Integrating Recommendations to Improve Treatment Outcomes in the Clinical Management of Allergic Conjunctivitis

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ABSTRACT

Allergic conjunctivitis (AC) is an inflammation of the conjunctiva due to allergens that come in contact with the eye. Seasonal AC and perennial AC are the most commonly encountered subtypes. Each can be identified by itching, tearing, and swelling or inflammation of the eye, and these symptoms can contribute to decreased quality of life for patients. Many patients will seek symptomatic relief with topical ophthalmic formulations. Pharmacists and pharmacy technicians should be familiar with the clinical presentation of AC to best recommend appropriate treatments for AC. This review illustrates counselling interactions between a patient and a pharmacist to provide a clear understanding about recommending over-the-counter treatment options for patients. Effective communication is a cornerstone for pharmacists and pharmacy technicians to optimize patient management and relay vital information for the management of AC, such as assisting patients with therapies that can help provide relief of symptoms.

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INTRODUCTION

Ocular allergy, or allergic conjunctivitis (AC), is a common inflammatory immunologic condition that is estimated to affect 20% to 40% of the US population and has been increasing in prevalence¹. A concern with AC diagnosis and treatment is that it is often either self-diagnosed by patients, or it is misdiagnosed, or underdiagnosed by health care providers. Patients with AC also have decreased

quality of life for various reasons (including bothersome symptoms and emotional effects), and the economic burden due to health care costs, medications, missed work, etc, is substantial^{2,3}. Patients presenting with AC will typically experience bilateral tearing, ocular redness, swelling, and the hallmark, and most bothersome, a symptom of pruritus (itching)⁴. Many patients with AC will also present with allergic rhinitis (nasal symptoms)⁵. It is estimated that up to 3 of 4 patients with allergic

rhinitis present with symptoms of AC. There is also a correlation between AC and patients with a predisposition to atopies (allergic disorders), such as asthma, eczema, and food allergies⁶. Taking a well-detailed history is particularly important when considering a diagnosis of AC in a patient. Specifically, asking about exposure to allergens and determining a timeline associated with exposure and symptoms is important. Whether the allergen is indoor or outdoor can indicate the type of AC as well as the best course of treatment. Allergens that commonly cause AC include pollen, grass, pet dander, mold, and dust mites⁷.

ETIOLOGY AND PATHOPHYSIOLOGY OF AC

There are several different subtypes of AC. Table 1^{1,2,5} provides a brief comparison. The most common immunologic process taking place in AC is a type I immunoglobulin E (IgE)-mediated hypersensitivity with mast cell activation with histamine release occurring immediately. Essentially, an allergen is identified by the immune system, and the body's response is to release histamine from mast cells to try to rid the body of the allergen⁸.

Table 1: Types of Allergic conjunctivitis

Particulars	SAC	PAC	GPC	VKC	AKC	CBC
Common causes	Outdoor allergens	Indoor allergens	Foreign body exposure	Allergens (Acute exacerbations)	Allergens (Acute exacerbations)	Foreign body exposure
Immunology	Type-I (IgE)	Type-I (IgE)	Type IV (T-cell) ± Type-I (IgE)	Type IV (T-cell) ± Type-I (IgE)	Type IV (T-cell) ± Type-I (IgE)	Type IV (T-cell)
Background	Atopy	Atopy	Presence of contact lenses (Especially soft), Prostheses	Children, Boys > girls atopy, Warm climate	Adult, severe atopy	Use of new products around eyes
Symptoms	ITRS ± rhinitis	ITRS ± rhinitis	Papillae, Blurred vision, ITRS	Severe ITRS, Papillae, Eyelidedema	ITRS, Eyelideczema	ITRS, Eyelideczema
Prevalence and persistence	Very common, intermittent	Common, Chronic	Rare, chronic	Rare, chronic ± intermittent	Very rare, chronic	Rare, chronic ± intermittent

AC-Allergic conjunctivitis, **AKC**- AtropicKeratoconjunctivitis, **CBC**- contact blepharoconjunctivitis, **GPC**- Gaintpapillary conjunctivitis, **IgE**- Immunoglobulin E, **ITRS**- Itching, tearing, redness, swelling, **PAC**- Perennial allergic conjunctivitis, **SAC**- Seasonal allergic conjunctivitis, **VKC**- Vernal keratoconjunctivitis

More severe forms of AC occur due to a delayed-type IV cell-mediated hypersensitivity with T-cell involvement. Benign cases can be treated with non-pharmacologic measures, as well as with both non-prescription or over-the-counter (OTC) and prescription items. These cases are often self-diagnosed by patients, or diagnosis and treatment are managed by general practitioners such as primary care physicians. More severe cases, however, require diagnosis and treatment by specialty practitioners such as ophthalmologists⁹.

Seasonal allergic conjunctivitis (SAC) is the most common form of AC and is considered benign. Patients typically present with ocular itching, redness, tearing, and swelling in response to outdoor allergens such as pollen and grass. Rhinitis often accompanies the ocular symptoms and

patients with SAC often have a history of atopy. The immune process of SAC is an IgE-mediated type 1 hypersensitivity reaction that causes an increase in mast cell presence and degranulation, as well as the subsequent release of histamine, which causes the typical AC symptoms¹⁰.

Perennial allergic conjunctivitis (PAC) is similar to SAC but is considered persistent (or chronic), with symptoms lasting more than 4 to 6 weeks. PAC is most often triggered by indoor allergens, such as dust mites, pet dander, mold, or pests such as cockroaches, and patients may have some additional symptoms such as foreign body sensation (eg, sand in the eye) as well as some burning of the conjunctiva.

Like SAC, PAC is also associated with a history of atopy, is an IgE-mediated type 1 hypersensitivity reaction, and is considered benign¹¹.

Giant papillary conjunctivitis (GPC) is a chronic form of AC but is due to the constant exposure of the conjunctiva to a foreign body, most commonly contact lenses or a prosthetic eye, and is considered moderate to severe. It is a T cell-mediated response, although a type I IgE-mediated hypersensitivity response can also occur if allergens attach to the contact lenses¹². Giant papillae (or round protuberances) of greater than 1 mm develop on the conjunctiva of both the upper and lower eyelids. Patients will also experience symptoms such as discharge, blurred vision, and photophobia¹³.

Vernal keratoconjunctivitis (VKC) is a severe form of AC that can lead to structural changes of the epithelium, development of giant papillae, and vision loss. VKC occurs most often in male children before 10 years of age with a history of atopy living in warmer countries surrounding the Mediterranean Sea and equatorial areas¹⁴. Presentation of VKC includes intense tearing, itching, redness, papillae, edema of the eyelid, and photophobia that can have a profound impact on a patient's quality of life. The immunology of VKC has characteristics of both type I IgE-mediated hypersensitivity as well as type IV T cell-mediated hypersensitivity that becomes a chronic lymphocyte-predominant condition¹⁵.

Atopic keratoconjunctivitis (AKC) is similar to VKC but is extremely rare and typically occurs in adults with a history of severe atopy. Like VKC, AKC is a combination of type I and type IV hypersensitivity processes and has a similar presentation and associated complications as VKC, with the addition of eczema, scarring, and corneal involvement¹⁶.

Contact blepharoconjunctivitis (CBC) is a type IV T cell-mediated hypersensitivity that consists of an antigen complex formation that develops between the eye and a foreign body or substance¹⁷. This can occur as a result of products applied around (but not directly to) the eye as well. There is no background of atopy associated with CBC, but symptoms can include contact dermatitis of the eyelid and conjunctival follicles in addition to the standard AC symptoms of tearing, itching, redness, and inflammation¹⁸.

BURDEN OF AC

AC, especially SAC and PAC, is very common. It is estimated that worldwide, AC affects 15% to 20% of

the population, with up to 40% of the US population impacted. SAC and PAC have a tremendous burden on individuals for various reasons. Quality of life is decreased with the presence of ocular symptoms in addition to frequent concurrent rhinitis. Patients report that these uncomfortable symptoms affect concentration and focus, cause emotional distress due to perception of AC, and can impair activities of daily living¹⁹. SAC and PAC are most frequently self-diagnosed by patients because the symptoms are more bothersome than alarming. Also, SAC and PAC are often inadequately treated or mistreated, which results in a further decrease in quality of life, productivity, and increased financial burden²⁰.

The financial burden of AC is estimated to be more than \$2 billion yearly for prescription items with expected non-prescription costs being far higher. Also, there are indirect costs such as decreased productivity at work, absenteeism, and out-of-pocket expenses. The combined costs, both direct and indirect, are estimated to be approximately \$6 billion and are increasing yearly²¹.

CLINICAL PRESENTATION

Patients presenting with AC have symptoms of itching, tearing, redness, and swelling. Patients often experience concurrent rhinitis. AC is typically bilateral as unilateral presentation often indicates bacterial or viral conjunctivitis. Fewer common symptoms include burning, irritation, or foreign body sensation²². SAC occurs intermittently with the season and outdoor allergen exposure changes while PAC is persistent or chronic due to continuous indoor allergen exposure. These are considered the most common forms of AC and are benign with minimal damage and only local sequelae²³.

Patients with more severe forms of AC, such as GPC, VKC, AKC, and CBC, will also experience itching, tearing, redness, and swelling but symptoms will likely be more intense. Also, these patients will present with more severe symptoms such as papillae, photosensitivity, and eyelid swelling or eczema. Patients with GPC will likely be contact lens wearers (soft lenses specifically) or will have prostheses, exposed sutures, or ocular surface abnormalities⁵.

DIAGNOSIS OF AC

To appropriately diagnose AC, a complete patient history, including evaluating the temporal relationship of symptoms and exposure to allergens (or identification of triggers), is imperative. Patients

should be asked about their symptoms, environmental exposures, aggravating and remitting factors (including non-pharmacologic and pharmacologic treatments tried), and ocular history including changes in vision or recent trauma²⁴. A complete history of medication use is also necessary as several OTC medications can contribute to or worsen AC symptoms if overused or if used inappropriately.

Based on the severity and duration of symptoms, a physical examination and/or allergen sensitivity tests may be required by a physician, ophthalmologist, allergist, or immunologist. Patients with AC often present with rhinitis, asthma, and symptoms of dry eye, which can make diagnosis more complicated, although ocular itching is the key symptom in all patients with AC⁴. Besides, some patients may present with symptoms that are more alarming and require immediate referral to a physician. Examples of symptoms requiring medical referral include mucus or discharge other than tearing, which may indicate infection (including viral or bacterial conjunctivitis), bleeding or other signs of trauma or injury, growths, recent exposure to chemicals, suspected foreign substance trapped or embedded in the eye, or if there is uncertainty that the cause of symptoms is exposure to an allergen²⁵.

TREATMENT GOALS

The goals of treatment for AC are improving quality of life, removing or avoiding the allergen, relieving symptoms, and ultimately minimizing inflammation to maintain the integrity of the ocular surface².

Non-Pharmacologic Recommendations

Non-pharmacologic measures represent the foundation of treatment for AC. The first step is to identify potential allergens via patient interview and develop a care plan for avoidance and/or reduced exposure. Once allergens are identified, avoidance is optimal but may be difficult to achieve; reduced exposure may be a more reasonable approach²⁶. Other non-pharmacologic recommendations include the application of cool compresses and the use of ophthalmic lubricants. Patients should be advised to resist the urge to rub their eyes as this may lead to degranulation of mast cells and worsening of symptoms. Contact lens wearers should consider switching to glasses when symptoms are at their peak or switching to disposable, daily wear contact lenses.

While non-pharmacologic recommendations alone provide minimal benefit, they provide an additive effect when used in combination with pharmacologic interventions²⁷.

Allergen Avoidance

Common outdoor allergens include pollen, molds, ragweed, and pollutants; indoor allergens include pets, molds, and dust mites. Recommendations concerning allergen avoidance are summarized in **Table 2**^{28,29}. Exposure to outdoor allergens can be reduced by keeping doors and windows closed and by monitoring pollen counts when planning outdoor activities. Indoor allergens can be minimized with regular cleaning, dusting, and vacuuming. Pets should be washed weekly and should not be allowed in the bedroom. House dust mites can be minimized by regular cleaning and using pillow and mattress covers.

If possible, carpet should be removed or vacuumed regularly using a vacuum bag equipped with a high-efficiency particulate air (HEPA) filter. HEPA filters should also be installed in heating and air conditioning ducts²⁹.

Ocular Lubricants

Ophthalmic lubricants, or artificial tears, work to dilute and potentially rinse away the allergen and other inflammatory mediators that may have accumulated on the eye surface. In addition to cleansing the eye surface of allergens, ocular lubricants act as a barrier to allergens and help to treat any comorbid dry eye disease.

Table 3³⁰⁻³⁸ features select common ocular lubricants that are available in drops, gels, and ointment dosage forms and contain a variety of thickening agents. For this table and all other medication-specific tables, please refer to individual prescribing information, labeling, and/or package insert for additional information including age-specific recommendations. Lipid-containing ocular lubricants are typically more expensive but may be more effective for patients with evaporative dry eyes as they help to prevent evaporation and improve the tear film stability³⁹.

Ocular lubricant drops provide temporary relief and must be used several times throughout the day for maximal benefit. Adverse effects (AEs) associated with ocular lubricants are limited and are typically related to the preservative rather than the active ingredient. Benzalkonium chloride (BAK) is a

common preservative in numerous ophthalmic products but has been associated with corneal damage. If artificial tears are used frequently (>4-6 times per day) or if use is prolonged, a preservative-

free formulation should be recommended. Ointment formulations offer a longer-lasting effect but cause blurry vision and should be reserved for use at bedtime⁴⁰.

Table 2: Recommendations for Allergen Avoidance

Allergen	Recommendation
Pollen/outdoor molds	<ul style="list-style-type: none"> • Monitor local pollen counts and plan outdoor activity accordingly • Keep house and car windows and vents closed • Wear protective eyewear such as sunglasses • Shower and wash hair before bed
Pets	<ul style="list-style-type: none"> • Allow in limited areas of the house (keep out of the bedroom) • Wash pets weekly • Vacuum regularly • Encase pillows and mattresses
Dust mites	<ul style="list-style-type: none"> • Wash bedding weekly in hot water and/or hot dryer • Remove stuffed animals from beds • Keep home humidity between 35% and 50%

Cool Compresses

Cool compresses may help reduce symptoms of eye and eyelid swelling. Using a clean cloth dampened with cold water or a frozen gel pack, cool compresses should be applied to closed eyelids for 5 to 10 minutes 3 or 4 times daily. The cooling effect leads to vasoconstriction and reduces itching and inflammation²⁶.

Pharmacologic Treatments

Based on pathophysiology and immunology, several medications can be used for the treatment of AC. Specifically, SAC and PAC can often be managed by patients, as well as their pharmacists and primary care providers or pediatricians, while patients with more severe forms of AC, such as VKC or AKC, should be followed by ocular specialists⁴¹.

First-line therapy should always be non-pharmacologic treatment. The preferred second-line therapy is the initiation of dual-activity agents that have both antihistamine and mast cell stabilizing activity. If symptoms are still not managed, a course of topical corticosteroids can be used as well as topical nonsteroidal anti-inflammatory drugs (NSAIDs), second-generation oral antihistamines,

and nasal corticosteroids for additional symptoms relief. If appropriate use of the aforementioned therapies does not yield sufficient relief, immunotherapy can be considered⁴².

Dual-activity Agents (Antihistamines With Mast Cell-stabilizing Properties)

Ophthalmic agents that have both antihistamine and mast cell-stabilizing activity are the preferred pharmacologic treatment for AC and are found to be better than antihistamines or mast cell stabilizers by themselves⁴³. They are the ocular agents most frequently prescribed by ophthalmic professionals and allergists. In SAC and PAC, the immune response to allergens is IgE mediated, which means that mast cell degranulation and subsequent release of histamine and other inflammatory mediators occur, causing the bothersome symptoms of ocular allergy⁴⁴. Therefore, working to both stabilize the mast cells (and subsequently decrease the release of histamine) and block histamine receptors would relieve the symptoms of AC and prevent or stop the hypersensitivity reaction from occurring. An additional benefit of the combination is the rapid relief of symptoms within minutes (due to antihistamine activity), as well as long-term efficacy

due to the regulation of the inflammatory response in the late phase of the hypersensitivity reaction^{44,45}.

Select common dual-activity agents are outlined in Table 4⁴⁶⁻⁵⁰. There are 2 available OTC dual-activity

agents that are considered to have comparable efficacy for mild AC: olopatadine 0.1%, 0.2%, and 0.7% and ketotifen 0.025% ophthalmic solutions⁴⁵. Olopatadine, the first dual-activity agent on the market, was prescription only for many years.

Table 3. Ocular Lubricants

Ocular lubricants	Brand name products
Carboxymethylcellulose	Refresh Celluvisc, Refresh Liquigel, Refresh Optive, Refresh Optive Mega-3 Preservative-Free
Glycerin	Refresh Optive, Refresh Optive Mega-3 Preservative-Free, Soothe Preservative Free
Hydroxypropylmethylcellulose	Systane Lubricant Eye Gel
Polyethylene glycol	Systane Ultra Eye Drops, Systane Ultra Preservative -Free
Polysorbate	Refresh Optive Mega-3 Preservative- Free
Polyvinyl alcohol	Refresh Classic
Povidone	Refresh Classic, Soothe Lubricant Eye Drops Maximum Hydration
Propylene glycol	Systane Balance, Systane Ultra Eye Drops, Systane Ultra Preservative-Free
Lipid lubricants	Brand name products
Castor oil	Refresh Optive Mega-3 Advanced
Mineral oil	Soothe XP Xtra Protection, Systane Balance
Phospholipids	Systane Balance
Ointments	Brand name products
Mineral oil	Refresh Lacri-Lube, Refresh P. M., Soothe Nighttime Lubricant, Systane Nighttime
White petrolatum	Refresh Lacri-Lube, Refresh P. M., Soothe Nighttime Lubricant, Systane Nighttime

This agent is considered to be the gold standard across all dual-activity OTC and prescription products. Olopatadine was first available as a 0.1% solution, dosed as 1 drop in each affected eye twice daily, and has since been approved for once-daily 0.2% solution and once-daily 0.7% solution (extra strength formulation). The primary difference between the 2 once-daily formulations is that 0.2% is found to relieve ocular itching for approximately 18 hours, whereas 0.7% relieves symptoms for upwards of 24 hours⁵¹. All formulations are for patients aged 2 years or older.

Ketotifen is available OTC under 2 different brand names as well as generic formulations. For patients aged 3 years or older, it is dosed 1 drop in the

affected eye(s) twice daily with 8 to 12 hours between doses. The only preservative-free dual-activity agent is ketotifen 0.035%, which will be made available OTC in spring 2021. All other products contain BAK, which can cause damage to the corneas and worsen ocular symptoms over time, so long-term use should be carefully evaluated⁵². With both, patients should stop use and ask a doctor if they experience eye pain, vision changes, increased eye redness, or itching that worsens or lasts for more than 72 hours^{52,53}.

The prescription-only dual-activity agents include alcaftadine 0.25%, azelastine 0.05%, bepotastine 1.5%, and epinastine 0.05%. Alcaftadine is dosed once daily in patients aged 2 years or older, has

minor ocular AEs, and has proven to be more beneficial for ocular itch than the other dual-activity agents⁵⁴. Azelastine, bepotastine, and epinastine are all dosed twice daily with azelastine and

epinastine indicated for patients older than 2 years and bepotastine indicated for patients 3 years or older.

Table 4: Dual acting ophthalmic agents

Generic name	Brand name	OTC/Rx	Dose	Clinical pearls
Ketotifen 0.025%	Alaway Zaditor	OTC	Twice daily	Allow 8-12 hours between doses; maximum two doses per day
Ketotifenfumarate 0.035%	Alaway preservative relief	OTC	Twice daily	Allow 8-12 hours between doses; maximum two doses per day; Does not contain preservative BAK
Olopatadine 0.1%	Pataday Twice daily relief	OTC	Twice daily	Allow 6-8 hours between doses; maximum two doses per day; Formerly Rx Patanol
Olopatadine 0.2%	Patadayonce daily relief	OTC	Once-daily	Provides 16 hours of relief, formerly Rx Pataday
Olopatadine 0.7%	Patadayonce daily relief extra strength	OTC	Once-daily	Provides 24 hours of relief, formerly Rx Pazeo
Alcaftadine 0.25%	Lastacaft	Rx	Once daily	Provides 16 hours of relief, found to be the most beneficial dual-acting agent for ocular itching
Azelastine 0.025%	Optivar	Rx	Twice daily	Provides 8 hours of relief, lower tolerability
Bepotastine 1.5%	Bepreve	Rx	Twice daily	Provides 8 hours of relief
Epinastine 0.05%	Elestat	Rx	Twice daily	Provides 8 hours of relief

Azelastine causes ocular stinging and burning as well as headache and was found to have lower tolerability than olopatadine. Azelastine is not considered a favorable option in the treatment of AC. Bepotastine provides relief for up to 8 hours, is considered well-tolerated with the most common AE being a mild taste, and is a prescription option⁵⁵. Epinastine also provides relief for 8 hours, is well-tolerated, and is a reasonable prescription option, but is not as effective as olopatadine⁵⁶.

Mast Cell Stabilizers

Select common additional topical and ocular agents are summarized in Table 5⁵⁷⁻⁶⁶. Mast cell stabilizers are seldom used as monotherapy but remain an option for the treatment of all IgE-mediated forms of AC: SAC, PAC, VKC, AKC, and possibly GPC. Mast cell stabilizers have specific administration requirements that may negatively affect patient

adherence and result in subtherapeutic patient outcomes. Specifically, the mast cell stabilizer ophthalmic solutions must be instilled frequently throughout the day and must be used for days to weeks before the benefit can be observed. The available mast cell stabilizers are cromolyn, lodoxamide, nedocromil, and pemirolast. In general, they have similar ocular AEs such as burning and stinging, and they differ only slightly in dosing frequency and approved age⁶⁷.

Topical Ocular Antihistamine (Single Acting)

Topical ocular antihistamines work directly to block histamine-1 (H₁) receptors in the eye⁶⁸. Given the ophthalmic dosage form, topical antihistamines have a quick onset (within 15 minutes) with minimal systemic AEs but are associated with burning and stinging upon administration. Of note, these agents are contraindicated in patients at risk of developing closed-angle glaucoma. The topical ocular

antihistamines emedastine (Emadine) and levocabastine (Livostin) have been discontinued. A topical version of cetirizine (Zerviate 0.24%) ophthalmic solution was launched in March 2020⁵⁸.

Ophthalmic cetirizine has been shown to relieve ocular symptoms (pruritus, erythema, and swelling) as well as nasal symptoms including rhinorrhea, nasal pruritus, and nasal congestion⁶⁹.

Table 5: Additional Topical & ocular agents

Generic name	Brand name	OTC/ Rx	Dose	Clinical pearls
Mast cell stabilizers				
Cromolyn 4%		Rx	1 or 2 drops 4-6 times daily	Should be initiated before expected allergen exposure symptom improvement can be expected after a few days & symptoms relief after weeks. Adherence is key.
Lodoxamine 0.1%	Alomide	Rx	1 or 2 drops QID	
Nedocromil 2%	Alocril	Rx	1 or 2 drops QID	
Pemirolast 0.1%	Alamast	Rx	1 or 2 drops QID	
Single – acting antihistamine				
Cetirizine 0.24%	Zerviate	Rx	1 drop BID	Doses should be administered 8 hours apart.
Decongestants				
Naphazoline 0.012%	Clear eyes redness relief	OTC	1 or 2 drops up to QID	Duration of use is limited (Products labeling states use beyond 72 hours requires further evaluation)
Tetrahydrozoline 0.05%	Visine original	OTC	1 or 2 drops up to QID	
Antihistamine / Decongestant combination				
Pheniramine / Naphazoline 0.3% / 0.025% 0.315% 0.02675%	Naphcon A Opocon - A	OCT	1 or 2 drops up to QID	Duration is limited due to decongestants
Corticosteroids				
Fluorometolone acetate 0.1%	FML	Rx	1 or 2 drops BID- QID	Counsel patients to shake before use (Suspension dosage form)
Loteprednolelabonate 0.2% 0.5%	Alrex Lotemax Lotemax gel	Rx	1 drop QID 1 or 2 drops QID	Duration of use is limited to 1-2 weeks due to cataracts and elevated IOP.
Prednosolone acetate 1%	Pred Forte	Rx	1 or 2 drops BID- QID	
NSAIDs				

Diclofenac 0.1%	Voltaren ophthalmic	Rx	1 drop QID	Short-time use. Rare adverse effects include keratitis, corneal ulceration, or perforation
Ketorolac 0.45%	Acuvail	Rx	1 drop BID	
Ketorolac 0.5%	Acular	Rx	1 drop QID	
Nepafenac 0.1%	Nevanac	Rx	1 drop TID	

IOP- Intraocular pressure; NSAID- Nonsteroidal anti-inflammatory drug

Table 6: OTC oral antihistamines & Intranasal corticosteroids

Generic name	Brand name	Typical adult Dose	Clinical pearls
Second-generation oral antihistamines			
Cetirizine	Zyrtec	One 10 mg tablet once daily; 5 mg for less severe symptoms	May cause sedation for patients
Fexofenadine	Allegra	One 180 mg tablet once daily or 60 mg twice daily	Unlikely to cause sedation for patients. Absorption is decreased if taken with fruit juices
Levocetirizine	Xyzal	One 5mg tablet once daily; 2.5 mg for less severe symptoms	May cause sedation for patients
Loratadine	Claritin	One 10 mg tablet once daily	Unlikely to cause sedation for patients
Intranasal corticosteroids			
Budesonide	Rhinocort	1 or 2 spray in each nostril once daily as recommended	≥ 6 years of age
Fluticasone furoate	Flonase sensimist		≥ 2 years of age
Fluticasone propionate	Flonase		≥ 4 years of age
Triamcinolone	Nasacort		≥ 2 years of age

The duration of action of cetirizine ophthalmic solution is approximately 8 to 12 hours; dosing is twice daily approximately 8 hours apart⁷⁰.

Topical Ocular Decongestants

The role of the topical ocular decongestants, tetrahydrozoline, and naphazoline, for the treatment of allergic conjunctivitis, is limited. These agents work to reduce ocular erythema and chemosis via vasoconstriction but do not relieve pruritus and do not provide additional symptomatic relief. Further, when used for more than a few days, ocular

decongestants are associated with tachyphylaxis (diminished response to successive administrations of a drug) and rebound ocular hyperemia (redness) known as conjunctivitis medicamentosa⁷¹. Product labeling indicates these agents should not be used for more than 72 hours without a referral for further evaluation. These agents are contraindicated during pregnancy and in patients with closed-angle glaucoma; use in patients with cardiovascular disease and hyperthyroidism should be avoided due to their activity as adrenergic agonists^{60,61}.

A longer-acting alpha-2 agonist, brimonidine 0.025% (Lumify), is available OTC but is just labeled for use to treat general ocular redness (it is not intended for the treatment of AC). The 0.025% OTC concentration is lower than the 0.15% and 0.2% that is indicated for glaucoma. The alpha-2 selectivity is associated with a lower risk of tachyphylaxis and rebound hyperemia⁷².

Topical Ocular Antihistamine/Decongestant Combinations

The topical ocular antihistamine pheniramine is available OTC in combination with ocular decongestants. Of note, the antihistamine antazoline, previously available in combination with naphazoline, is no longer commercially available. Although this combination works quickly (within 3-15 minutes) to treat both the itching and redness associated with AC, the duration of relief is short, so this product must be dosed frequently (up to 4 times daily). The rebound congestion associated with the decongestant limits the duration of use. As previously described, product labeling for these agents also specifies that they should not be used for more than 72 hours without a referral for further evaluation. Thus, the overall utility of these agents in the treatment of AC is limited⁷³. The precautions and contraindications to individual antihistamine and decongestant agents previously mentioned applying to the combination as well.

Topical Corticosteroids

Topical corticosteroids are extremely effective for all forms of AC and all levels of severity. They are, however, associated with a great deal of potential ocular damage, such as cataracts, increased intraocular pressure (IOP), and increased risk of infections. Therefore, topical corticosteroids are used only intermittently, and their duration of use is typically limited to 1 to 2 weeks. Some of the commonly used topical corticosteroids are fluorometholone, loteprednol, and prednisolone. The topical corticosteroids typically contain the preservative BAK, which also limits their use in AC⁷⁴.

Topical NSAIDs

Although topical NSAIDs are not used frequently, they are an option if patients continue to have symptoms while using a dual-activity product. Topical NSAIDs can be considered during severe exacerbations of symptoms and in more severe forms of AC, such as VKC and AKC, or if topical

corticosteroid therapy is not preferred for a patient⁷⁵. The agents often used include diclofenac, ketorolac, and nepafenac. The AEs associated with topical NSAID use include substantial irritation, burning, and stinging, which can limit their use, and in rare cases, corneal ulceration or keratitis can occur. The topical NSAIDs typically contain BAK as a preservative, which also limits their use. They are typically only used short-term (for approximately 1 week) and are not considered a mainstay of therapy⁷⁶.

Oral Antihistamines

Select common OTC oral antihistamines and intranasal corticosteroids are covered in **Table 6**.⁷⁷⁻⁸⁴. Oral antihistamines are effective in treating both nasal and ocular allergy symptoms. Although effective, first-generation antihistamines such as diphenhydramine and chlorpheniramine are rarely used due to central nervous system-related AEs, including sedation and confusion as well as anticholinergic AEs (urinary retention, dry eyes, and dry mouth). Second-generation antihistamines cetirizine, fexofenadine, levocetirizine, and loratadine, are available OTC and are preferred due to their favorable AE profile (minimal sedation). The average onset of action with these agents is 150 minutes; therefore, topical ocular antihistamines may be preferred. For added benefit, oral antihistamines may be used in combination with topical ocular agents that do not include an antihistamine^{85,86}.

Intranasal Corticosteroids

Intranasal corticosteroids are often considered the most effective treatment option for allergic rhinitis, owing to their ability to address multiple components of the allergic response; corticosteroids suppress the immune response, are anti-inflammatory, and reduce mast cell proliferation. Intranasal corticosteroids are effective for both nasal and ocular symptoms. Given that the majority (>80%) of patients with AC also have comorbid allergic rhinitis, intranasal corticosteroids may be the most effective treatment option using one agent to treat all symptoms^{85,87}. The onset of action of intranasal corticosteroids is generally delayed with maximal improvement taking up to 2 weeks; however, ocular symptoms including pruritus, redness, and tearing have been shown to improve in 2 to 5 days⁸⁸. AEs with intranasal corticosteroids are typically limited to local irritation and epistaxis. Patients with glaucoma or at risk of glaucoma should be monitored for increased IOP; patients should also be monitored for

cataracts. Pediatric patients should be monitored for growth suppression. Proper administration technique is important; patients should be counseled to spray away from the septum. Although rare, repeatedly spraying at the septum may lead to nasal septal perforation⁸⁹.

OPTIMIZING PATIENT CARE

The Role of The Pharmacist

Patients experiencing AC typically self-diagnose and self-treat with OTC treatment options to relieve their ocular symptoms of itching, redness, tearing, swelling, photophobia, and general discomfort. Unfortunately, patients may not truly understand their condition or how to appropriately treat it. Patients may inappropriately believe they have dry eye, red eye, an eye infection, or may fail to recognize that their nasal and ocular symptoms are related. Most recently, the novel COVID-19 illness may also include ocular symptoms such as discharge and congestion⁹⁰. Therefore, pharmacists must be prepared to evaluate and assess patients with symptoms. This means that they should be able to identify patients with mild AC who can be treated with OTC medications as well as identify the potentially more severe forms of AC (or if something other than AC is suspected) that require referral to a primary care physician, allergist, ophthalmologist, or other health care professional. Patients who report eye pain, changes in vision, or trauma to the eye (including exposures to chemicals) are not appropriate candidates for OTC recommendations and should be referred to their provider for further evaluation⁹¹.

During the patient interview, pharmacists must identify when symptoms began and what new exposures to allergens may have occurred, and try to determine the cause of the patient's allergic reaction. When mild SAC or PAC is suspected, pharmacists should counsel patients regarding the various non-pharmacologic, or foundational, treatments first and foremost. This includes allergen avoidance with appropriate recommendations to minimize exposure. When symptoms are moderate or if they do not respond to non-pharmacologic recommendations, pharmacists should be prepared to assist patients in selecting the most appropriate OTC product. Product selection should be based on patient preferences (eg, patients may prefer an oral dosage form versus an eye drop); the indication of the product and symptoms the product is likely to relieve; as well as the pharmacokinetic properties of the drug, including onset and duration of

therapy. As the duration of therapy of several ophthalmic products is limited to minimize potential severe AEs, pharmacists should monitor patients who may be overusing or inappropriately refilling ophthalmic products⁹¹.

Pharmacists must counsel patients on the proper use of their treatment recommendations. Patients should be educated on proper instillation of both ophthalmic drops and ophthalmic ointments as well as appropriate contact lens care. Patient treatment expectations should be addressed, including potential AEs, the onset of symptom relief, as well as duration. Most ocular agents cause some degree of local irritation; patients should be reassured that these AEs are typically transient⁹². If the irritation or any additional AEs become intolerable, patients should be referred to their provider. Pharmacists should also counsel patients on the importance of adherence to scheduled medication such as the dual-activity agents. If a dose is missed, patients should be instructed to use their medication as soon as they remember, unless it is too close to their next dose. Then, patients should skip their dose and resume with their next scheduled dose; patients should not use 2 doses at once. Finally, pharmacists can provide information on when to follow up; for example, if patients experience an inadequate response to the recommended treatment, patients should contact the pharmacist for further evaluation and potential referral to a provider for prescription options. For instance, a patient who is experiencing control of symptoms during the day after initiating an OTC ophthalmic medication but continues to experience symptoms throughout the night may benefit from switching to a product that provides more long-lasting relief⁹³.

Contact Lens Care

Patients who wear contact lenses are at increased risk of infection and further complications. Contact lens wearers must disinfect their lenses daily (or dispose of their lenses if the patient has daily wear contacts). Patients should also be reminded to always wash their hands when inserting and removing contact lenses to avoid the introduction of microorganisms, allergens, or other contaminants to the eye. When counseling contact lens wearers with AC, they should be advised to wear their glasses or switch to daily wear contacts if possible. These patients should also be aware that most ophthalmic products require lens removal for use and a wait time of at least 5 minutes before reinserting⁹⁴. Specific products may recommend waiting an

additional amount of time or advise not to wear contact lenses at all when using the product.

How to Administer an Ophthalmic Medication

Best practices on how to properly administer ophthalmic products are discussed in **Figure**.⁹⁵⁻⁹⁸ Before using an ophthalmic product, patients should wash their hands. If the product is a suspension, they should be instructed to shake the product before use. Once the product is open, patients should be mindful not to contaminate the product by touching the tip of the bottle or tube; it is prudent to place the cap of the product on its side on a clean tissue. When ready to instill the ophthalmic product, patients should tilt their head back slightly and pull the lower eyelid down to create a pouch for the drop, gel, or ointment⁹⁹.

When using ophthalmic drops, the bottle should be held upside down above the eye, and the bottle should be squeezed lightly to release a drop of the medication. Again, patients should be cognizant not to touch the tip of the applicator to their eye to avoid potential contamination. Once the drop has been instilled into the eye, the patient should release their lower eyelid and gently close their eye. They should not blink or “squeeze shut” their eye as this may cause the drop to be expelled. The patient should then block the nasolacrimal duct by gently pressing on the inner eye for 1-2 minutes; this will prevent the medication from draining through the duct and will maximize medication contact time¹⁰⁰.

When using ophthalmic ointments, patients should squeeze the tube gently to dispense a thin ribbon, approximately 0.25 to 0.5 inches in length, into the pouch created by pulling down the lower eyelid. Then the patient should release the lid, blink gently, and keep the eye closed for 1 to 2 minutes. Ophthalmic ointments are likely to cause blurry vision and if possible, should be administered at bedtime. After using either drops or ointments, patients should wash their hands and be sure to put the cap back on the product to minimize contamination¹⁰¹.

If patients are using multiple ophthalmic products, they should apply the least viscous product first (drops first, followed by gels, then ointments). Patients should wait 5 minutes between products if administering 2 different drop formulations. If using an ointment and drops, patients should wait for 10 minutes after drops to apply the ointment¹⁰².

Role of the Pharmacy Technician

Pharmacy technicians play an essential role in patient care by assisting the pharmacist. Pharmacy technicians can help to identify patients who appear to be experiencing AC and referring these patients to the pharmacist when appropriate. There are numerous medications in multiple dosage forms available for the treatment of AC. Technicians should become familiar with products available to treat AC and remain updated as new products become available¹⁰³. OTC products, in particular, are updated frequently; technicians should also be aware of new product packaging and new brand name extensions as well as any products that have been discontinued. Most importantly, pharmacy technicians can play a key role in assisting patients to locate OTC products as recommended by the pharmacist. Technicians can also provide handouts on appropriate administration techniques when dispensing eye drops or eye ointments or when a patient purchases an OTC ophthalmic product¹⁰⁴.

CHALLENGES AND LIMITATION

Misdiagnosis and under treatment are two major needs in this area. The prevalence of allergic conjunctivitis is high, but treatment adherence is low since it is primarily a self-diagnosed condition with self-treatment. Due to a lack of clear “best practice” guidelines, primary care physicians are limited in their approach to allergic conjunctivitis management. The inadequacy of head-to-head studies of various agents to provide the best choice of topical anti-inflammatory therapy for the specific patient is one major drawback. Primary care diagnostic criteria must be improved and made more clear. There is a necessity of advanced guidelines for the specialist for optimum patient care. Generally, ocular allergy is undertreated and overdiagnosed by eye specialists, as well as underdiagnosed and undertreated by primary health care physicians, who commonly prescribe ocular corticosteroids to these patients. So, it is the sole responsibility of the health care professionals for the best treatment of this type of disorder¹⁰⁵.

FUTURE PROSPECTIVE OF THE STUDY

The eye's anatomy leads to the reduced bioavailability of the topical ophthalmic formulations applied to the eye. To overcome these limitations, much more research is invested towards the ocular drug-delivery system. In addition to the different formulations and treatments for AC mentioned in this review, nanotechnology is another growing approach in this field. These include nanoparticles, nanomicelles, nanosuspensions, and dendrimers

which helps in increasing bioavailability because of their particle size and other unique characteristics. But these nanoformulations rapidly clear from the precorneal pocket. So, mucoadhesive nanoformulations are in the developing stage. Glucocorticoids as a nanosuspension formula have been found to increase ocular bioavailability in several studies. Other studies are focusing on vaccines, edible rice, mechanical barrier gels, and even probiotics as alternatives¹⁰⁶.

CONCLUSION

AC is a very common condition that affects millions of people every year. Specifically, SAC and PAC are mild but can have bothersome symptoms that can heavily impact the quality of life, especially when improperly diagnosed or treated. Fortunately, there are nonpharmacologic as well as OTC and prescription treatment options available. With the help of the pharmacist and pharmacy technician, patients are better able to select safe and proper products, review proper eye care and ophthalmic administration technique, and successfully manage the symptoms of AC.

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CONFLICT OF INTEREST

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