Novel Drug Delivery Systems

What is new in drug delivery systems for the front of the eye, and how might next-generation devices change patient care and outcomes?

By Lori Baker-Schena, MBA, EdD, Contributing Writer

EYEDROPS ARE NOTORIOUSLY HARD FOR PATIENTS TO administer properly. In one report, researchers found that 92% of eyedrop-naive postoperative cataract patients improperly administered their drops—including missing the eye, instilling an incorrect number of drops, contaminating the bottle tip, and failing to wash hands before drop instillation.[1] Because of the inherent difficulty with eyedrops (not to mention forgetting to take drops as prescribed), medications designed to lower intraocular pressure (IOP), decrease inflammation, and lessen pain can be rendered ineffective.

As drug delivery is the holy grail of anterior segment treatment, much research and development has been taking place in this arena, and novel approaches to delivery are coming to market. What is new in anterior segment drug delivery systems, and how is next-generation drug delivery changing patient care and outcomes? *EyeNet* turned to Emmett T. Cunningham, MD, PhD, MPH, founder of the Ophthalmic Innovation Summit, to identify a few of the current and emerging technologies; and several *EyeNet* editorial board members helped round out the list.

For each product—starting with those that have recently received FDA approval—an ophthalmologist familiar with the product (see financial disclosures, page 52) provided insight and opinions.

Dexycu

Manufacturer: EyePoint Pharmaceuticals
Status: FDA approved Feb. 9, 2018
Interviewing Edward J. Holland, MD

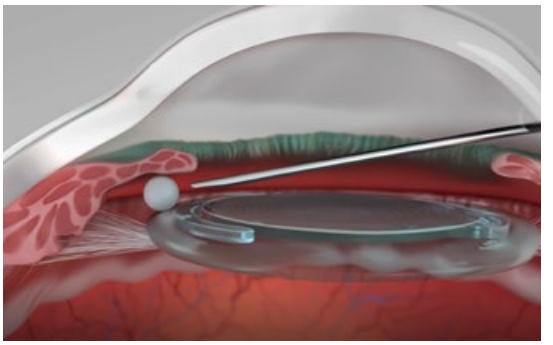
How does this technology work?
Dexycu is an anterior chamber intracameral dexamethasone drug delivery suspension that provides medication for up to 21 days with a single application to treat postoperative inflammation in patients undergoing cataract surgery. The suspension is delivered in a single injection through a cannula into the sulcus immediately following cataract surgery. Dexycu utilizes the company's proprietary bioerodable Verisome technology, which allows for sustained release of small molecules in a suspension that can be customized to release between one and six months.

What are the benefits of this device?
Dexycu is an alternative to topical corticosteroids and has two major benefits. First, the dexamethasone is placed directly where the inflammation is located, so the patient receives a higher concentration of the drug. Second, because Dexycu is used in place of steroid eyedrops, it avoids many of the issues with topical medications, such as patient difficulties with adherence to the dosing regimen and potential ocular surface complications.

In addition, Dexycu was granted pass-through status (effective Oct. 1, 2018) and assigned a J-code (J1095; effective Jan. 1, 2019).

What are the research findings?
Results from a randomized, placebo-controlled phase 3 trial involving 394 patients found that the dexamethasone drug delivery suspension was safe and effective in treating inflammation after cataract surgery.[2] Patients were randomized to 5-µL injections of placebo or 5-µL injections of 342-µg or 517-µg dexamethasone drug delivery suspension. Anterior chamber cell and flare clearing at postoperative day 8 was achieved in 33.8% of eyes in the placebo group and 63.1% and 67.3% of eyes in the 342-µg and 517-µg groups, respectively.

What are the drawbacks to this device?
The most common adverse reactions within the first 90 days postoperatively were an increase in IOP, corneal edema, and iritis. In no group did mean IOP surpass 21 mm Hg, and increases of 10 mm Hg or more over baseline were reported in 13% of placebo patients, 21% of patients who received 342 µg, and 29% of patients who received



517 µg of the drug. Corneal edema was reported in 10% of placebo patients, 6.3% of patients who received 342 µg of the drug, and 7.6% of patients who received a 517-µg dose. Iritis was more common in the placebo group (13.8%) than in the 342-µg group (2.5%) or 517-µg dosage group (3.2%). No serious ocular adverse events were reported up to 90 days following surgery.[2]

How has the device affected patient quality of life?
I have listened to patients over the years, and they just don't like eyedrops. They need three different medications following cataract surgery, and a significant number of patients have problems with them. We should all strive for solutions to drug delivery challenges. Dexycu, as a possible alternative to corticosteroid drops, is a great start.

Dextenza

Manufacturer: Ocular Therapeutix
Status: FDA approved Dec. 3, 2018
Interviewing Joseph P. Gira, MD

How does this technology work?
This sustained-release, preservative-free insert, which contains a 0.4-mg dose of dexamethasone, is implanted into the lacrimal canaliculus immediately following cataract surgery. The insert swells on contact with moisture from the tear fluid, and it continues to expand until firmly secured in the canaliculus. The proprietary hydrogel plug-like device is designed to remain in the vertical canaliculus for 30 days as it delivers the drug. During the monthlong period, the dexamethasone insert softens, liquefies, and is cleared through the nasolacrimal duct—eliminating the need for removal.

What are the benefits of this device?
The outcomes with the insert are similar to eyedrops, yet the patient does not need to take drops, thus eliminating the risk of poor patient compli-

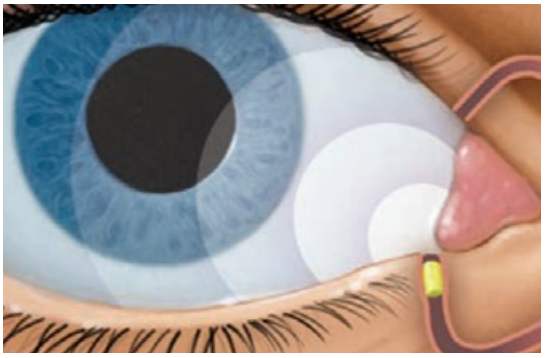
ance. Other benefits include the constant low-dose drug load on the ocular surface, the absence of preservatives, and improved bioavailability.

What are the research findings?
Results from a parallel-arm, double-masked phase 3 study involving 438 patients at 21 sites who were randomized to receive the sustained-release intracanalicular dexamethasone insert or a placebo demonstrated the insert was safe and effective in treating ocular pain and inflammation following cataract surgery.[3] At day 14 after placement, 52.3% of patients in the insert group had an absence of anterior chamber cells compared with 31.1% in the placebo group. Additionally, at day 8, 79.6% of patients in the insert group had an absence of ocular pain compared with 61.3% in the placebo group. Patients in the insert group experienced a decrease in inflammation as early as day 4 after surgery and a decrease in pain as early as day 1.

What are the drawbacks to this device?
The insert is contraindicated for active corneal, conjunctival, or canalicular infections.

How has the device affected patient quality of life?
We conducted a qualitative survey evaluating the experience of 25 patients after Dextenza implantation.[4] Most patients (92%) reported the highest level of overall product satisfaction. They described the insert as comfortable and convenient. Compared to previous topical therapy, 96% of the participants rated their experience with the insert as "very" or "extremely" convenient, with 88% saying they would request the insert again if they were to undergo another cataract surgery. While more extensive evaluation is needed, it appears that patients prefer the insert over topical alternatives. It is comfortable and convenient.

Note: The company reports that it applied to CMS for pass-through status and a J-code.



Bimatoprost SR

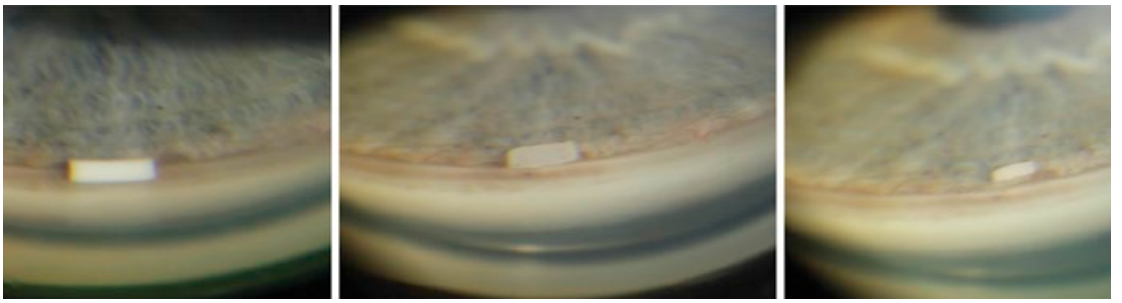
Manufacturer: Allergan
Status: Phase 3 trial data submitted to the FDA, and NDA filing expected mid-2019
Interviewing E. Randy Craven, MD

How does this technology work?
Bimatoprost SR is the first-in-class sustained-release, biodegradable implant for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension. It is placed in the anterior chamber through an injector system using a 27-gauge needle, much like doing a paracentesis. Then it drifts down to the inferior iridocorneal angle, where it slowly dissolves over many months. Interestingly, the total weight of the drug in the implant is equal to one drop of the topical Lumigan.

What are the benefits of this implant?
I see this as having huge potential benefit to glaucoma patients who do not want to deal with drops and are fearful of a laser or incisional surgery. Pseudophakic patients are ideal. Additionally, this biodegradable device reassures me that patients are receiving medication, which alleviates my noncompliance fears.

What are the research findings?
Results from the phase 1/2 clinical trial demonstrated that Bimatoprost SR provided rapid, sustained IOP lowering.[5] The Bimatoprost SR dose strengths were 6-µg, 10-µg, 15-µg, or 20-µg, and the overall mean IOP reduction from baseline at four months in the Bimatoprost SR eyes ranged from 7.2 mm Hg to 9.5 mm Hg while topical bimatoprost-treated fellow eyes had a reduction of 8.4 mm Hg. In the phase 3 trials, we found dosing between 10-µg and 15-µg worked well. In addition, we were surprised to learn that for one in four patients, a single injection worked for 24 months.

What are the drawbacks to this implant?
After insertion, I look for a 30% pressure reduction. However, once the pressure creeps up, the patient may need more treatment. We can insert another implant, and we have had a few patients with a couple of these stacked up in the angle. The implant slowly dissolves over time. However, many patients have residual implant visible for over a year and others do not. We need to figure out how many of them can be placed in the eye. It is nice having the drops as a backup.



Also, anytime you insert something in the eye, it can cause side effects, so we are watching the long-term data to see if the product is safe.

How has the device affected patient quality of life?
Most strikingly, while long-term bimatoprost drops can cause red, irritated eyes, the implant does not cause reddening, much to the delight of my patients. And, of course, patients can benefit from sustained drug control without having to deal with drops.

Piezo-Print Microdose Delivery

Manufacturer: Eyenovia

Status: Phase 3 trial studying topical latanoprost (MicroProst) is expected in 2019. Other microdose drugs for mydriasis, myopia, and dry eye are in the pipeline.

Interviewing Robert N. Weinreb, MD

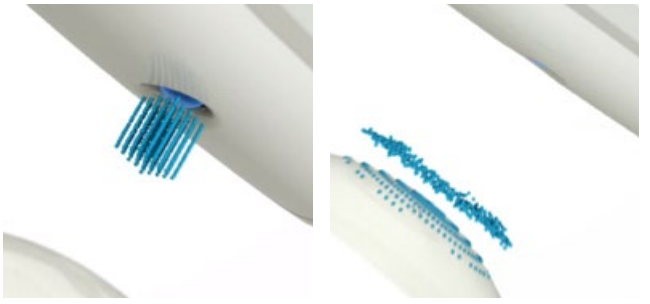
How does this technology work?
The concept of piezo-print technology is reminiscent of how inkjet printers deliver a pixel-sharp fluid spray of droplets to create images. This ophthalmic dispenser releases a precisely calibrated and tightly collimated stream of aqueous ocular medication microdroplets. The medication is dispersed at the micron level, using electrostatic droplet charging for high-adhesive ocular surface coating. Piezo-print microdosing delivers drugs in less than 80 milliseconds, faster than the eye's 100-ms blink reflex.

What are the benefits of this device?
It offers a tremendous opportunity to provide safer, better-tolerated, and effective medications that can be more readily and reliably delivered to the patient. Two previous phase 2 clinical trials studying topical phenylephrine showed that microdosing achieved a pharmacodynamics effect equivalent to conventional eyedrop dosing, but with a 75% reduction in total drug dose and preservative delivery to the eye.[6] Microdose delivery avoids problems associated with drug overflow and systemic absorption, and it may increase local drug bioavailability and absorption in the eye.

What are the research findings?
Results from a phase 2 study of a 0.4-µg microdose of latanoprost demonstrated significant IOP reduction.[7] In the study, 60 eyes of 30 healthy volunteers received single 8-µL microdoses of 0.005% latanoprost on the mornings of days 1 and 2. Diurnal IOP was measured before and two days after microdosing. The microdose of latanoprost reduced the baseline IOP by 26% at day 1 postadministration and by 30% at day 2. All the patients were able to self-administer the microdoses following training, and no adverse effects were reported. In addition, no part of the dispenser touched the eye or periocular area.

What are the drawbacks to this device?
One drawback is that the technology has not been used in large numbers of patients to demonstrate efficacy, safety, and tolerability. In addition, the microdose needs to be directly compared to the 1.6-µg dosing of a standard eyedropper in a randomized controlled study.

How has the device affected patient quality of life?
The technology directly addresses the challenges set forth in a quote by C. Everett Koop, MD, former U.S. Surgeon General: "Drugs don't work in patients who don't take them."



Lewis RA et al. *Am J Ophthalmol.* 2017;175:137-147.

iDose

Manufacturer: Glaukos
Status: Currently in phase 3 trials
Interviewing Mark J. Gallardo, MD

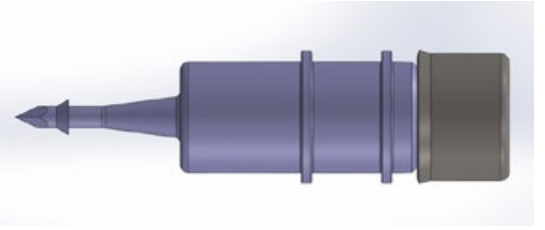
How does this technology work?
iDose is a titanium implant (1.8 mm × 0.5 mm) loaded with a proprietary formulation of travoprost. It is designed to continuously elute therapeutic levels of the drug into the anterior chamber. Phase 2 data suggest potential efficacy up to 12 months, after which the implant is designed to be removed and replaced with a new iDose device. The implant is placed through a clear corneal incision using an injector similar to the iStent inject (two stents placed during a single procedure). The device has an anchor that is placed through Schlemm's canal into the sclera to maintain the device in a fixed location.

What are the benefits of this device?
The most compelling aspect of the iDose is that by implanting the device intracamerally, we are avoiding all the adverse effects of topical prostaglandin analogs: periorbital fat atrophy, blepharitis, hypertrichosis, conjunctival hyperemia. Minimizing the need for topical therapy also reduces the eyes' exposure to benzalkonium chloride, which has been shown to exacerbate ocular surface disease and induce apoptosis of the endothelial cells lining trabecular columns. Once the efficacy of the device has diminished, it can be grasped, removed, and then replaced.

What are the research findings?
In a Jan. 10, 2018, press release, the company reported that it was conducting a 154-patient, randomized double blind phase 2 trial, which evaluated two models of the iDose delivery system with two different travoprost elution rates, compared to topical timolol ophthalmic solution, 0.5%. Results from a 12-month interim cohort of 49 implant patients showed that they achieved an approximate 30% reduction in mean IOP vs. baseline IOP during the first 12 months, with a favorable safety profile.[8]

What are the drawbacks to this device?
Because a corneal incision and anterior chamber maintenance with viscoelastic is required for device implantation, we must perform this procedure in an OR. So we have to weigh the risk and benefits of subjecting the patient to a minor surgical procedure if done as a stand-alone procedure. Our decision may be guided by duration of efficacy of the device. As far as long-term efficacy, the phase 3 studies should provide the information, as the studies have a three-year follow-up.

How has the device affected patient quality of life?
There are multiple flaws in asking patients to perpetually use drops to manage their glaucoma. The cost of medications is rising; compliance decreases as the number of medications increases; and topical therapy has been associated with multiple adverse side effects of the eye and ocular adnexa. This device provides us with another tool to battle glaucoma and improve a patient's quality of life by minimizing the need for topical therapy.

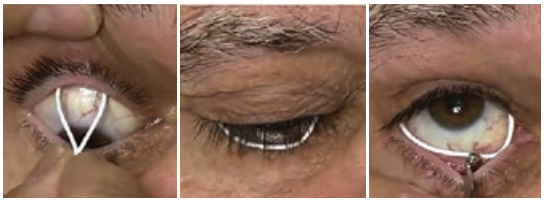


Bimatoprost Ring

Manufacturer: Allergan
Status: Phase 2 and open-label extension (OLE) complete
Interviewing James B. Brandt, MD

How does this technology work?
The technology is deceptively simple. The ring is a soft, flexible ocular insert containing 13 mg bimatoprost mixed into a silicone matrix placed over an inner polypropylene support structure. The drug release occurs when the patient's tears come in contact with the device, causing molecular diffusion of the drug through the silicone matrix. Manufactured in diameters ranging from 24 to 29 mm, the ring sits circumferentially in the fornices on top of the conjunctiva and elutes bimatoprost for up to six months at a time. Insertion can be compared to placing a contact lens.

What are the benefits of this device?
My concern about the injectable devices is that inserting needles inside eyes is not without risk, even if this risk is small. The biggest advantage to this platform over injectable devices is safety and reversibility. It is also quite easy to insert, and virtually all the patients in the study hardly felt the device after a few days. In addition, the patient is aware if the device is dislodged or falls out, and he or she can seek attention immediately.



What are the research findings?
Results from the phase 2 study demonstrated a clinically relevant reduction in mean IOP over a six-month period with the bimatoprost ring.[9] Patients with open-angle glaucoma or ocular hypertension were randomized to receive either a bimatoprost insert and twice-daily artificial tears or a placebo insert and twice-daily timolol drops (0.5% solution) for six months. A mean reduction of 3.2 to 6.4 mm Hg from baseline IOP was observed with the ring group compared with 4.2 to 6.4 mm Hg for the timolol group. A 13-month open-label extension of the study showed a median IOP reduction of 4 mm Hg, with the rings remaining in place for 95% of patients.[10]

What are the drawbacks to this device?
The challenge for the sustained-release devices under development for glaucoma is that many patients need more than one drug to achieve their clinical target IOP. As exciting as sustained-release medicines are, we cannot promise patients a drug-free life because none of these platforms allows for loading of more than one drug. The ring platform has the potential to carry more than one drug, but we're probably years away from commercialization of multidrug rings. In the meantime, patients can take another drop on top of the ring.

How has the device affected patient quality of life?
The safety-efficacy balance is ideal for the large population of patients with ocular hypertension or early glaucoma who respond to prostaglandins but are inconsistent with eyedrops. Interestingly, a side effect of the ring is the production of mucus, and in patients with a history of dry eyes, patients find that their dry eye symptoms improve as the device stimulates more mucin to enter the tear film.

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Meet the Experts

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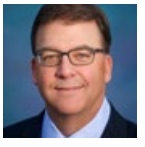

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See disclosure key, page 10.