic medications, eye drops, occupy a peculiar and dangerous position. Historically, the false premise that eye drops are innocuous formulations, often equated with mere eye hygiene solutions, has been constructed in the popular imagination, and not infrequently in the perception of health professionals. The fact that they are administered in small vials, topically, creates the illusion that their action and toxicity are confined to the microenvironment of the eye. Consequently, the sharing of these medications among family members and the acquisition without professional guidance reach alarming prevalences, masking critical diagnoses and delaying appropriate therapeutic interventions.

However, this presumption of local confinement is a dangerous pharmacokinetic fallacy. The human eye interacts with tiny water volumes. Conjunctival fornix and tear film have physiological volumes of a maximum of 7 to 10 µL, while gout instilled in a standard commercial vial dispenses a volume between 30 and 50 µL[4]. This volumetric excess, associated with the eyelid reflex, directs approximately 80% of the drug to the nasolacrimal drainage system. When it reaches the nasal and pharyngeal mucous membranes, the active ingredient is absorbed by dense capillary beds, escaping hepatic first-pass metabolism[4]. In terms of systemic bioavailability, a fraction of ophthalmic drop reaches the circulation with kinetics similar to that of an intravenous administration.

The underestimation of this absorption route triggers iatrogenic events on two fronts: local and systemic. In the ocular microenvironment, the chronic and unsupervised use of corticosteroids, often used to treat nonspecific complaints of red eye, induces alterations in the extracellular matrix of the trabecular meshwork, increasing the resistance to the flow of aqueous humor and culminating in cortisonic glaucoma, a silent and irreversible optic

neuropathy[5, 6]. In addition, posterior subcapsular cataract and facilitation of fungal and herpetic ulcerative keratitis are added. From a systemic point of view, the impact is equally severe: topical vasoconstrictors (such as naphazoline) can trigger hypertensive crises and tachyarrhythmias, while ophthalmic beta-blockers (such as timolol), without proper tear point occlusion maneuvers, have been documented as a cause of profound bradycardia, atrioventricular blocks, and lethal bronchospasm in susceptible patients[4, 7].

In view of the anatomical-pharmacological complexity and the high potential for serious adverse events, this chapter is justified as a critical instrument for general practitioners. In Primary Care, in Emergency Care Units and in clinical wards, the generalist is the gatekeeper: routinely the first evaluator of acute ophthalmologic complaints, and the one responsible for elucidating cardiovascular or respiratory decompensations that may, in fact, be adverse drug reactions of ocular origin. Understanding eye drops as a high-potency systemic drug, identifying the red flags of each class, and intervening in the prescriptive cascade are non-negotiable skills. The chapter also dedicates a specific section to patients using advanced ophthalmologic treatments (intravitreal injections, extended-release implants, therapies prescribed for dry eye), which are increasingly present in primary care.

## 2 RATIONAL USE OF MEDICINES: CONCEPTUAL FRAMEWORK

The transition from a scenario of harmful self-medication to a safe prescriptive practice requires the understanding that the drug is a critical input, whose therapeutic value is inseparable from its inherent risk. To structure this premise, the World Health Organization (WHO), at the Nairobi Conference in 1985, coined the classic definition of the Rational Use of Medicines (RMU): the patient receives the appropriate medicine for his clinical need, in the correct dose, for an adequate period of time and at the lowest possible cost to himself and the community[8]. The application of this concept faces formidable barriers in fragmented health systems; It is estimated that more than half of the drugs prescribed, dispensed or sold globally are inadequate, and that half of patients fail to take them correctly[9].

In Brazil, the institutionalization of this precept gained normative force through the National Medicines Policy (PNM) and the creation of the National Committee for the Promotion of the Rational Use of Medicines (CNPURM), linked to the Ministry of Health. The CNPURM acts as an articulating instance that transcends mere market regulation, proposing guidelines that range from the continuing education of health professionals to the population's health literacy[10]. May 5 is established as the National Day for the Rational Use of Medicines, a time frame that serves as an annual alert on the impact of drug iatrogenesis, unmapped interactions, and antimicrobial resistance.

The technical-operational support for the guarantee of the URM rests on the National Health Surveillance Agency (Anvisa), whose role extends far beyond the registration of new molecules. The clinical approval phase (Phase III) occurs in tightly controlled environments, with homogeneous populations and often insufficient statistical power to detect rare or long-term adverse reactions. True safety validation occurs in Phase IV, in the real world, through pharmacovigilance. In Brazil, this activity is operated by the VigiMed system, Anvisa's platform for reporting adverse events by doctors, pharmacists and patients. The generalist is a central part of this ecosystem, as it often detects the first clinical sign of systemic toxicity not foreseen in the package insert.

By narrowing this conceptual framework to the reality of topical ocular formulations, a serious care gap is faced. Eye drops represent a real blind spot in URM promotion policies. During medication reconciliation, a critical step in hospital admission and primary care consultations, traditional anamnesis often fails to inquire about the use of ophthalmic solutions, and patients themselves omit this information because they do not categorize the eye drops as medication. This anamnestic silence prevents the identification of adverse events, underreports reactions to VigiMed, and perpetuates clinical myopia in relation to systemic risks. Promoting the rational use of eye drops requires, primarily, that the generalist rescues these medications from invisibility.

Clinical pearl

The question: Do you take any medication? it is insufficient. Replace in your anamnesis routine with: Do you use any eye drops, eye ointments, nose drops, patches or sprays? This simple reformulation detects omitted eye drops, nasal decongestants (with hypertensive risk analogous to that of ocular vasoconstrictor drops), nasal corticosteroids, and topical cutaneous with relevant systemic absorption.

## 3 OCULAR PHARMACOKINETICS AND SYSTEMIC ABSORPTION

To understand the magnitude of the systemic effects induced by eye drops, it is imperative to deconstruct the vision of the eye as an isolated compartment. The ocular surface is a highly specialized anatomical interface, designed to maintain homeostasis through a continuous renewal of the tear film and an extremely efficient drainage system. When a medicated drop is instilled, it abruptly subverts this fragile volumetric balance.

The inferior conjunctival fornix, the standard anatomical site for eye drop instillation, holds a maximum fluid volume between 7 and 10 µL. Due to physicochemical limitations of surface tension at the tip of commercial drippers, a standard droplet dispenses volume between 30 and 50 µL[4]. This immediate water surplus, which represents 3 to 5 times the

anatomical retention capacity, activates the eyelid reflex. During blinking, the contraction of the tear portion of the orbicularis muscle generates negative pressure in the tear sac, acting as a suction pump (tear pump).

Consequently, it is estimated that up to **80% of the volume of the administered drop** is rapidly pumped through the lacrimal canaliculi into the nasolacrimal duct, emptying into the lower meatus of the nasal cavity[4, 7]. The nasal mucosa and nasopharynx have a dense and highly permeable capillary bed: the drugs absorbed in this region reach the systemic circulation directly, completely escaping the hepatic portal system and **first-pass metabolism**.

## 3.1 THE TIMOLOL PARADIGM

The most emblematic clinical example of this pharmacokinetic route is the use of non-selective topical beta-blockers, such as timolol maleate, which are widely prescribed for the treatment of open-angle glaucoma. Each 50 µL drop of 0.5% solution contains approximately 0.25 mg timolol; One drop in each eye delivers about 0.5 mg to the patient[11]. Although the absolute amount is small when compared to the usual oral dose (10 to 20 mg), the fraction absorbed by the nasal mucosa reaches the systemic circulation in a manner analogous to an intravenous administration, escaping first-pass hepatic metabolism. Pharmacokinetic studies with topical timolol 0.5% document detectable plasma concentrations sufficient to induce clinically relevant systemic β-blocker effects in susceptible patients[11].

For the general practitioner, the non-recognition of this absorption route can be catastrophic. Blockade of cardiac β1-adrenergic receptors can induce severe sinus bradycardia, atrioventricular blocks, and syncope, often investigated as primary cardiovascular events of obscure etiology. At the same time, antagonism of β2-adrenergic receptors in the respiratory tract can trigger refractory and potentially lethal bronchospasm attacks in patients with asthma or chronic obstructive pulmonary disease (COPD)[7].

RED FLAG: investigate eye drops

Faced with any patient, especially the elderly, with unexplained bradycardia, syncope, new atrioventricular block, refractory bronchospasm, or COPD decompensation with no clear trigger, actively inquire about the use of glaucoma eye drops. Presentation may occur months or years after the start of treatment.

## 3.2 PRACTICAL GUIDANCE FOR RISK MITIGATION

The intervention of the non-ophthalmologist is based on simple but very high-impact prophylactic guidelines that radically alter the systemic bioavailability of the drug. Every

prescription or prescription renewal of eye drops must be accompanied by the teaching of the following techniques:

**Lacrimal point occlusion (OPL).** It is the most effective maneuver to prevent systemic toxicity. It consists of instructing the patient to, immediately after instillation of the droplet, lightly press the medial corner of the eye (over the lacrimal canaliculi) with the index finger for 2 to 3 minutes. Classic studies have shown that OPL substantially reduces systemic absorption, while increasing the contact time of the drug with the cornea, optimizing intraocular efficacy[12].

**Passive eyelid closure.** In conjunction with the OPL, the patient should keep the eyes closed gently (without squeezing the eyelids, which would activate the tear pump) for 3 minutes.

**Interval between eye drops.** When multiple eye drops are prescribed, immediate sequential instillation causes the *washout effect*, where the second drop expels the first into the nasolacrimal duct prior to corneal absorption. The general practitioner should advise a minimum interval of 5 minutes between the application of different medications[4].

## 4 CLASSES OF EYE DROPS: INDICATIONS, INAPPROPRIATE USE AND RISKS

Topical ophthalmic formulations encompass a broad pharmacological spectrum. For the general practitioner, the mastery of the primary indications of each class must invariably be accompanied by the understanding of its toxicity. The classes of most frequent use are detailed below, with emphasis on those most susceptible to irrational use. For the reader who wishes to delve deeper into drug-induced ocular toxicology, Fraunfelder's classic reference work brings together in consultation format the ocular and systemic toxicities associated with hundreds of ophthalmic and general-purpose molecules[35].

### 4.1 EYE LUBRICANTS (ARTIFICIAL TEARS)

The premise that artificial tears are innocuous and can be used *ad libitum* is one of the most dangerous fallacies in the management of Dry Eye Syndrome. Although the active ingredients (sodium hyaluronate, carboxymethylcellulose, hydroxypropyl methylcellulose, propylene glycol) are biologically inert, the real toxicological villain in multidose formulations lies in the vehicle: preservatives[13].

Benzalkonium chloride (BAK) is the most widely used preservative in the ophthalmic industry and is present in approximately **70% of topical formulations**[13]. It is a quaternary ammonium compound with a detergent mechanism of action: at concentrations of 0.05 to 0.1% it induces cell necrosis; in 0.01% it induces apoptosis. Commercial formulations use

BAK at 0.004 to 0.02%. Chronic use of BAK-containing lubricants disrupts the lipid layer of the tear film, induces **apoptosis of the goblet cells** of the conjunctiva (responsible for mucin secretion), and causes desquamation of the corneal epithelium[13]. A vicious cycle is thus created: the patient instills the eye drops to relieve dryness, but the preservative exacerbates the inflammation of the ocular surface, requiring increasingly frequent instillations, the **paradoxical iatrogenic dry eye**.

As an innovation and damage mitigation, the industry has transitioned to formulations with fast-dissipating oxidative preservatives (sodium perborate that breaks down into water and oxygen; stabilized oxychlor/Purite® complex that breaks down into chloride and oxygen; SofZia®, system with borates and zinc) or for vials with valved systems totally preservative-free (*preservative-free*), gold standard in chronic use[13, 14].

## 4.2 CLINICAL PEARL

Patients who need lubricant more than 4 times a day, which includes most patients with moderate to severe Dry Eye Syndrome, should be prescribed a preservative-free formulation (single-dose vial or multidose vial with valve/COMOD®/ABAK® system). The cost is higher, but the tolerability over the months is unmatched and the grip increases.

It is worth noting that comparative evidence between specific formulations of artificial tears is limited. The most recent Cochrane review on the topic (43 randomised controlled trials, 3,497 participants) rated the overall quality of the evidence as low, with substantial publication bias (18 additional trials with 2,079 participants were registered without disclosure of results), and did not establish clear superiority between formulations[15]. In practice, the choice is often based on individual tolerance, desired viscosity and, critically, the presence or absence of BAK.

## 4.3 VASOCONSTRICTORS

It is the most misused therapeutic class over the counter of Brazilian pharmacies. Topical vasoconstrictors (naphazoline, tetrahydrozoline, phenylephrine) are α-adrenergic agonists that promote rapid constriction of the conjunctival capillary network, resulting in immediate cosmetic whitening of red eye. The commercial appeal is based exclusively on the aesthetic effect, masking the underlying etiology, which can range from visual fatigue to acute uveitis[16].

The central risk of this class is the induction of **tachyphylaxis** and **rebound hyperemia** (conjunctivitis medicamentosa). Continued use leads to desensitization and *downregulation* of postsynaptic α-adrenergic receptors. When the effect of the drug ceases,

severe paradoxical vasodilation occurs, and the patient, chronically reddened by the medication itself, becomes clinically dependent on shorter and shorter instillations[16].

Systemic effects differ between agents. Imidazole derivatives (naphazoline, tetrahydrozoline, oxymetazoline) can cross the blood-brain barrier in children, causing severe central nervous system depression, bradycardia, hypothermia, and even coma; are formally contraindicated in pediatrics. Phenylephrine (pure α1-agonist) has hypertensive crisis and tachyarrhythmia as its main risk. Commercial combinations common in Brazil associate vasoconstrictor with antihistamine (e.g., nafazolin plus pheniramine), and their own package inserts carry explicit warnings for patients with narrow-angle glaucoma, cardiovascular disease, arterial hypertension and prostatic hyperplasia, comorbidities that are exactly prevalent in the elderly population that most consumes these products without guidance[17].

### 4.4 ANTI-ALLERGY DRUGS

The topical treatment of allergic conjunctivitis has evolved significantly, but conceptual confusion in pharmacies often pushes the allergic patient to vasoconstrictors. Historically, the arsenal relied only on pure antihistamines (short-acting H1 blockers) or mast cell stabilizers (sodium cromoglycate, which requires weeks of prophylactic use to achieve effectiveness)[18].

The class was revolutionized by dual-acting agents (olopatadine, ketotifen, alcaftadine, epinastin). These molecules act simultaneously as competitive H1 receptor antagonists (immediate relief of pruritus) and as mast cell membrane stabilisers (prevention of subsequent degranulation). For the generalist, identifying pruritus as a cardinal symptom of allergic etiology and directly prescribing a dual-action agent avoids the chronicity of the condition and keeps the patient away from iatrogenic self-medication with naphazoline[18].

### 4.5 TOPICAL ANTIBIOTICS

The empirical and indiscriminate prescription of ophthalmic antibiotics (aminoglycosides such as tobramycin and gentamicin; fluoroquinolones such as ciprofloxacin, moxifloxacin, and besifloxacin) in an empirical and indiscriminate manner is one of the major failures in primary care screening. The vast majority of acute community-based infectious conjunctivitis is of viral etiology, predominantly adenovirus, presenting with aqueous/mucoid secretion, preauricular lymph node enlargement, and self-limiting status in 1 to 2 weeks[19].

The differential diagnosis of conjunctivitis is feasible at the bedside and is summarized in Table 1.

**Table 1**

*Differential diagnosis of acute conjunctivitis: clinical presentation, secretion, associated symptoms and initial management*

| Type | Typical presentation | Secretion | Associated symptoms | Initial conduct |
|---|---|---|---|---|
| **Viral** (adenovirus) | Unilateral onset, progresses to the second eye in 1 to 5 days; epidemic context; Recent VAT. | Aqueous or mucoid. | Palpable preauricular lymph node; feeling of sand; mild photophobia. | Cold compresses, preservative-free tears, strict hand hygiene. No antibiotic. |
| **Bacterial** | Bilateral from the beginning; eyelids glued in the morning. | Purulent, thick, abundant. | No lymph node; little pain; preserved vision. | Most are self-limited within 5 to 7 days; topical antibiotic (fluoroquinolone or polymyxin plus trimethoprim) accelerates resolution. |
| **Hyperacute** (gonococcal) | Evolution in 12 to 24 h; sexually active young people; newborns. | Profuse, frankly purulent, explosive. | Significant eyelid edema; corneal perforation may be present. | Ophthalmic emergency. Forward immediately; systemic antibiotic therapy (ceftriaxone). |
| **Allergic** | Seasonal or perennial; bilateral; atopic history. | Mucoid, scarce. | **Pruritus is the cardinal symptom**; chemosis; eyelid edema. | Topical dual-action antihistamine; avoid scratching; To ward off allergens. |
| **Toxic/medicated** | Prolonged use of eye drops (BAK, vasoconstrictors). | Variable. | Persistent hyperemia; burning; paradoxical worsening. | Suspend the offending agent; preservative-free lubricant; reassess prescription. |

Source: prepared by the authors, based on references [19] and [32] and the AAO Preferred Practice Pattern for conjunctivitis (2024).

The irrational use of topical antibiotics not only exposes the ocular surface to direct toxicity (aminoglycosides are highly epitheliotoxic and slow corneal healing), but places ophthalmology at the center of the global breakdown of antimicrobial resistance. Surveillance studies such as ARMOR (Antibiotic Resistance Monitoring in Ocular Microorganisms) demonstrate alarming rates of *Staphylococcus aureus* strains (including MRSA) and *Staphylococcus epidermidis* of the periocular flora resistant to fourth-generation fluoroquinolones, making serious intraocular infections, such as post-surgical endophthalmitis or corneal ulcers, progressively untreatable[20].

### 4.6 RED FLAG: NEVER TREAT AS CONJUNCTIVITIS

The following findings exclude the diagnosis of simple conjunctivitis and require urgent ophthalmologic referral: decreased visual acuity, profound eye pain (not just superficial burning), intense photophobia, colored halos around lights, anisocoria, ciliary hyperemia (hyperemia close to the limbus, rather than diffuse), recent contact lens use with a red eye, trauma or chemical exposure, and history of previous ocular surgery. In either of these scenarios, empirical topical antibiotic masks the diagnosis and delays the vision-saving treatment.

## 5 TOPICAL CORTICOSTEROIDS: THE HEART OF THE CONCERNS

As anticipated in the Introduction, the inadvertent use of topical corticosteroids is the most documented cause of severe and irreversible ocular morbidity due to self-medication or reckless empirical prescription. This section, absent in earlier versions of this chapter, now occupies the place the theme deserves.

### 5.1 WHY CORTICOSTEROIDS WORK, AND WHY IT'S PART OF THE PROBLEM

Topical corticosteroids (dexamethasone, prednisolone, fluorometholone, loteprednol, difluprednate) are potent anti-inflammatory drugs, indispensable in the treatment of uveitis, intraocular surgeries, sterile keratitis, refractory severe allergic conjunctivitis, and various segmental inflammations. Its anti-inflammatory effect is so clinically evident, the eye turns white and the patient is comfortable in a few days, that it creates a cognitive trap: both patients and non-specialist professionals tend to perpetuate automatic prescriptions and renewals, without reevaluation.

Corticosteroids differ in relative potency and ability to elevate intraocular pressure (IOP). In descending order of hypertensive risk: difluprednat, dexamethasone, prednisolone, loteprednol, and fluorometholone. In generalist practice, the first action is to assume that **any patient in chronic use of any topical corticosteroid is at risk**, and that this risk is greater the more potent the agent.

### 5.2 CORTISONIC GLAUCOMA: SILENT NEUROPATHY

The mechanism of **cortisone glaucoma** is distinct from primary open-angle glaucoma. Corticosteroids induce changes in the trabecular meshwork: increased deposition of extracellular matrix (fibronectin, IV collagen, glycosaminoglycans), formation of *cross-linked actin networks* (CLAN), and decreased expression of metalloproteinases. The result

is increased resistance to aqueous humor flow, with **progressive and silent elevation of IOP**[5, 6].

The clinically decisive points for the generalist are: a) approximately 1/3 to 1/2 of the population is a responder to corticosteroids, with a significant increase in IOP with prolonged topical use; b) IOP elevation typically manifests between 2 and 6 weeks of continuous use, but may occur earlier in severe responders; c) cortisonic glaucoma is silent, the patient does not feel elevated IOP and the damage to the optic nerve, once installed, is irreversible; d) after corticosteroid discontinuation, IOP often normalizes within days to weeks, but the lost visual field does not return.

The package insert for prednisolone acetate 1%, the gold standard ophthalmic corticosteroid, is explicit in warning that prolonged use can result in glaucoma with damage to the optic nerve, visual acuity and visual field defects, and posterior subcapsular cataracts, and recommends that **if the product is used for 10 days or more, intraocular pressure should be routinely monitored**[21]. This recommendation should be taken as dogma by the generalist: no topical corticosteroid is benign after 10 days.

### 5.3 POSTERIOR SUBCAPSULAR CATARACT

The second major ocular effect of chronic topical corticosteroids is posterior subcapsular cataract, a central opacity that affects vision early, particularly for reading and bright light. Unlike senile (nuclear) cataracts, posterior subcapsular cataracts can compromise visual acuity with a few weeks to months of prolonged corticosteroid use. It is dose-dependent and relatively independent of the relative potency of the agent.

### 5.4 INFECTION FACILITATION: THE PITFALL OF MISDIAGNOSIS

Corticosteroids locally suppress the immune response, and this converts self-limiting infections into severe conditions. Three scenarios are worth mentioning:

**Herpetic keratitis.** Ocular herpes simplex (dendritic epithelial keratitis) is one of the absolute contraindications to topical corticosteroids alone. Administration of corticosteroids in a patient with undiagnosed dendrite may progress to severe stromal keratitis, desematocele, and perforation. Herpetic keratitis presents as a red eye with a foreign body sensation, corneal hypoesthesia, and the classic dendritic tree figure seen with fluorescein[21].

**Fungal keratitis.** In patients with a history of ocular trauma due to plant material (twig, leaf, soil) or contact lens wearers, corticosteroids without antifungals transform fungal

keratitis into a therapeutic disaster, with a prolonged clinical course and an outcome that is often blind.

***Acanthamoeba.*** In contact lens wearers with poor hygiene, especially exposure to tap water or swimming pools, *Acanthamoeba keratitis* can be treated initially as bacterial with associated corticosteroids, with progressive worsening.

RED FLAG: never prescribe without an ophthalmologist

Commercial combinations that associate corticosteroids with antibiotics (dexamethasone plus tobramycin, dexamethasone plus neomycin and polymyxin, prednisolone plus sulfacetamide) are widely sold in Brazil and widely misused. The generalist should not prescribe them empirically for red eye. The presence of the antibiotic does not protect against herpes, fungus or amoeba; on the contrary, it can mask the clinical worsening. Any prescription of eye drops with corticosteroids must be made or authorized by an ophthalmologist, with a defined plan of duration and reevaluation.

### 5.5 THE PATIENT WHO SELF-MEDICATES WITH CORTICOSTEROIDS

A recurring scenario in Brazil: a patient who once received a combined eye drop (corticosteroid plus antibiotic) for conjunctivitis, thought it worked well, and started to buy and use it repeatedly, without guidance. Years later, he presents with slowly progressive visual loss. Examination reveals advanced optic disc cavitation and significant visual field loss: **irreversible cortisonic glaucoma**.

The general practitioner can stop this cascade by simply actively asking, at any visit of a patient with chronic ocular complaint, about the use of eye drops and, specifically, about **which bottles the patient keeps at home and uses on their own**. Corticosteroid review and discontinuation, referral to an ophthalmologist for IOP measurement, fundoscopy, and campimetry are interventions that can preserve useful vision for the rest of the patient's life.

## 6 SELF-MEDICATION WITH EYE DROPS IN BRAZIL: SOCIOCULTURAL CONTEXT

Ophthalmic self-medication in Brazil is rooted in sociocultural and economic determinants. Although the National Survey on Access, Use, and Promotion of Rational Use of Medicines (PNAUM) does not isolate eye drops as a primary category in its consolidated reports, it is observed in Brazilian clinical practice that two groups are especially vulnerable to the irrational use of eye drops.

**The first group** is young and middle-aged adults with occupational complaints related to prolonged use of screens (Computer Vision Syndrome), who present asthenopia and compensatory hyperemia and spontaneously resort to topical vasoconstrictors for the

cosmetic appeal of eye whitening. **The second group** is the geriatric population, in which the physiological Dry Eye Syndrome of aging and glaucoma overlap with systemic polypharmacy. In this age group, the sharing of vials, the lending of medicines between spouses, family members or neighbors, is a common practice, subjecting the elderly to risks of toxicity by beta-blockers or corticosteroids not prescribed for them.

There is specific literature on the misuse of over-the-counter drugs in the elderly. A North American study with the elderly showed that more than 1/3 use at least one IPM, and that concomitant use with prescriptions or supplements is frequent, creating potential for interactions. Adverse events related to OTCs are implicated in emergency hospitalizations in this population, and misuse was characterized into four categories: related to age, interaction with other medications, worsening of existing conditions, and deviation from package insert instructions[22]. Although the study addresses MIPs in general, its conclusions apply directly to the ophthalmic setting, where lubricants, ocular decongestants, and antihistamine/vasoconstrictor combination products are classic examples of MIPs with the potential for misuse.

Two regulatory and commercial factors support this panorama in Brazil. The first is the classification of many ophthalmic formulations (simple lubricants and decongestants) as Over-the-Counter Drugs (OTC), according to Anvisa's Collegiate Board Resolution (RDC) No. 98/2016. The free disposal of these bottles on the shelves and counters of pharmacies, without a pharmacist barrier, creates a cognitive bias of zero risk. The second factor is advertising: advertising for eye decongestants aggressively focuses on whitening and immediate relief, omitting or minimizing the risks of rebound effect and systemic contraindications.

## 7 BENZALKONIUM CHLORIDE AND THE TRANSITION TO PRESERVATIVE-FREE FORMULATIONS

The topic of preservatives in eye drops deserves its own treatment in this chapter, given its specific relevance for patients with chronic use of ocular medication, especially glaucomatous medication, but also patients with Dry Eye Syndrome, who constitute a significant portion of elderly patients treated in primary care.

### 7.1 WHY BAK IS PROBLEMATIC

Benzalkonium chloride (BAK) is a quaternary ammonium molecule and the most widely used preservative in eye drops, present in **approximately 70% of topical formulations**[13]. There is an uncomfortable rule of thumb in this field: *the antimicrobial*

*efficacy of a preservative is inversely proportional to its safety for the ocular surface*. BAK is a cationic detergent that acts by altering the permeability of the cell membrane: at concentrations of 0.05 to 0.1% it induces necrosis, and at 0.01% it induces apoptosis. Commercial formulations use BAK in concentrations between 0.004 and 0.02%.

Why is BAK still so widely used? It's not just inertia. BAK increases the penetration of the active ingredient into the anterior chamber precisely because of its detergent properties, compromising the corneal barrier in order to facilitate the delivery of the drug. But this same commitment is what generates chronic toxicity.

The toxicological mechanisms described are threefold: detergent effect on the tear film (altering the outer lipid layer); direct toxic effect on the corneal and conjunctival epithelium (loss of goblet cells, squamous metaplasia, apoptosis); and immunoallergic effect. There is also a deeper mechanistic axis, mitochondrial: due to its cationic nature, BAK selectively interacts with mitochondria (the only negatively charged intracellular compartment), induces mitochondrial fragmentation and oxidative stress, and can inhibit mitochondrial function by more than 90%[13]. Mitochondrial dysfunction is now described as a contributor to ocular surface disease, age-associated corneal diseases, and normal corneal aging.

## 7.2 CLINICAL MAGNITUDE

The consistency of the literature is remarkable. The prevalence of ocular surface disease (OSD) among chronic glaucomatous patients on preserved topical therapy with BAK is reported to be between **30% and 70%,** compared with only 5% to 30% in adults of the same age without glaucoma[13]. The total dose of BAK, number of medications, drops per day, duration of therapy, correlates with the prevalence and severity of OSD.

Clinical manifestations in glaucomatous patients under BAK include pain and discomfort (burning, pruritus, foreign body sensation), paradoxical tearing, increased corneal and conjunctival staining by fluorescein, reduced tear film breakdown time (BUT), reduced Schirmer tear film breakage, increased punctate keratitis, and worsening OSDI (Ocular Surface Disease Index) scores. There are also surgical consequences: BAK-induced subepithelial inflammation and conjunctival fibrosis reduce the success of trabeculectomy (filtering surgery for glaucoma) and there is a higher rate of cataract surgery in eyes under prolonged hypotensive therapy[13].

## 7.3 THE SWITCH EVIDENCE: ODDONE STUDY 2024

A prospective, multicenter study conducted by Oddone et al. in 2024 provides the best recent evidence for the generalist. In 38 patients with open-angle glaucoma or ocular hypertension, using latanoprost with BAK and presenting with signs and symptoms of OSD, with uncontrolled IOP, switching to the fixed combination tafluprost plus timolol without preservative (PF-TTFC) resulted, after 3 months, in[23]:

a) reduction in mean 24-hour IOP from 17.8 mmHg (95% CI 17.1 to 18.6) to 15.3 mmHg (95% CI 14.6 to 16.1), $p < 0.001$;

b) better night control (-2.9 mmHg) than day control (-2.3 mmHg);

c) improvement of fluorescein corneal staining in 52.6% of the patients; worsening by only 10.5%;

d) improvement of conjunctival hyperemia in 63.3%; worsening by only 5.3%;

e) significant reduction in the mean size of corneal wing cells under in vivo confocal microscopy, with $p < 0.005$, suggesting recovery of the epithelium.

The study is particularly relevant because the effect combines additional pharmacological action (timolol) with the removal of BAK, and demonstrates that **the transition to PF does not compromise blood pressure control**, it may even improve it. Konstas et al., in a 2021 review, get straight to the point: ideally, future antiglaucomatous therapy should be 100% preservative-free, recognizing that cost, global availability, and the absence of long-term comparative studies limit this immediate transition[24].

## 7.4 PRACTICAL IMPLICATIONS FOR THE GENERALIST

The generalist does not replace the ophthalmologist in the management of glaucoma, but can, and should, intervene in the following situations: a) patient on polytherapy for glaucoma (2 or more eye drops) reporting burning, dryness, persistent hyperemia or intolerance: discuss with the ophthalmologist the possibility of migration to formulations without preservatives; b) patient with pre-existing Dry Eye Syndrome (Sjögren's, elderly, contact lens wearer) starting glaucoma eye drops: guide preservative-free formulation from the beginning; c) patient in the preoperative period of filtering surgery or cataract: reducing the burden of BAK can improve surgical outcomes; d) patients in chronic use of any eye drops (including lubricants) more than 4 times a day: prescribe a formulation without preservatives.

It is worth noting that even the classic timolol has a preservative-free version available in a single-dose vial; the pharmaceutical infrastructure for PF exists, and the remaining bottleneck is more economical and logistical than pharmacological[11, 31].

## 8 THE PATIENT USING ADVANCED OPHTHALMIC TREATMENTS

This section addresses a growing reality of primary care: patients who have specialized eye treatments, monthly intravitreal injections, extended-release implants, prescription dry eye therapies, frequently arrive at the generalist's office and the emergency room. The generalist does not need to be an expert in these treatments, but needs to recognize the patient, identify complications, conduct the initial approach, and refer appropriately.

### 8.1 THE PATIENT WHO HAS INTRAVITREAL INJECTIONS (ANTI-VEGF)

Intravitreal antiangiogenic agents (bevacizumab, ranibizumab, aflibercept, faricimab) have revolutionized the treatment of retinal diseases that until two decades ago were an important cause of blindness: age-related macular degeneration (AMD) in the neovascular form, diabetic macular edema, and retinal venous occlusion[25]. These patients, typically elderly people with diabetes or vascular disease, receive intravitreal injections on a monthly or bi-monthly basis for consecutive months or years. The sustained efficacy of aflibercept in neovascular AMD was demonstrated with maintenance of visual gain at 96 weeks in the VIEW 1 and VIEW 2 studies[34].

***What the generalist needs to recognize***

**Infective endophthalmitis** is the most devastating and most urgent complication of intravitreal injections. The reported incidence ranges from 0.01% to 0.26%, but the visual outcome is often catastrophic if treatment is delayed. The most common agents are coagulase-negative staphylococci (*S. epidermidis*) of the conjunctival flora and viridans streptococci of the oral flora[25].

RED FLAG: Same-day forwarding

Patient who has received intravitreal injection within the last 7 to 14 days and presents with:

a) decrease in visual acuity (even slight);

b) deep eye pain (not just superficial burning);

c) severe ocular hyperemia;

d) hypopyum (yellowish liquid level in the anterior chamber, visible to inspection);

must be referred on the same day to the ophthalmologist on duty. Treatment is intravitreal antibiotic injection or vitrectomy within hours. Not prescribing topical antibiotics in the ER delays diagnosis without treating the intraocular infection.

Other relevant complications include **retinal detachment** (up to 0.6%; may manifest as sudden perception of floaters, flashes of light, or dark curtain in the visual field); **vitreous**

**hemorrhage** (0.02% to 4.5%; suddenly blurry or opaque vision); and **acute IOP elevation** (usually self-limited, resolves within hours of anti-VEGF injection)[25].

***Systemic effects: what we know***

Intravitreal anti-VEGF targets the systemic circulation and reduces plasma VEGF. The literature on systemic effects is mixed: most large studies have not demonstrated a significant increase in cardiovascular events (infarction, stroke, thromboembolic events) in general populations, but signs of increased risk persist in subgroups, particularly in type 2 diabetics, in which a recent analysis associated anti-VEGF with a higher cumulative incidence of systemic adverse events at 5 years (37.0% vs 18.4%)[25]. For the generalist, the recommendation is clinical surveillance of blood pressure, cardiovascular and renal control in these patients, without reflex alarm.

**Clinical pearl**

**Do not discontinue anticoagulation or antiplatelet therapy for intravitreal injections without discussing with the ophthalmologist who is applying the treatment. The ocular hemorrhagic risk of the procedure is low and does not justify the interruption of the antithrombotic in patients with a firm cardiovascular indication, the interruption carries a substantial risk of thromboembolic event.**

## 8.2 THE PATIENT WITH AN EXTENDED-RELEASE INTRAOCULAR IMPLANT

Several extended-release ocular implants are now in clinical use in Brazil and worldwide, offering sustained therapy for months to years with a single application. The main ones include Ozurdex® (biodegradable dexamethasone, 6 months clearance) for diabetic macular edema, venous occlusion edema, and uveitis; Iluvien® (non-biodegradable fluocinolone, 36 months) for chronic diabetic macular edema; Yutiq® (fluocinolone, 36 months) for posterior uveitis; and Durysta® (biodegradable intracameral bimatoprost, 3 to 4 months) for glaucoma[26, 33].

For the generalist, two scenarios demand attention:

**Implant migration from Ozurdex to the anterior chamber.** In pseudophakic patients with compromised posterior capsule, the dexamethasone implant may migrate to the anterior chamber within the first few days after injection, causing acute corneal edema[27]. The patient presents with red eye, pain, blurriness and, on examination, the implant cylinder can be seen in the anterior chamber. **Refer immediately: early removal reduces the risk of permanent corneal decompensation.**

**Implant-induced cortisonic glaucoma.** Patients with Ozurdex, Iluvien, and Yutiq are at substantial risk of IOP elevation, intravitreal triamcinolone, a similar agent, elevates IOP

in up to 2/3 of patients[25]. IOP monitoring is the responsibility of the ophthalmologist, but the generalist who detects ocular hypertension in a patient with previous implantation must ensure that ophthalmologic follow-up is up to date.

### 8.3 THE PATIENT ON PRESCRIPTION DRY EYE THERAPY

Dry eye is a multifactorial ocular surface disease characterized by loss of tear film homeostasis, in which lacrimal hyperosmolarity, inflammation, ocular surface damage, and sensorineural abnormalities play etiological roles[28, 30]. The overall prevalence, considering symptoms, varies between 5% and 50% depending on the population. The tear film is structured in three layers (lipid, aqueous, mucinic), and the disease can be classified as aqueous deficient, evaporative (most common, linked to meibomian gland dysfunction) and mixed.

The patient with moderate to severe dry eye often receives staggered therapy that includes not only lubricants but also prescription anti-inflammatory agents such as cyclosporine 0.05% (Restasis®), cyclosporine 0.1% (Verkazia®/Ikervis®), and lifitegrast 0.5% (Xiidra®). These therapies need continuous use for months to achieve full effectiveness, and adherence is often compromised by burning sensation at the beginning of treatment, cost, and complexity of the regimen[28].

Clinical pearl

When seeing a patient using cyclosporine or topical lifitegrast referring to not being noticeable  Reinforcing adhesion and ensuring adequate concomitant lubrication (preferably preservative-free) is more useful than suggesting treatment change on your own.

Other interventions for dry eye that the patient may mention include **punctal plugs** (occluders of the tear canaliculi to increase the permanence of natural tears and eye drops), whose evidence of benefit is, according to Cochrane, limited, and whose relevant adverse events include epiphora (excessive tearing) in up to 82% of patients in some studies and spontaneous loss in up to 30%[29]; **warm compresses** and **intense pulsed light (IPL)** for meibomian dysfunction; and **autologous serum** in refractory cases.

## 9 STRATEGIES FOR RATIONAL USE AND THE ROLE OF THE GENERALIST

Reversing the irrationality in the use of eye drops requires a systemic approach, in which the general practitioner acts as the main *gatekeeper* of the patient's health. The strategies are divided into direct clinical actions and technological integrations.

## 9.1 MEDICATION RECONCILIATION AND HEALTH LITERACY

The most immediate change should occur in the anamnesis. The generalist should abandon the passive question (Do you take any medication?) and adopt active search: Do you use any eye drops, eye ointments, nose drops, patches or sprays?. When identifying the use, patient education should be incisive: explain the anatomy of nasolacrimal drainage and teach in person the Lacrimal Point Occlusion (OPL) technique and the need for a 5-minute interval between different vials.

## 9.2 PRESCRIPTIVE SECURITY

The prescription of eye drops does not allow for ambiguity. Generic prescriptions containing only 1 drop every 8 hours are unacceptable. The prescription must specify: a) laterality (OE, left eye; OD, right eye; AO, both eyes); b) the exact concentration of the solution; c) the duration of treatment, especially for antibiotics and corticosteroids, avoiding inadvertent continuous use; d) explicit guidelines on not touching the tip of the bottle on the eyelashes to avoid contamination of the reservoir.

## 9.3 TELEMEDICINE AS A SCREENING TOOL

The expansion of telemedicine in Primary Care offers a window of opportunity for red-eye complaints. Although fine diagnosis by slit lamp is impossible remotely, the physician can differentiate alarm signs that require immediate ophthalmological referral (sudden low visual acuity, profound eye pain, severe photophobia, colored halos, anisocoria, trauma, chemical exposure) from self-limited allergic or viral conditions that can be managed initially without antibiotics, preventing the patient from resorting to self-medication at the pharmacy.

## 9.4 ACTIVE PHARMACOVIGILANCE

The generalist is the front line of detection of systemic adverse drug reactions (ADRs) resulting from eye drops. In the face of refractory bradycardia in an elderly person (investigate the use of topical timolol), iatrogenic Cushing's syndrome (investigate abusive ocular corticosteroids) or herpetic keratitis in a patient with a history of previous use of combined corticosteroids, it is an ethical and epidemiological duty to notify Anvisa through the VigiMed platform. It is this data feed that allows the regulatory agency to issue health alerts and, eventually, reclassify the sales status of certain compounds.

**Summary table: ophthalmic therapeutic classes**

The following table consolidates, in a quick consultation format, the main classes of eye drops involved in irrational use, their predominant risks, and the expected conduct of the general practitioner.

**Table 2**

*Summary table of ophthalmic therapeutic classes: examples, local risk, systemic risk and practical conduct of the general practitioner*

| Class | Common examples | Local (ocular) risk | Main systemic risk | Practical conduct of the generalist |
|---|---|---|---|---|
| **Corticosteroids** | Dexamethasone, prednisolone, fluorometholone, loteprednol, difluprednate. | Cortisonic glaucoma (irreversible); posterior subcapsular cataract; masking of herpetic, fungal, and amoebic keratitis. | Suppression of the hypothalamic-pituitary-adrenal axis (rare, in chronic abusive use). | Never prescribe empirically for red eye. Every prescription authorized by an ophthalmologist. Monitor IOP if use longer than 10 days. |
| **Vasoconstrictors** | Naphazoline, phenylephrine, tetrahydrozoline, oxymetazoline. | Severe rebound effect (chronic hyperemia); conjunctivitis, drug-related. | Hypertensive crises and tachyarrhythmias (all); CNS depression in children (particularly imidazoles, contraindicated). | Investigate the underlying cause (allergy, dryness, visual fatigue). Discourage purely cosmetic use. |
| **Beta-blockers** | Timolol (treatment of glaucoma). | Dry eye, hyperemia, contact allergy. | Severe bradycardia, atrioventricular blocks, lethal bronchospasm (asthma/COPD). | To investigate use in older people with syncope or unexplained bradycardia. Teach OPL technique. |
| **Antibiotics** | Tobramycin, ciprofloxacin, moxifloxacin, gentamicin. | Corneal epithelial toxicity, delayed healing. | Promotion of antimicrobial resistance (One Health concept). | Avoid empirical prescription for watery secretions (viral suspicion). Restrict to purulent frames with defined criteria. |
| **Lubricants (with preservatives)** | Benzalkonium chloride (BAK) formulas. | Tear film rupture, epithelial cell apoptosis, exacerbation of Dry Eye Syndrome. | Null systemic relevance. | For chronic use (more than 4 times/day), prescribe a preservative-free formulation (without preservatives). |

| Class | Common examples | Local (ocular) risk | Main systemic risk | Practical conduct of the generalist |
|---|---|---|---|---|
| **Prostaglandin analogues** | Latanoprost, bimatoprost, travoprost, tafluprost. | Irreversible darkening of the iris; eyelash growth; periorbital fat atrophy; conjunctival hyperemia. | Clinically minimal systemic relevance. | Reassure the patient about expected aesthetic changes, to avoid abandonment of glaucoma treatment. |
| **Antihistamines/dual action** | Olopatadine, ketotifen, alcaftadine, epinastin. | Well tolerated; Occasional initial irritation. | Minimum. | First-line for allergic conjunctivitis with pruritus. It adequately replaces vasoconstrictors in this indication. |
| **Immunomodulators (for dry eye)** | Cyclosporine 0.05% and 0.1%; lifitegrast 0.5%. | Frequent initial burning; intolerance in some patients. | Negligible systemic absorption. | Strengthen adherence: clinical effect requires 3 to 6 months. Follow up together with an ophthalmologist. |

Source: prepared by the authors, based on the references cited throughout the chapter.

## 10 FINAL CONSIDERATIONS

The underestimation of topical ophthalmic drugs is a historical error that exacts an unacceptable price in terms of visual morbidity and systemic morbidity and mortality. As demonstrated throughout this chapter, a drop of eye drops carries real pharmacological potential: it crosses mucosal barriers, escapes hepatic metabolism, and interacts with systemic receptors.

The mitigation of cortisonic glaucoma, antimicrobial resistance on the ocular surface and cardiovascular crises by sympathomimetics and beta-blockers is not the exclusive task of the ophthalmologist. On the contrary, the change of this paradigm rests firmly in the hands of the general practitioner. It is in Primary Care, in the clinical ward and in the emergency room that medication reconciliation saves lives. And it is also in these spaces that the generalist must recognize the patient using advanced ophthalmological treatments (intravitreal injections, implants, therapies prescribed for dry eye) to identify complications in time, refer appropriately, and not interfere harmfully with specialized conducts.

The rational use of ophthalmic drugs requires, above all, the recovery of respect for ophthalmic drop: it is not a cosmetic, it is not an innocuous solution; It is a full-fledged drug that requires precise indication, exact dosage, and strict clinical surveillance. The integration between primary care and ophthalmology, via active communication, medication

reconciliation and timely referral, is the way for this therapeutic category to stop being a blind spot in the health system.

***Editorial note on figures and images.*** *This chapter contains no pictures or images. All visual elements used are tables (Table 1 and Table 2), prepared by the author based on the references cited; Specific sources are indicated at the bottom of each table.*

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