



IN YOUR PRACTICE: Botox Aids the Ocular Surface

Did you know that Botox is being used off-label for epiphora, entropion, and the healing of ocular surfaces? Five experts talk about these little-known uses for the neurotoxin.

By Reena Mukamal, Contributing Writer

The use of botulinumtoxinA (BTX-A, commonly known as Botox) was pioneered in the 1970s by Alan B. Scott, MD, an ophthalmologist who injected it into extraocular muscles to treat strabismus. Since then, the drug has been approved for a wide variety of difficult-to-treat medical indications, transforming how physicians treat health conditions ranging from migraine to urinary incontinence.

Beyond its FDA-approved treatments, BTX-A is increasingly being used off-label in ophthalmology. It may be common knowledge that the drug is used off-label to treat conditions including nystagmus and upper eyelid retraction (associated with thyroid eye disease). But a group of off-label uses, which secondarily benefit the ocular surface, is less well-known and includes treatment of epiphora, entropion, and chemical tarsorrhaphy. Five experts take a look at these lesser-known uses for BTX-A and share their perspectives and practices.

Epiphora

Excessive tearing can stem from abnormalities in tear secretion and/or obstruction of the lacrimal outflow drainage system. “A common analogy is the connection between the faucet, sink, and drain. When you have an overflow, either the lacrimal gland (faucet) or the lacrimal drainage system (drain) can be the source of the problem,” said

John P. Fezza, MD, at Center for Sight in Sarasota, Florida. BTX-A is being used off-label to treat patients with both etiologies. However, there may be other contributors to epiphora, including lid abnormalities, ocular surface disease, or trichiasis, cautioned Dr. Fezza, and those conditions should be addressed first.

Hypersecretion. Hypersecretion etiologies include primary hypersecretion of the lacrimal gland, which is rare, and gustatory hyperlacrimation, or “crocodile tears,” which is caused by aberrant nerve regeneration after facial nerve injury. “Botox is one of my first-line treatments for hypersecretion, particularly in patients with crocodile tears,” said Amina I. Malik, MD, at Houston Methodist Hospital. “It offers a quick and effective option, which can easily be done in the office,” she explained.

Obstruction. While some studies have found better outcomes using Botox for hypersecretion than for obstruction, others agree that it can be beneficial even for patients with an obstruction.¹ When epiphora stems from a physical obstruction in the lacrimal drainage pathway, surgery is often necessary to fix the outflow problem, but some patients may not be good surgical candidates for various reasons, said Ted H. Wojno, MD, at Emory Eye Center. In these cases, “turning the faucet down a bit can help,” he said.

Dr. Malik offers Botox to patients with an obstruction who cannot safely discontinue blood-thinning medication for a dacryocystorhinostomy. She also uses the treatment as a stop-gap measure to relieve symptoms in patients who are awaiting surgery.

Regimen. No matter the etiology, ophthalmologists treat epiphora with similar Botox regimens. “I use a 30-gauge needle and inject 5 units transcutaneously into the lacrimal gland, underneath the orbital rim,” said Andrew R. Harrison, MD, at the University of Minnesota, Minneapolis. Likewise, Dr. Malik typically injects 5 units directly into the palpebral lobe using a 30-gauge 0.5-inch needle (Fig. 1) after applying a proparacaine-soaked cotton-tipped applicator directly over the gland for about 30 seconds to provide anesthesia. And Dr. Wojno recommends using topical anesthetic and putting the needle right into the center of the palpebral lobe of the lacrimal gland under direct visualization. Dr. Fezza prefers to start with a dosage of 3 to 4 units.

All five experts report success rates of 70% to 80%, with symptom relief lasting approximately three to four months. Dosage can be increased, as needed, and injection can be repeated three or four times per year.

Entropion

The repeated rubbing of the eyelashes against the cornea, which happens in entropion, can result in corneal damage. Of the four main types of entropion—senile (also called involucional), spastic, cicatricial, and congenital—Botox can be used to treat both the senile and spastic etiologies.

Senile entropion. The most common form of the condition, senile entropion is “often caused by horizontal lid laxity and an overriding preseptal orbicularis muscle,” said Dr. Malik. Although surgery is often the first line of treatment for senile entropion, some patients are unable to have an operation or must face a long wait time. In either case, Femida Kherani, MD, at the University of British Columbia, Vancouver, advised that injecting Botox into the orbicularis muscle can be an effective way to relieve symptoms by relaxing the muscle, and it can also improve the eyelid position.

Dr. Fezza cautioned that prior to giving a Botox injection, it’s important to make sure that the patient doesn’t have excessive lower lid laxity because the lid could start sagging. But, Dr. Malik added, “Even with some lid laxity present, Botox can still be helpful to decrease the degree of rotation, al-



EPIPHORA. 30-gauge, 0.5-inch needle being injected directly into palpebral lobe of lacrimal gland to treat epiphora.

though it may not fully restore the lid to its normal anatomic position.”

Spastic entropion. Primarily caused by infection, irritation, and/or inflammation, spastic entropion results in continual orbicularis oculi muscle contraction, which causes inward rotation of the lower eyelid. “Some experts believe spastic entropion is actually a form of senile entropion,” said Dr. Wojno.

Regardless, said Dr. Harrison, “it’s important to treat whatever is causing the spasm—corneal ulcer, severe dry eye, or something else—along with the spasm itself.” He partners with a cornea specialist to address all components of the condition.

Other nonsurgical approaches. Although eyelid taping and bandaged contact lenses also offer nonsurgical options for temporary relief, they have some downsides compared with Botox. Dr. Fezza noted that tape can be “chronically irritating to some patients. It can be challenging to put on and can easily fall off.” And Dr. Malik cautioned that the bandaged contact lens carries a risk, though low, of infectious keratitis.

Regimens. Both types of entropion are treated with the same Botox regimen. “I use a 32-gauge needle and inject a total of 10 to 15 units into the pretarsal and preseptal orbicularis oculi muscles, putting 2.5 to 5 units in three to four injection spots spread across the lower eyelid,” said Dr. Harrison. Similarly, Dr. Malik prepares the lower lid with betadine before she injects “a total of 15 units of Botox, distributing the injections equally between the medial, central, and lateral sites, 3 mm below the eyelash margin of the lid,” she said. Dr. Fezza targets the pretarsal muscle specifically because, he said, “it is more responsible for involuntary blinking.”

Symptom relief lasts between two to four months before injections need to be repeated, according to all the experts.

Protection of the Ocular Surface

Surgical versus chemical tarsorrhaphy. Surgical tarsorrhaphy is used to help the ocular surface heal in cases of corneal ulceration or exposure, persistent corneal epithelial defects, exposure keratopathy, dry eye syndrome, and progressive corneal melting, but it has some downsides. Although it creates a complete and tight closure of the eyelids, suture tarsorrhaphy can be disfiguring, said Dr. Harrison. Other disadvantages include limited peripheral vision and permanent scarring of the lid margins, said Dr. Fezza.

As an alternative, “Botox injected directly into the levator palpebrae muscle to create a ptosis of the eyelid offers a gentler ‘chemical tarsorrhaphy,’” said Dr. Harrison. However, this type of closure is not as predictable or secure as a surgical one. It’s

also not an option for patients who need immediate protection of the cornea, as it takes two to three days to begin working, cautioned Dr. Wojno.

When to induce ptosis. Dr. Malik performs chemical tarsorrhaphy in patients with exposure keratopathy. Similarly, Dr. Harrison often uses Botox to help a nonhealing corneal epithelial defect or corneal ulcer. But for patients who have a chronic corneal or surface issue or longstanding facial paralysis, he would recommend a more permanent solution.

Dr. Wojno recommends chemical tarsorrhaphy rather than sutures on a case-by-case basis. “In my experience, the vast majority of patients will opt for the surgery. For those patients who simply refuse surgery or cannot come off blood

Know the Neurotoxins

Mechanism. BTX-A is a neurotoxin derived from the bacterium, *Clostridium botulinum*. If this toxin is ingested in contaminated food, it can cause paralysis and even death. However, when the toxin is injected in small doses into targeted areas, it prevents the release of acetylcholine from presynaptic motor neurons at the neuromuscular junction, causing temporary muscle paralysis.

Duration. Eventually, the neuromuscular blockage wears off, allowing muscle function to return. Therapeutic benefits can be maintained with repeated injections. Typically, the neuromodulator begins working within three to five days of injection, reaching peak efficacy within seven to 14 days, according to Dr. Malik. The duration of the clinical effect varies depending on which botulinum toxin serotype and formulation are used, but it typically lasts three to four months in most patients, though the newest formulation, Daxxify, may last six months.

FDA-approved preparations. The seven serotypes of botulinum toxin type neurotoxins are produced from different strains of the bacterium (A-G), but only serotypes A and B are approved by the FDA for clinical use. Several different formulations of these serotypes are available today:

- OnabotulinumtoxinA (Botox)
- DaxibotulinumtoxinA-lanm (Daxxify)
- AbobotulinumtoxinA (Dysport)
- PrabotulinumtoxinA-xvfs (Jeuveau)
- RimabotulinumtoxinB (Mybloc)
- IncobotulinumtoxinA (Xeomin)

These preparations vary in several ways,

including protein size of the neurotoxin complex, potency, intracellular protein target, and storage requirements.¹ For example, “Botox has to be refrigerated, while Xeomin does not,” said Dr. Kherani. The dosing regimens vary between the types of neuromodulators. Currently, only Xeomin and Botox have ophthalmic-related indications.

DaxibotulinumtoxinA. In September, the FDA approved a new formulation of botulinumtoxinA called Daxxify, or Daxi (Revance Therapeutics). It is made with the same core ingredient of botulinum type A molecules, but a peptide is used for stabilization rather than human serum albumin.² This results in a longer-lasting effect, according to the manufacturer. Although BTX-A injections typically maintain their therapeutic effect for three to four months, Daxi reportedly lasts 50% longer, or up to six months.

Daxi has been studied in more than 3,800 patients, with results showing that the neuromodulator is effective for treating cervical dystonia and glabellar lines.² Ophthalmic applications have not been tested yet, but Dr. Fezza, who was involved in the clinical trials of Daxi, said, “It appears to be a very potent and safe drug with a longer-lasting effect.” Dr. Kherani added, “I am excited to try Daxi and expect patients will appreciate the longevity of this new neuromodulator.”

1 Samizadeh S et al. *Clin Cosmetic Investig Dermatol.* 2018;11:273-287.

2 Solish N et al. *Drugs.* 2021; 81(18):2091-2101.

thinning medication, Botox is a good option,” he said. And he added that it’s important to collaborate closely with the patient’s cornea surgeon or specialist before deciding on an approach.

Dosing. Because each patient’s eyelid position is slightly different, there is some variability in the dosing of Botox to induce ptosis. Patients with a widely open eye may need a higher dose than patients who already have some preexisting ptosis, said Dr. Malik. “I use a 30-gauge, 0.5-inch needle and start with 5 to 7.5 units injected directly into the levator palpebrae muscle, 1 centimeter below the superior orbital rim, aligned with the midpupillary plane. If there’s not sufficient ptosis at the one-week follow-up mark, then I inject another 5 units,” she said.

Injection site. Dr. Kherani injects 10 units into the upper eyelid above the tarsal plate directly into the levator muscle. “I prefer to inject transcutaneously,” she said. Dr. Fezza, on the other hand, everts the upper lid and injects about 3 units of Botox through the conjunctiva in the midpupillary line of the levator and Mueller muscles. And Dr. Wojno injects 15 to 20 units into the pretarsal and preseptal orbicularis centrally. “That will diffuse into the levator muscle and cause protective ptosis,” he explained.

Risks and Adverse Effects

While the therapeutic benefits of Botox in ophthalmology practice often outweigh the risks, there are potential adverse effects and complications. “Contraindications to Botox include patients who are pregnant or breastfeeding, who have myasthenia gravis, or those who are taking aminoglycoside antibiotics,” said Dr. Fezza. Specifically, the prescribing information for onabotulinumtoxinA advises close observation of patients taking aminoglycosides because the antibiotics may interfere with neuromuscular transmission, as well as of patients with neuromuscular disorders because they may experience muscle weakness, diplopia, or ptosis. Animal studies have shown an adverse effect on the fetus, but the drug’s effect on pregnant women and on lactation is unknown.²

Ptosis. The most common side effect of Botox injection for ophthalmic use is unwanted ptosis, and it is seen most often in the treatment of epiphora. Dr. Harrison encounters it in 10% to 15% of patients who receive BTX-A injections into the lacrimal gland. The toxin spreads into the levator muscle, causing ptosis, said Dr. Wojno.

Dr. Malik noted that precise injection directly into the center of the lacrimal gland can decrease risk. And all five doctors recommend starting with the lowest possible dose because higher doses

increase the risk of side effects.

“Keeping the volume of the toxin low can also play a role in mitigating side effects,” said Dr. Kherani. “When injecting into the lacrimal gland, I dilute 1 cc for 100 units to create a concentrated droplet that won’t diffuse as far from the injection site.” If ptosis does occur, it can be reversed using Upneeq (RVL Pharmaceuticals) or apraclonidine, she said.

Dry eye. Although some studies have looked at Botox as a treatment for dry eye symptoms,³ the five experts reported dry eye as a side effect and potential contraindication for Botox injections in and around the eyes. Dr. Malik exercises caution in injecting Botox around the eyes in patients with dry eye syndrome, as Botox injections can worsen dryness.

“Botox relaxes the orbicularis oculi muscles, so patients may not have the same power to contract,” said Dr. Kherani. “Consequently, patients may have a reduced functional blink, which could contribute to dry eye symptoms.” And Dr. Fezza pointed out, “In addition to denervating eye muscles, Botox injections can denervate the lacrimal gland and cause a worsening of dry eye symptoms by decreasing aqueous outflow.”

“If dry eye occurs after treatment, I would decrease the dosage, increase the interval between injections, and, of course, treat the dry eye symptoms with supportive measures, including lubrication and anti-inflammatory drops,” said Dr. Kherani.

Diplopia. Double vision is another possible side effect of Botox injection, but it is extremely uncommon. “Rarely, diplopia could occur if you are trying to inject into the lacrimal gland and get inadvertent diffusion into the lateral rectus muscle. To prevent this, the needle should be directed superolaterally and injected directly into the gland away from the lateral rectus muscle, avoiding the bulbar surface of the eye,” Dr. Fezza advised.

Toxin that spreads into the superior rectus muscle could also lead to double vision, according to Dr. Harrison, although he’s never seen this happen. Beyond precise injection, said Dr. Malik, “I tell patients not to rub the eye after treatment to help decrease the risk of spreading the toxin to adjacent tissues.” Additionally, Dr. Kherani prefers to use small volumes to minimize diffusion, particularly in the lacrimal gland.

Ectropion. Ectropion and tearing can occur as adverse effects of Botox treatment for entropion. “This is rare, however, occurring in less than 5% of patients,” said Dr. Harrison. Dr. Kherani noted that using a lower dose can help reduce the risks.

Systemic problems. In rare cases, the toxin can spread systemically beyond target tissues and lead to swallowing, breathing problems, or weakness. “I’ve been treating patients with Botox for ophthalmic indications since 1983, and I’ve never once encountered these rare side effects. They are highly unlikely, given the low doses used in ophthalmology injections,” said Dr. Wojno.

Resistance to therapy. Patients who repeatedly receive high doses of botulinum toxin can develop immune resistance. “Because we use such low doses in ophthalmology, resistance is extremely rare,” said Dr. Wojno. And Dr. Malik advised, “Always start with lowest dose possible and maximize intervals between treatments to minimize cumulative lifetime dosages.”

1 Singh S et al. *Oman J Ophthalmol.* 2019;12:104-107.

2 Botox prescribing information. www.rxabbvie.com/pdf/botox-cosmetic_pi.pdf. Accessed Nov. 8, 2022.

3 Choi EW et al. *Medicina.* 2021;57:247.

Meet the Experts



John P. Fezza, MD Director of cosmetic and facial surgery at Center for Sight in Sarasota, Fla. *Financial disclosures: Allergan: C,L; Revance Therapeutics: C,L; Merz: C; Visant Medical: P,PS.*



Andrew R. Harrison, MD Associate professor of ophthalmology and visual neuro-sciences at the University of Minnesota, Minneapolis. *Financial disclosures: Horizon: C,L; RVL Pharmaceuticals: C,L.*



Femida Kherani, MD Clinical associate professor of ophthalmology and visual sciences at the University of British Columbia, Vancouver. *Financial disclosures: Allergan: C; Horizon: C; Novartis: L; Santen: C; Sun Pharma: C; Tarsus: C.*



Amina I. Malik, MD Chief of ophthalmic plastic and reconstructive surgery at Houston Methodist Hospital, Houston. *Financial disclosures: None.*



Ted H. Wojno, MD Professor of ophthalmology and director of oculoplastics, orbital and cosmetic surgery at Emory Eye Center, Atlanta. *Financial disclosures: Horizon: C; Thieme Publishers: P.*

See the disclosure key, page 8.

Introducing Fortisite™

(Tobramycin 1.5% and Vancomycin 5% Ophthalmic Solution)*

Now Available in 503B

Tobramycin 1.5%



Vancomycin 5%



imprimis Rx
A HARROW COMPANY



Two **fortified** antibiotics in one patent-pending compounded formulation.*

From your trusted pharmacy partner.



100% Replacement Guarantee
No expiration-related financial risk; simple worry-free return policy



Refrigerated Formulation
3 x stability with a refrigerated formulation (150 days) vs. frozen (45 days)



Fast and Easy Ordering
Same day shipping if order is received by 12pm PST (3pm EST)



Scan to order now or visit
order.imprimisrx.com/tobra-vanc

Customer Care
844-446-6979

*For professional use only. ImprimisRx specializes in customizing medications to meet unique patient and practitioner needs. No compound medication is reviewed by the FDA for safety or efficacy. ImprimisRx does not compound copies of commercially available products. These ingredients carry risks. Visit imprimisrx.com/productinformation/ for full product details. References available upon request.

ImprimisRx and Fortisite are trademarks of Harrow IP, LLC. ©2022 ImprimisRx. All rights reserved. FORTI-00004 12/22