

THE DARK SIDE OF MEDICATION

Many systemic and topical drugs can cause or worsen dry eye disease.

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Dry eye disease (DED) is a common ophthalmic disorder that affects a predominantly older population and is diagnosed in women twice as often as in men.^{1,2}

The risk of developing DED increases in patients with

certain systemic disorders, particularly diabetes: 54% and 70% of patients with type 1 and type 2 diabetes, respectively, develop DED.³ In some patients, DED symptoms are exacerbated by topical and/or systemic medications that interfere with proper tear production or induce allergic or inflammatory responses in optical and periocular tissues. The sensitivity of DED patients to different medications varies, and clinicians must be aware of all prescribed and over-the-counter drugs in use in order to diagnose a causative agent.

PRESERVATIVE PROBLEMS

Preservatives in multiuse eye drop bottles are a well-studied factor in ocular surface disease. Benzalkonium chloride (BAK) is an effective detergent-type antimicrobial used in 70% of all ophthalmic medications,⁴ but its utility as a preservative is offset by its toxicity to the ocular surface. Corneal and conjunctival toxicity have been demonstrated in vitro,^{5,6} while BAK's disruption of tear film production and stability has been demonstrated in vivo.⁷⁻⁹ Because of the damaging effects of BAK, some medications now use gentler oxidative-type preservatives such as stabilized oxychloro complex (Purite; Allergan) or the ionic buffer system sofZia (Alcon), both of which cause less ocular surface damage and discomfort.^{10,11} Other eye drops, including the glaucoma medications timolol, dorzolamide/timolol fixed combination, latanoprost, and tafluprost, as well as numerous over-the-counter artificial tears, are available in preservative-free formulations. When feasible, these medications may be the best choices for DED patients.¹²⁻¹⁴ Second-tier alternatives are medicines containing milder, non-BAK preservatives, followed by BAK-containing options.

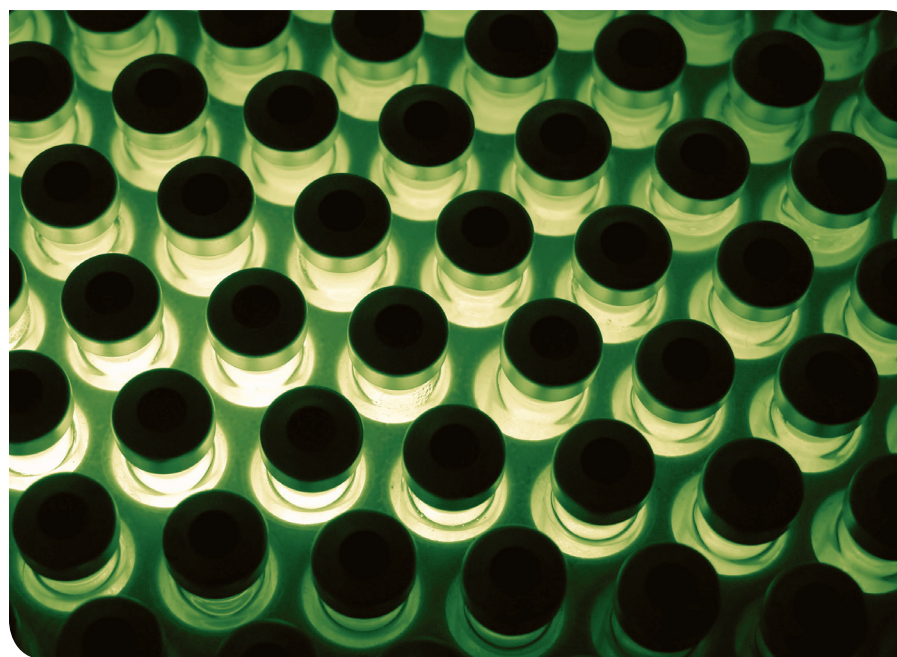
Glaucoma medications, while generally well tolerated, induce adverse effects that may be exacerbated in DED patients. Some of these effects may be due to the presence of BAK in certain formulations, but each class of glaucoma medication also contributes to DED symptoms directly.

PROSTAGLANDINS AND PROSTAMIDES

Prostaglandins (PGAs) and prostamides reduce IOP by increasing uveoscleral outflow, and these agents are often the first line of glaucoma treatment. PGA use increases chalazion formation and subsequent abnormalities in the tear film¹⁵ and induces conjunctival inflammation.^{16,17} BAK-free alternatives are available for some PGAs and have fewer adverse effects.¹⁸

β-BLOCKERS

β-blockers are competitive antagonists of β-adrenergic receptors that reduce aqueous humor production. Many β-blocker formulations contain BAK, which accounts for some of the discomfort reported from their use. However,





AT A GLANCE

- In some patients, dry eye disease (DED) symptoms are exacerbated by medications that interfere with proper tear production or induce allergic or inflammatory responses in optical and periocular tissues.
- Preservatives in multiuse eye drop bottles such as benzalkonium chloride are toxic to the ocular surface. Some medications now use gentler oxidative-type preservatives that cause less ocular surface damage and discomfort. Other eye drops are available in preservative-free formulations.
- Systemic medications are implicated in the aggravation of DED as well. β -blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and diuretics induce DED. Anticholinergics, particularly antihistamines and antidepressants, also cause adverse effects.

timolol reduces tear production and turnover more than other BAK-containing medications,¹⁹ while nonpreserved β -blockers cause more ocular surface damage than PGAs and brimonidine,²⁰ indicating that the active ingredient promotes DED symptoms directly.

α -AGONISTS

The α -agonist brimonidine lowers IOP through the concurrent decrease of aqueous humor production and increase in uveoscleral outflow.²¹ Allergic conjunctivitis and anterior uveitis often occur following long-term use of 0.2% brimonidine drops, which are preserved with BAK.²²⁻²⁴ More recently, formulations using 0.15% and 0.1% brimonidine and the preservative Purite have been shown to lower IOP as effectively as 0.2% brimonidine, but with a reduction in ocular allergy of at least 41%.²⁵

CARBONIC ANHYDRASE INHIBITORS

The carbonic anhydrase inhibitors dorzolamide (Trusopt; Mundipharma Ophthalmology Products) and brinzolamide (Azopt; Alcon) reduce aqueous production and are often used as adjunctive therapy in combination with other glaucoma medications. Burning or stinging during instillation are common adverse effects of dorzolamide, likely because of its low pH of 5.6.²⁶ Less discomfort is reported with brinzolamide, which has a pH of 7.5, close to that of tears.

OPHTHALMIC ANTIBIOTICS

Ophthalmic antibiotics and over-the-counter drops, including lubricants, are often preserved with BAK or another irritating antimicrobial, chlorobutanol.²⁷ Recently, manufacturers have begun to use milder antimicrobials in artificial tears and lubricants, although BAK or chlorobutanol remains an ingredient in some.¹⁴ Two brands of the antibiotic moxifloxacin, Vigamox and Moxeza (both from Alcon), are preservative-free.

SYSTEMIC MEDICATIONS

Systemic medications are implicated in the aggravation of DED as well, although most studies have focused on classes of drugs rather than specific medications. Antihypertensives, including β -blockers,^{28,29} angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists,³⁰ and diuretics³¹ induce DED. Anticholinergics, particularly antihistamines and antidepressants, also cause adverse effects^{32,33}; antipsychotics are implicated because they cause dry mouth, a condition that shares a close pathophysiology with dry eye.³⁴

Exogenous estrogen plays a complex role in the regulation of DED; physiological doses ameliorate symptoms in premenopausal women, but its use in hormone replacement therapy increases risk in postmenopausal women.³⁵ Common over-the-counter analgesics such as aspirin³² and ibuprofen³⁶ cause dry eye, particularly at higher doses. Topical retinoids such as retinoic acid and isotretinoin (Accutane; Hoffmann-LaRoche) disrupt meibomian gland function and result in reduced oil production and perturbation of the tear film.^{37,38}

DED is a common condition that increases in prevalence with a variety of risk factors that include age, sex, and diabetes. Interplay of these factors with the use of any of a number of medications can aggravate symptoms; in fact, concurrent use of five or more prescription or over-the-counter drugs may itself be a risk factor.³⁴ The role of medications in exacerbating symptoms in DED patients is complex and variable. It is therefore important to consider all medications used by a patient when developing a treatment plan to address DED. ■

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