Over-the-Counter Ocular Decongestants in the United States – Mechanisms of Action and Clinical Utility for Management of Ocular Redness

Lester O Hosten1
Christopher Snyder2
1Clinical and Medical Affairs, Bausch + Lomb, Bridgewater, NJ, USA; 2Regional Director Medical Science, Bausch + Lomb, Birmingham, AL, USA

Abstract: To manage ocular redness effectively, health-care practitioners require an understanding of the pathophysiology, clinical features and differential diagnosis of ocular redness, as well as comprehensive knowledge of medical therapies available and their pharmacologic properties. This review aims to provide a clinically relevant summary of the current literature on the mechanism of action, efficacy, and safety of current over-the-counter (OTC) decongestants available for reduction of ocular redness due to minor irritations. Currently marketed OTC products indicated for such use in the United States include topical solutions of tetrahydrozoline 0.05%, naphazoline 0.012% to 0.03%, and brimonidine 0.025%. All 3 agents are adrenergic receptor agonists but vary in their receptor-binding profiles: tetrahydrozoline is a selective α1 receptor agonist; naphazoline is a mixed α1/α2 receptor agonist; and brimonidine is a selective α2 receptor agonist. These OTC decongestants produce vasoconstriction of conjunctival blood vessels, which results in a rapid reduction in ocular redness. In general, ocular adverse events reported in published studies of these OTC decongestants were minimal, mild, and transient, with no significant adverse systemic effects. However, ocular decongestants with α1-adrenergic receptor agonist activity can be associated with loss of effectiveness with continued use (ie, tachyphylaxis) and rebound redness upon treatment discontinuation. In clinical trials of the selective α2-adrenergic receptor agonist brimonidine 0.025%, tachyphylaxis was not observed, and rebound redness was rarely reported.

Keywords: brimonidine, naphazoline, ocular redness, ocular decongestant, over-the-counter, tetrahydrozoline

Introduction
Ocular redness, or hyperemia, is a common ophthalmic sign, occurring with or without symptoms and may be associated with reduced quality of life due to associated discomfort and/or cosmetic concerns. Ocular redness is often associated with conjunctivitis and has a number of potential causes including infectious agents (eg, bacterial or viral conjunctivitis), exposure to allergens (eg, pollen, animal dander) or environmental irritants (eg, smoke, air pollution), eye strain, fatigue, dry eye, and contact lens wear.1–3

For noninfectious and nonallergic ocular redness caused by minor, nonspecific eye irritations with no apparent underlying pathology, topical application of over-the-counter (OTC) ocular decongestants may be considered to reduce ocular redness through the constriction of conjunctival blood vessels.4,5 In this review, we
provide a brief overview of the current understanding of the regulation of vascular tone in the eye followed by a summary of clinically relevant peer-reviewed literature on the mechanism of action, efficacy, and safety of currently marketed OTC decongestants available for reduction of ocular redness due to minor irritations in the United States: topical solutions of tetrahydrozoline 0.05%, naphazoline 0.012% to 0.03%, and brimonidine 0.025%. With this information, health-care providers will be better able to recommend an OTC decongestant(s) appropriate for their patients while minimizing adverse drug reactions.

**Regulation of Vascular Tone**

Ocular redness results from vasodilation of conjunctival blood vessels. Research on the control of vascular tone in the eye is limited; however, results from in vitro and animal studies on the regulation of other (ie, non-ocular) blood vessels provide pertinent information applicable to understanding the mechanistic basis of ocular redness (Figure 1). In mammalian species, vascular tone is primarily mediated by activity at adrenergic receptors found on vascular smooth muscle, vascular endothelium, and nerve cell terminals. Contractile activity of vascular smooth muscle cells alters the diameter of resistance (ie, arteries, arterioles) and capacitance (ie, veins, venules) vessels. In vascular smooth muscle cells, stimulation of $\alpha_1$- and/or $\alpha_2$-adrenergic receptors leads to vasoconstriction, whereas stimulation of $\beta$-adrenergic receptors leads to vasodilation; in addition, stimulation of $\alpha_1$, $\alpha_2$, and/or $\beta$-adrenergic receptors on vascular endothelial cells leads to vasodilation via a process possibly mediated by increased nitric oxide release. Presynaptic neuronal $\alpha_2$- and $\beta$-adrenergic receptors function as autoreceptors; stimulation of these receptors decreases norepinephrine release from neuron terminals, which may also contribute to vasodilation. Thus, basal vascular tone is a consequence of the vasoconstrictive and vasodilatory activity mediated by norepinephrine, and ocular redness occurs when vasodilation predominates.

By analogy, the vasoactive effect of a drug with adrenergic receptor agonist activity is also thought to depend on the balance between vasoconstrictive and vasodilatory activity. In addition, anatomic differences in the distribution of $\alpha_1$- and $\alpha_2$-adrenergic receptors are expected and have been noted, with $\alpha_1$-adrenergic receptors observed on both arteries and veins and $\alpha_2$-adrenergic receptors observed predominantly on veins. Consequently, the effects of medications that target ocular $\alpha$-adrenergic receptors are largely dependent on the receptor type they activate ($\alpha_1$ vs $\alpha_2$), blood vessel type primarily impacted (artery vs vein), and ocular distribution (vascular smooth muscle, vascular endothelium, synapse).

**Methods**

For data on the mechanisms of action, efficacy, and safety of US OTC decongestant products, a literature search of the Medline database was conducted in June 2020 using the following search terms: (“ocular decongestant” OR “phenylephrine” OR “tetrahydrozoline” OR “naphazoline” OR “oxymetazoline” OR “brimonidine”) AND (“conjunctival hyperemia” OR “ocular hyperemia” OR “ocular redness” OR “ocular erythema” OR “eye redness” OR “eye erythema” OR “eye hyperemia”). Searches were limited to English language publications, with no date restriction. Articles were considered relevant if they included research data or clinical information regarding ocular use for hyperemia in humans or described potential mechanisms of action. Reference lists in relevant publications were reviewed to identify additional articles for inclusion. Also accessed were abstract archives spanning 2013–2019 from scientific meetings for eye care professionals (American Optometric Association/American Optometric Student Association, American Academy of Optometry, Vision Sciences Society, American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, and American Ophthalmological Society). Additional articles not identified by the formal searches were included at the discretion of the authors.

**Ocular Decongestants**

Currently available OTC ocular decongestants in the United States (US) are all $\alpha$-adrenergic receptor agonists but vary in their receptor-binding profiles (Table 1). First-generation ocular decongestants included phenylephrine, tetrahydrozoline, naphazoline, and oxymetazoline. Phenylephrine, a sympathomimetic amine with selective affinity for $\alpha_1$-adrenergic receptors, and oxymetazoline, an imidazole derivative with an affinity of ~5:1 for $\alpha_2$: $\alpha_1$ receptors, are no longer actively marketed in the US, although oxymetazoline may be available through e-commerce channels. Tetrahydrozoline hydrochloride, an imidazole derivative that has been available since the 1950s, is a selective $\alpha_1$-adrenergic receptor agonist.

Naphazoline hydrochloride, another imidazole derivative, is a mixed $\alpha_1$/$\alpha_2$ receptor agonist with a binding affinity of
Naphazoline (0.1%) received US Food and Drug Administration (FDA) approval in 1974 as a prescription ocular decongestant and is now available OTC in lower concentration solutions (0.012–0.03%) for the purpose of redness relief.

Brimonidine tartrate, an adrenergic receptor agonist with markedly greater binding affinity for \( \alpha_2 \) receptors relative to \( \alpha_1 \) receptors (1000:1), is the first selective \( \alpha_2 \)-adrenergic receptor agonist for relief of ocular redness. Brimonidine was first approved in 1996, in an ophthalmic solution with a concentration of 0.2%, for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension and was subsequently approved in 2013, in a topical gel with a concentration of 0.33%, for the treatment of persistent facial erythema of rosacea. Off-label use of brimonidine prior to laser in situ keratomileusis (LASIK) and pterygium surgery demonstrated that brimonidine was effective at reducing subconjunctival hemorrhage and ocular redness at prescription ophthalmic strength and lower
Brimonidine, in an ophthalmic solution (eg, brimonidine) all produce receptor agonists (eg, tetrahydrozoline). Selective constriction of venules (eg, naphazoline), and selective α2 receptor agonists (eg, brimonidine) all produce constriction of conjunctival blood vessels through activation of adrenergic receptors, which, in turn, initiates vascular smooth muscle contraction via activation of G-protein signaling cascades that culminate in vascular smooth muscle contraction.

**Mechanisms of Action**

There is a wide distribution of α-adrenergic receptors in the eye, including smooth muscle cells and blood vessels (eg, conjunctiva, iris-ciliary structures, aqueous outflow tract). Selective α1 receptor agonists (eg, tetrahydrozoline) mixed α1/α2 receptor agonists (eg, naphazoline), and selective α2 receptor agonists (eg, brimonidine) all produce constriction of conjunctival blood vessels through activation of adrenergic receptors, which, in turn, initiates G-protein signaling cascades that culminate in vascular smooth muscle contraction. More specifically, activation of α1-adrenergic receptors, which are linked to Gq proteins, produces vascular smooth muscle contraction via the inositol triphosphate (IP3) signal transduction pathway, whereas activation of α2-adrenergic receptors, which are linked to Gq proteins, produces vascular smooth muscle contraction as a result of decreased intracellular cyclic adenosine monophosphate (cAMP).

Because of differences in α-adrenergic receptor distribution, ocular decongestants with α1-adrenergic receptor agonist activity are understood to produce constriction of both conjunctival arterioles and venules; whereas a selective α2-adrenergic receptor agonist, such as brimonidine, is thought to have its primary site of action on conjunctival venules (Figure 2). Selective constriction of venules has the potential advantage of sustaining the availability of oxygen to the surrounding tissue, which would otherwise be decreased with arteriole constriction, and has implications with respect to the potential for ocular redness rebound, discussed next. Moreover, given that veins in the conjunctiva are known to be more numerous than arteries, and, by analogy to other tissues, veins in the conjunctiva are likely located more superficially as opposed to arteries, it follows that preferential constriction of conjunctival venules is expected to have a significant impact on redness even with little change in arterial caliber. Studies involving imaging and/or oximetry would be useful towards understanding vasoconstriction by adrenergic receptor agonists in conjunctival tissue.

**Tachyphylaxis and Rebound Redness**

Although ocular decongestants that act via stimulation of α1-adrenergic receptors are effective for the temporary relief of ocular redness, sustained use of α1- or mixed α1/α2-adrenergic receptor agonists has been associated with tachyphylaxis (tolerance or loss of effectiveness). Tachyphylaxis is thought to be due to a tolerance-related reduction of the α1-adrenergic receptor response, possibly through sequestration and internalization of α1-adrenergic receptors and subsequent downregulation of surface α1-adrenergic receptors. While it is unknown whether the distribution of ocular α2-adrenergic receptors changes with continued use of α2-adrenergic agonists, the available literature on vasoconstriction in other tissues suggests that tachyphylaxis is driven primarily by changes in α1-adrenergic receptors. It is notable that studies of the selective α2-adrenergic receptor agonist brimonidine did not show evidence of tachyphylaxis of effect with long-term use at the high doses investigated for lowering intraocular pressure in patients with glaucoma (0.2%) or for treatment of facial erythema of rosacea (0.5%).

Use of α1- or mixed α1/α2-adrenergic receptor agonist has also been associated with rebound redness upon

### Table 1: Representative Over-the-Counter Ocular Decongestants in the United States for the Treatment of Eye Redness

| Generic Name       | Brand Name                                                                 | Concentration, % | AR Agonist Subtype |
|--------------------|----------------------------------------------------------------------------|------------------|--------------------|
| Tetrahydrozoline HCl | Clear Eyes Traveler’s Eye Relief (Prestige Brands) | 0.05             | α1                 |
|                    | Roche Ice (Roche Pharmaceutical)                                          |                  |                    |
|                    | Visine (Johnson & Johnson)                                                 |                  |                    |
| Naphazoline HCl    | Bausch + Lomb Advanced Eye Relief (Bausch + Lomb)                        | 0.012            | Mixed α1/α2        |
|                    | Bausch + Lomb Advanced Eye Relief Maximum (Bausch + Lomb)                 | 0.03             | α2                 |
|                    | Clear Eyes (Prestige Brands)                                               | 0.03             | α2                 |
|                    | Roche Cool (Roche Pharmaceutical)                                          | 0.012            |                    |
|                    | Roche Cool Max (Roche Pharmaceutical)                                      | 0.03             |                    |
| Brimonidine tartrate| Lumify (Bausch + Lomb)                                                     | 0.025            | α2                 |

**Notes:**

- Trademarks are property of their respective owners.
- Abbreviations: AR, adrenergic receptor; HCl, hydrochloride.

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doses (0.025%). Brimonidine, in an ophthalmic solution with the lower concentration of 0.025%, received FDA approval in 2017 to reduce the redness of the eye due to minor irritations.
As $\alpha_1$-adrenergic receptors are preferentially expressed in arterial vessels, rebound redness may be mediated by vasoconstrictor-induced tissue ischemia and subsequent release of vasodilators. Less rebound redness would be expected after discontinuation of selective $\alpha_2$-adrenergic receptor agonists because they produce vasoconstriction through a venular mechanism of action. There is some speculation, based on data from studies of non-ocular tissues that rebound congestion after discontinuation may also be mediated, in part, by downregulation and uncoupling of $\alpha_1$-adrenergic receptors, which decrease vascular tone (eg, by decreasing sensitivity to endogenous circulating norepinephrine) resulting in rebound vasodilation and congestion, although this is far from clear. Ongoing research, specifically in conjunctival tissue, may provide a better understanding of the potential for tachyphylaxis and rebound redness of current ocular decongestants.

Clinical Efficacy and Safety

Selective $\alpha_1$-Adrenergic Receptor and Mixed $\alpha_1/\alpha_2$-Adrenergic Receptor Agonists

The effectiveness of tetrahydrozoline for reducing ocular redness was evaluated in an unmasked, controlled clinical study and a large case series of patients with conjunctivitis of varying etiology. In the controlled clinical study, therapeutic response was evaluated in 65 patients with mild to severe conjunctival redness resulting from a variety of ophthalmic conditions (ie, chronic hyperemia, chemical and physical trauma, blepharitis, actinic conjunctivitis, thyrotropic exophthalmos, recurrent chalazia, keratitis) after study medication was instilled in 1 eye. Tetrahydrozoline 0.1% (2...
drops, 3 times per day for 2–30 days) provided rapid (< 1 min) and enduring (up to 4 hrs) conjunctival blanching. A weaker solution of tetrahydrozoline (0.05%) produced similar results when assessed in additional 62 patients.

Although this was a controlled study in that tetrahydrozoline was administered in only 1 eye, the study report does not include evaluation of therapeutic response in treated versus untreated eyes. In the case series, tetrahydrozoline 0.05% (1 drop, 2–4 times per day for 2 weeks to 2 months) was evaluated in 1156 patients (age range, 3–91 years) with allergic or chronic conjunctivitis. In the 348 patients with allergic conjunctivitis, tetrahydrozoline 0.05% was an effective decongestant whether with (97.4%) or without (93.5%) concomitant oral antihistamine therapy. Effectiveness of tetrahydrozoline 0.05% was also observed in 88.7% of the 808 patients with chronic conjunctivitis. Across patient groups, improvement in redness was typically noted immediately, with duration of effect between 1 and 4 hrs. In these studies, minimal side effects were observed; tetrahydrozoline 0.05% did not alter pupil size or raise intraocular pressure and was apparently safe for use in patients with cataracts.

Naphazoline was evaluated as an ocular decongestant in a case series of more than 100 patients with redness of various etiologies (eg, allergic conjunctivitis; chronic conjunctivitis; keratitis; corneal pannus; bulbar congestion due to chemical burns, trauma, chronic iridocyclitis, endophthalmitis, or post-operative states). Naphazoline 0.1% (various dosing regimens) produced constriction of superficial conjunctival and corneal capillaries resulting in reduced redness; this effect had an immediate onset and lasted for several hours. However, increases in intraocular pressure and pupil dilation were observed in some cases. Of note, the concentration of naphazoline used in this case series (0.1%) was substantially greater than that of currently marketed OTC naphazoline products (0.012–0.03%). Additional studies (reported in Gossel, 1983) demonstrated that pre-treatment with naphazoline (in one eye versus no treatment in the other eye, dosing regimen not reported) protected against vasodilation caused by exposure to chlorinated water and that effectiveness was comparable for naphazoline 0.012% and 0.1%.

Subsequent studies of first-generation ocular decongestants, including 3 head-to-head comparisons of tetrahydrozoline and naphazoline, used doses consistent with current OTC products. In a small, double-masked study of 6 healthy adults with no ocular disease, effects on histamine-induced erythema were evaluated for naphazoline (0.1%, 0.05%, 0.02%, 0.012%), tetrahydrozoline (0.05%), and phenylephrine (0.12%). Naphazoline 0.02% demonstrated significantly more blanching of the conjunctiva compared with lower-dose naphazoline (0.012%), tetrahydrozoline, and phenylephrine (data combined for analysis); higher doses of naphazoline (0.1% and 0.05%) did not differ significantly from the 0.02% dose.

In another small double-masked study of healthy adults (n = 8; baseline ocular redness not reported), naphazoline (0.02%) instilled in one eye and tetrahydrozoline (0.05%) instilled in the other eye were evaluated after single-use (1 drop) and exaggerated-use (8 times per day for 9 days, and 4 times on the morning of Day 10) administration. Ocular redness, as judged based on photographs taken at various times up to 24 hrs after the last treatment, was significantly reduced from baseline for up to 8 hrs post-treatment after single-dose tetrahydrozoline or naphazoline, with significantly greater improvement for naphazoline versus tetrahydrozoline at some time points; in the exaggerated use condition, significant redness reduction was observed (for up to 6 hrs) only with naphazoline.

In a safety study of naphazoline 0.012%, tetrahydrozoline 0.05%, and phenylephrine 0.12% conducted in 40 adults with no apparent ocular disease (reported in Adamczyk & Jaanus, 2008), no significant changes in pupil size or anterior chamber depth were observed. Phenylephrine produced minimal effects on intraocular pressure, assessed 30 mins after administration; compared with phenylephrine, average intraocular pressure was significantly lowered with tetrahydrozoline and somewhat increased with naphazoline.

As indicated above, use of $\alpha_1$- or mixed $\alpha_1/\alpha_2$-adrenergic receptor agonists can be associated with tachyphylaxis and/or rebound redness upon treatment discontinuation. As such, evidence of tachyphylaxis and rebound redness associated with sustained use of first-generation OTC ocular decongestants (ie, $\alpha_1$- or mixed $\alpha_1/\alpha_2$-adrenergic receptor agonists) are based on reported FDA safety data, in addition to other, smaller published studies.

Tachyphylaxis has been documented after repeated daily use of tetrahydrozoline over as few as 5 to 10 days. In a case series of 5 patients diagnosed with conjunctivitis medicamentosa, rebound redness was observed upon discontinuation of naphazoline or tetrahydrozoline after days, weeks, or months of continuous use. In a case series of 70 patients who used OTC decongestant eyedrops (naphazoline, tetrahydrozoline, phenylephrine) daily (mean 3.7 ± 2.2 times per day) for a median of 3 years, conjunctival
redness was noted in 50 patients (the remainder were diagnosed with either follicular conjunctivitis [17 patients] or eczematoid blepharoconjunctivitis [3 patients]). These 50 cases of conjunctival redness, despite the use of first-generation ocular decongestants, provided evidence of loss of efficacy and/or rebound dilation of conjunctival blood vessels. Between 1969 and 1984, there were approximately 280 adverse events reported to the FDA from OTC use of tetrahydrozoline, with more than 90 reported as conjunctivitis and described by consumers as “eyes turned redder” or “eyes redder than before.” Another 45 reports listed “no drug effect” with comments such as “eyes still red.” In 1988, the FDA made the decision to include the warning “overuse of this product may produce increased redness of the eye” for all ophthalmic OTC products containing vasoconstrictors in use at that time (eg, tetrahydrozoline, naphazoline).

Accidental ingestion is an additional concern with first-generation ocular decongestants. Data collected between 1985 and 2012 from the FDA Adverse Event Reporting System showed that 53 out of 96 cases (55.2%) of accidental ingestion of products containing tetrahydrozoline, oxymetazoline, or naphazoline by children aged 1 month to 5 years resulted in hospitalization. In 2012, the FDA warned the public that accidental ingestion by young children of a small amount (1–2 mL) of OTC eye drops (tetrahydrozoline, oxymetazoline, or naphazoline) may cause serious adverse events (eg, coma, decreased heart rate, sedation).

Selective α2-Adrenergic Receptor Agonist

Clinical trials of low-dose brimonidine (0.025%) ophthalmic solution used rigorous study design methodology (randomized, double-masked, vehicle-controlled). In these studies, a total of 117 adults (≥18 years) with ocular redness of undetermined etiology were randomly assigned (in a 2:1 ratio) to bilateral treatment with low-dose brimonidine or vehicle, instilled 4 times daily for 4 weeks. Compared with vehicle, low-dose brimonidine demonstrated a significant reduction at all post-dose time points in both investigator- and subject-assessed ocular redness, evaluated using the Ora Calibra® Ocular Hyperemia Scale. Low-dose brimonidine had a rapid (<1 min) onset of action and was effective for up to 8 hrs (Figure 3). Investigator ratings of ocular redness on Day 15 and Day 29 were examined for signs of tachyphylaxis. Mean decrease in redness score from pre-dose to 5 mins post-dose was significantly greater for low-dose brimonidine compared with vehicle on Day 15 and Day 29, as it was on Day 1, indicating that there was no evidence of tachyphylaxis. Across investigator assessments, there was 1 brimonidine-treated participant (1.3%) with rebound redness. Based on these results, brimonidine 0.025% currently does not carry the “overuse” warning mandated for ocular products containing other vasoconstrictors.

Brimonidine also demonstrated redness reduction in a study of 60 patients with a history of allergic conjunctivitis in which brimonidine (0.01%, 0.025%), oxymetazoline (0.025%), and vehicle (placebo) were compared using a conjunctival allergen challenge model. Both doses of brimonidine significantly reduced mean conjunctival redness scores at 7, 15, and 20 mins post-instillation compared with placebo and oxymetazoline (all P < 0.05). Interestingly, mean conjunctival redness scores for oxymetazoline were not significantly different compared with placebo at any time point.

The safety of low-dose (0.025%) brimonidine ophthalmic solution was evaluated in 4 clinical studies conducted in 635 pediatric, adult, and geriatric participants. An integrated analysis of the safety data indicated that the incidence of ocular adverse events was low and similar between treatment groups, with the most common adverse events (occurring in ≥2% of participants in either group) being reduced visual acuity (low-dose brimonidine, 4.0%; vehicle, 4.3%) and conjunctival redness (low-dose brimonidine, 2.6%; vehicle, 2.9%). Fatigue and drowsiness have been observed during treatment with brimonidine 0.2% ophthalmic solution in patients with glaucoma or ocular hypertension, with reports of severe fatigue or somnolence in some pediatric patients. However, no clinically significant systemic adverse events were observed in either adults or children in studies of low-dose brimonidine, with mild fatigue reported in only 1 adult participant (0.2% of participants); there were no reports of somnolence and no meaningful changes in heart rate or blood pressure. Similarly, ocular allergic reactions have been reported in studies of brimonidine 0.2% and 0.15% but allergic conjunctivitis was not reported in the analysis of the 4 safety studies of brimonidine 0.025%, suggesting a dose-dependent relationship between allergic responses and brimonidine treatment, although further study is needed. In this safety analysis, which excluded patients with elevated intraocular pressure (>22 mm Hg) and/or a diagnosis of glaucoma, mean intraocular pressure was unchanged (within 1 mm Hg of baseline) during 4 weeks of treatment with low-dose brimonidine.
The toxicity of brimonidine in young children (≤ 5 years of age) was evaluated based on 176 unintentional exposures, nearly all (89.2%) via accidental ingestion, to brimonidine solutions (0.1–0.2%) used for lowering intraocular pressure and compiled by the US national Toxic Exposure Surveillance System. Such exposure resulted in hospitalization in 15.7% of cases. Based on the mean dose associated with brimonidine toxicity in children (1.11 mg/kg) obtained from this analysis, the small amount of brimonidine contained in a full 7.5 mL bottle of 0.025% solution for ocular use (ie, 1.88 mg) is unlikely to result in significant effects in children if accidentally ingested.

Discussion

For ocular redness due to minor irritations or without an apparent cause, patients may consider OTC products for redness relief and seek advice on such products from various health-care providers, including pharmacists, primary care physicians and eyecare practitioners. Before recommending an OTC ocular decongestant, the health-care provider should make recommendations for the management of ocular redness that address the underlying cause, where known. At least a detailed patient history, and a comprehensive eye exam (by an eyecare practitioner) when possible, assists in differentiating the underlying cause(s) of ocular redness so that appropriate treatment can be initiated. Mild infectious and noninfectious conjunctivitis may be managed by a primary care provider, but more serious cases (eg, persistent or recurring, cornea involvement, marked pain, decreased visual acuity) warrant management by an eye care practitioner. Appropriate treatment regimens vary based on the differential diagnosis of the patient’s ocular redness. Treatment of conjunctivitis resulting from a viral infection is usually supportive (eg, cold compresses, artificial tears); management of bacterial conjunctivitis may include topical antibiotics. Initial treatment options for management of allergic conjunctivitis accompanied by mild-to-moderate itching include topical antihistamines and mast-cell stabilizers; these products are reviewed elsewhere.

When ocular redness is deemed to be due to minor irritations, an OTC ocular decongestant may be recommended for the management of the redness. Understanding the mechanism of action, efficacy, and safety of currently US-marketed over-the-counter (OTC) decongestants is helpful when making the decision on which product(s) to recommend.
The active ingredient in currently US-marketed OTC ocular decongestants is an α-adrenergic receptor agonist that exerts its effect by stimulating α1- and/or α2-adrenergic receptors on vascular smooth muscle, resulting in vasoconstriction of conjunctival blood vessels and reduction in ocular redness. Ophthalmic solutions of tetrahydrozoline 0.05% (a selective α1 receptor agonist), naphazoline 0.012% to 0.03% (a mixed α1/α2 receptor agonist), and brimonidine 0.025% (a selective α2 receptor agonist) all provide rapid reduction in ocular redness with sustained relief for hours after instillation. In general, ocular adverse events with these products were minimal, mild, and transient in clinical studies of OTC ocular decongestants, with no reported evidence of adverse systemic effects when administered at the relatively low concentrations required for relief of ocular redness. While various efficacy studies have been conducted and reported in the literature, only more-recent clinical trials, conducted on the selective α2-adrenergic receptor agonist brimonidine, used rigorous study design methodologies to evaluate efficacy and safety. In contrast to older ocular decongestants that act via the α1-adrenergic receptor, brimonidine showed no evidence of tachyphylaxis in clinical studies. Brimonidine also was rarely associated with rebound redness in randomized controlled trials. Well-designed comparative studies are needed to evaluate the effects of recently approved (brimonidine) versus older (tetrahydrozoline, naphazoline) agents for ocular redness reduction.

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