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COMMENTARY

Adopting Interventional Glaucoma Via Sustained-Release Therapies: The Wide-Ranging Impact of Procedural Pharmaceuticals in Ophthalmology

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ABSTRACT

Topical medical therapy is the most common approach to the treatment of many ocular conditions. While effective, topical therapy has numerous important limitations. Eye drops can have unpleasant or even dangerous side effects, are often difficult to self-administer, and the application of multiple drops per day, possibly from multiple different bottles, can be burdensome. Perhaps the most important limitation of topical medical therapy is non-adherence, a complex multifactorial behavior that increases the risk of poor outcomes associated with undertreatment. There is growing interest in a class of therapeutics termed "procedural pharmaceuticals" (PPs), which remove the responsibility of self-dosing from patients. An array of PPs are available for the treatment of a variety of ocular conditions, such as those for glaucoma, retina, and cataract surgery; and many more will emerge in coming years. A paradigm shift away from patient-administered therapy toward provider-administered therapy will have important implications for both providers and patients. This paper explores the impact that PPs have had, and will have, on the clinical practice of ophthalmology.

Keywords: Medication; Intervention/interventional; Glaucoma; Procedure; Provider; Adherence

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Key Summary Points
Topical eyedrops are the most common initial therapy for the treatment of many ocular conditions.
However, topical medications have numerous important limitations such as local and systemic side effects, ocular surface disease, difficulty with self-administration, and high rates of non-adherence.
As an alternative to topical therapy, provider-administered procedural pharmaceuticals (PPs) have been developed across ophthalmology.
This article covers PPs in glaucoma, retina, and cataract surgery settings, and explores the impact they have had on the clinical practice of ophthalmology.
With particular emphasis on glaucoma, the article illustrates how PPs can help enable a shift toward earlier, more proactive glaucoma treatment (coined "interventional glaucoma") and ultimately better management of the disease.

INTRODUCTION

Medical therapy is the most common form of treatment for many acute and chronic ocular conditions. Topical application onto the ocular surface is the most prevalent route of medicine delivery, relying on trans-corneal drug transmission to reach the desired ocular tissues. For the treatment of glaucoma, daily topical treatment has become a convenient and low-effort option for physicians, who need only to write a prescription. In contrast, daily topical treatment for patients can be a burden, as they must successfully self-administer therapy one or more times daily for a lifetime. Eyedrop instillation can be technically challenging and difficult for many patients to perform consistently. Nonadherence with therapy is common and is a major risk factor for progressive glaucoma and poor visual outcomes [1, 2]. In recognition of these limitations of topical medical therapy, there is growing interest in procedural pharmaceuticals (PPs). PPs are treatments that combine an active drug agent with an implant or administration modality in order to directly deliver medication to targeted tissue or anatomical structures. These treatments are administered by the provider as an alternative to daily self-administered topical treatments. As the number of PP options for common ocular conditions expands, paradigms are changing and novel treatment patterns are evolving. This paper explores the multifaceted impact of PPs on patient care and on clinical outcomes in ophthalmology.

ADHERENCE: LESSONS FROM GLAUCOMA

For more than 150 years—since the isolation of physostigmine from the bean of the Calabar plant in 1862—topical medical therapy has been the mainstay of treatment for glaucoma [3]. Over this time period, dozens of topical medications in a variety of drug classes have been developed that lower intraocular pressure (IOP) through a variety of mechanisms. One or more of these medications is traditionally prescribed as first-line therapy for glaucoma, and many patients ultimately require two or more medications for adequate IOP control [4, 5]. In addition to the burden and hassle of self-administration, topical therapy is associated with numerous side effects. For a variety of complex reasons, nonadherence with topical therapy is common and increases the risk of disease progression. To address these limitations, the glaucoma treatment paradigm is undergoing significant evolution. Selective laser trabeculoplasty (SLT) has become the preferred first-line therapy for many providers and patients [6, 7], and the advent of minimally invasive glaucoma surgery (MIGS) is expanding surgical indications to include patients with early or mild disease who do not otherwise warrant the risks of traditional filtering surgery. The recent development and commercialization of several sustained-release glaucoma drug delivery platforms is poised to further disrupt the treatment paradigm. The emerging paradigm,

coined "interventional glaucoma," [8–10] advocates safe, early, proactive procedural intervention instead of the former reliance on extended topical drop therapy. The therapies in this interventional paradigm—SLT, MIGS, and sustained-release options—are physician-administered and represent a significant change in mindset to the approach of glaucoma clinical practice.

Physician-administered medical therapy offers significant benefits over topical medical therapy in glaucoma. One of the most important benefits is the reduction or elimination of nonadherence to daily medicine use. Many patients with glaucoma—estimates in the literature range from 30 to 80% [2, 11–14]—miss doses periodically. Nonadherence in glaucoma is multifactorial, complex, and incompletely characterized [15–17]. The behavior can be broadly divided into intentional and unintentional categories. In the former, nonadherence may be rooted in a belief that the therapy is ineffective or unnecessary, or it may represent an effort to avoid unpleasant side effects [18]. In the latter, which represents the majority of all nonadherence [19], factors such as physical or cognitive limitations may preclude consistent dosing. Successful delivery of medication from a bottle to the eye on a consistent schedule requires organization, memory, and dexterity. In the aging glaucoma population, memory impairment and dementia, as well as physical maladies such as arthritis and tremor, are common comorbidities that limit patients' ability to adhere to topical therapy. Even among those without physical or cognitive limitations, errors made during the instillation process are common—up to 76% of patients miss the eye entirely [20–23]—and can lead to premature medication depletion, as well as medication nonadherence unbeknownst to the patient [24–26].

Nonadherence compromises IOP control and increases the risk of glaucoma progression and vision loss [1, 2, 11, 27]. Rossi and colleagues evaluated adherence among patients with glaucoma with stable versus progressing visual field testing using a dosing aid to monitor adherence; they found that the median adherence rates were 85% among stable patients and 21% among progressing patients ($p < 0.001$) [2]. Sleath and coworkers conducted a cross-sectional study to characterize the relationship between topical medication adherence (measured by a medication events monitoring system) and severity of glaucoma (measured by visual field testing). They reported that patients taking fewer than 80% of prescribed doses were significantly more likely to have worse visual field defects compared to more adherent patients [11]. In a similar study, Konstas and colleagues demonstrated a significant relationship between nonadherence and greater visual field loss [27]. Newman-Casey and colleagues tapped the Collaborative Initial Glaucoma Treatment Study data set to evaluate the effect of self-reported nonadherence on visual field progression and found that the rate of visual field loss over time was highly correlated with the frequency of missed doses [1].

In addition to nonadherence and its associated risk of glaucoma progression, topical medical therapy is associated with significant burden to the patient. Topical medical therapy can be time-consuming, both from a medication instillation perspective as well as a medication acquisition perspective. For instance, patients on a multiple medication regimen are advised to wait at least 5 min between medications to avoid the washout effect, and patients may require monthly trips to the pharmacy to obtain refills. The cost of medications and delayed access to refills pose additional barriers to adherence.

In addition to the burden of scheduled dosing of medicine, topical therapy is associated with multiple adverse effects that can compromise patient safety and satisfaction. Side effects of therapy can range from mild tolerability issues to frank safety concerns. For instance, topical prostaglandin analogues cause a host of issues such as conjunctival hyperemia, iris color change, eyelash growth, and eyelid pigmentation [28], as well as a constellation of findings that include deepening of the upper eyelid sulcus, upper eyelid ptosis, orbital fat atrophy, and enophthalmos collectively termed prostaglandin-associated periorbitopathy [29]. Side effects may also be systemic. Topical beta-blockers achieve sufficient systemic plasma levels to induce systemic beta-blockade with associated symptoms that can include bradycardia, cardiac arrhythmias, depression, erectile dysfunction, and even death

[30, 31]. Many patients with glaucoma have systemic comorbidities that render some topical medications relatively or absolutely contraindicated, and many of these patients are receiving a variety of systemic medications that can pose interaction risks with glaucoma therapies, such as the use of brimonidine in patients on certain antidepressant medications [32].

Perhaps the most common side effect associated with topical medical therapy for glaucoma is the development of ocular surface disease (OSD). Various studies have demonstrated that the chronic use of topical glaucoma medications causes OSD in roughly 50% of patients [33–39]. OSD has been associated with the use of virtually every class of glaucoma medications and is likely mediated by toxicities related to the near-ubiquitous preservative benzalkonium chloride (BAK) [40]. The chronic ocular surface toxicity and inflammation triggered by BAK can even increase the risk of failure of subsequent glaucoma surgery [41]. Symptoms of OSD adversely affect quality of life in patients with glaucoma [42, 43]. Indeed, in a willingness-to-pay analysis, 72% of patients indicated they would pay more (a mean of USD $62 more) for a drop that did not cause burning/stinging [44]. OSD and other side effects can promote nonadherence, setting up a vicious cycle of higher IOP, more medications, worse OSD symptoms, further nonadherence, and eventual disease progression [45].

A paradigm shift from topical medical therapy to PPs for glaucoma would be expected to improve or eliminate nonadherence, reduce side effects, and improve patients' visual outcomes. There are currently two glaucoma PPs available in the United States: the bimatoprost SR intracameral implant (Durysta, Allergan, an AbbVie Company) and the travoprost intracameral implant (iDose, Glaukos). Both are sustained-release formulations of prostaglandin analogues. The bimatoprost implant is rod-shaped and incorporates bimatoprost into a biodegradable polymer matrix [46, 47]. It is administered by injection into the anterior chamber, where it is unanchored and free-floating, and was designed to provide IOP control for 3–4 months. In phase 3 trials, the implant provided IOP reduction that was noninferior to topical timolol maleate at 12 weeks [46, 47]. The most common side effect was hyperemia (27%). Other side effects occurring in 5–10% of eyes included foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, IOP increased, corneal endothelial cell loss, vision blurred, iritis, and headache. Repeated dosing at a 4-month interval demonstrated that 5.4% of patients had some level of reduction of corneal endothelial cell density and ultimately bimatoprost SR was FDA-approved for one-time administration [48]. The travoprost implant consists of a drug reservoir and a semipermeable membrane through which the drug elutes. The reservoir anchors for scleral fixation within the iridocorneal angle that stabilizes the device in position [49]. In a phase 2 study, the majority of subjects remained well controlled at 36 months [49]. In a phase 3 trial, the implant provided IOP reduction that was noninferior to timolol at 12 weeks [49] and 12 months [50]. Side effects occurring in 2–6% of eyes included dry eye, iritis, increased IOP, and visual field defect. No clinically meaningful changes in mean endothelial cell density were seen at 3 months with the travoprost implant, and no eyes in the trial experienced a ≥ 30% reduction in endothelial cell density from baseline.

In addition to better controlling IOP, a paradigm shift from topical medical therapy to PPs would also be expected to improve patients' overall treatment experience. For example, in the randomized pivotal trial of the iStent *inject* trabecular micro-bypass device, greater reductions in medication use in the micro-bypass group compared to the cataract-only group correlated with greater improvement in quality of life [51]. Similar correlations between medication reduction and improved quality of life have been shown with other MIGS procedures, albeit in less robust real-world studies [52, 53]. The landmark Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) demonstrated that newly diagnosed patients receiving primary SLT at the time of diagnosis had less glaucoma progression and required glaucoma surgery less often than patients receiving primary topical medical therapy [54], underscoring the benefit of eliminating nonadherence from the treatment paradigm by eschewing topical medical therapy for a physician-administered option. Interestingly,

the LiGHT trial failed to show a difference in quality of life among patients receiving primary therapy with SLT versus topical medications. Given the detrimental effects of topical therapy on ocular health and patient satisfaction, this was an unexpected finding and likely arose from the use of an instrument that measures the effect of glaucoma—and not glaucoma therapy—on quality of life, as both treatment groups were balanced for glaucoma status. To robustly demonstrate the benefits of physician-administered therapies on quality of life and patient satisfaction for patients, providers, and payors, there remains a significant unmet need for an instrument that assesses the impact of glaucoma *therapy* on quality of life.

The widespread adoption of PPs in glaucoma care may pose some challenges. Clinical workflow will be impacted by a more procedure-oriented approach to glaucoma. Likewise, surgical volume may rise given that some glaucoma PPs may require surgical implantation. There will be a learning curve for some providers, and there may be a shift in the distribution of patients with glaucoma among provider practices, as the many early-to-moderate patients with glaucoma being managed by optometrists will require the surgical skills of ophthalmologists and some comprehensive ophthalmologist may elect not to incorporate PP skills into their repertoires. There are also potential risks and complications (albeit small) of PPs that may be greater than their topical counterparts, including the risks of the delivery procedure.

Given that currently available glaucoma PPs are also available as topical medications, it remains to be seen how patients, providers, and payors will value their attributes and adopt these new treatment options into practice patterns.

EFFICACY: LESSONS FROM RETINA

The development and broad implementation of vascular endothelial growth factor (VEGF) inhibitors for a variety of posterior segment conditions represents one of the most impactful treatment paradigm changes in the history of ophthalmology [55]. For example, nearly overnight, the treatment paradigm for center-involving neovascular age-related macular degeneration (nARMD) evolved from vision-destroying laser ablation to vision-restoring medication injections. Twenty years ago, the preferred treatment for a subfoveal nARMD lesion was to photocoagulate the macula and sacrifice central vision in the short term to ensure a smaller central scotoma compared to the untreated natural history of nARMD. Now, patients can expect visual stabilization and even visual gains with anti-VEGF therapy. In the past two decades, next-generation anti-VEGF agents and novel therapeutics that target parallel disease pathways have increased dose durability from monthly to every 2–4 months to decrease the treatment burden, resulting in improved safety, cost, and overall patient experience.

Anti-VEGF medications are injected intravitreally at various intervals by the provider. Unlike glaucoma PPs, there are no alternative patient-administered drug equivalents—every dose of anti-VEGF therapy for every patient must be administered by the provider. Consequently, the high acceptance of regular intraocular injections by patients, providers, and payors is attributable to the lack of any alternative topical vision-saving therapy and may not fully reflect patients' or providers' attitudes and acceptance of the procedural nature of the treatment. Nevertheless, the universal adoption of anti-VEGF therapy as preferred therapy for a variety of retinal disorders speaks to the potential for broad acceptance of PPs if patients, providers, and payors understand their value—but it will be incumbent upon researchers to demonstrate this value through well-designed clinical trials with appropriate patient-centric endpoints, and upon providers to communicate this value to patients and payors.

The arrival of the anti-VEGF era was also demonstrative of the enormous impact that a shift to PPs has on the delivery of healthcare. The clinical workflow of the retina practice was immediately challenged and burdened by the need to evaluate and treat patients on a monthly basis, as the early studies implemented monthly therapy as the initial standard retreatment interval [56]. Overnight, patients who had been seen one or two times yearly were now seen monthly,

and retina practices had to quickly pivot to a procedure-based model of care as every patient required reinjection at every visit [57, 58]. Patients and their families incurred significant travel burden [59], and providers had to adapt many aspects of clinical practice. The increased patient volume required additional staff to manage the clinical work-up and frequent diagnostic imaging to guide treatment decisions. Business models were forced to adapt as well. Active inventories of multiple expensive drugs had to be maintained on-site for easy access, and inventory had to be carefully managed to minimize drug loss due to expiration before use [60]. Additional human resources became necessary to ensure that preauthorization/precertification was in place to avoid leaving patients with large out-of-pocket expenses or practices taking the losses for treatments administered without prior authorization. To ease the burden for all parties, efforts were made to shift from monthly to as-needed retreatment strategies. However, outcomes were shown to be inferior to routine monthly treatment [61–65], and fluctuations in retinal thickness could result in retinal damage over time [66, 67]. Eventually, individualized treat-and-extend intervals were established to optimize outcomes while minimizing burden [68–70], and newer drugs with longer dosing intervals further decreased the patient burden [71–74].

As PPs become more widely available for a diversity of ocular conditions, comprehensive and specialty eye care providers will face the same challenges the retina community has dealt with for nearly 20 years. Not all solutions adopted in the retina space will generalize to other practice settings, but many of the lessons learned throughout the anti-VEGF era will provide a blueprint for the incorporation of PPs into other therapeutic areas in ophthalmology.

SAFETY: LESSONS FROM CATARACT SURGERY

Cataract surgery is the most commonly performed surgical procedure on adults, with an estimated 3.7 million cases per year in the United States and 20 million worldwide [75]. Every aspect of modern cataract surgery has been precision-designed for perfection, including automated biometry, intraoperative aberrometry, intraocular lenses (IOLs) and IOL formulas, wound architecture (self-sealing/no-suture), and phacoemulsification and femtosecond laser techniques [76]. Together, these advances provide high rates of spectacle independence, which in turn yields improved quality of life [77] and cost-effectiveness over spectacles [78, 79]. This technical evolution has produced a procedure with consistent and predictably excellent outcomes, resulting in high patient expectations. Also, while the preoperative and intraoperative aspects of cataract surgery are within surgeons' control, preventing postoperative inflammation and infection depends on patent adherence to a complex regimen of postoperative anti-inflammatory and antimicrobial eye drops.

Inflammation is among the most common postoperative complications of virtually all surgical procedures, including phacoemulsification. Unlike many non-ocular procedures—in which inflammation is a critical component of the healing process—the immune privilege of the eye coupled with the unique nature of self-sealing phacoemulsification incisions through the avascular cornea render postoperative inflammation more of a liability than an asset in the healing process. Postoperative ocular inflammation occurs in approximately 95% of eyes [80] and increases the risk of discomfort, visual impairment, and cystoid macular edema (CME) [81, 82], the latter of which is the most common cause of vision loss after cataract surgery [83].

Postoperative infectious endophthalmitis is a much rarer complication of modern cataract surgery, but can be visually devastating. The incidence of acute postoperative endophthalmitis is approximately 0.063% (or approximately 1 in 160 cases) following phacoemulsification with topical postoperative antibiotic prophylaxis [84]. Outcomes depend on prompt recognition and evidence-based management, with approximately 25% of eyes achieving final visual acuity of worse than 20/100 and 5% having no light perception [85].

Unlike the remarkable technological evolution of the phacoemulsification procedure since

it was first described by Kelman in 1967 [86], the standard approach to the control of postoperative inflammation and infection—topical eye drops administered by the patient—has remained virtually unchanged over the past 50 years. Postoperative cataract patients are tasked with the responsibility to self-administer a complex regimen of up to 3 medications over the weeks following surgery, each having its own dosing schedule coupled with a variable taper over time [87]. The complexity of this regimen contributes to nonadherence [16, 24, 88–92], increasing the risk of discomfort, delayed or decreased visual recovery, and patient dissatisfaction [93]. Even when trying to adhere, many cataract patients are unfamiliar with the technique of eye drop instillation and fail to properly self-dose the medications [94], further increasing the risk of poor outcomes related to inflammation and/or infection.

Placing responsibility for postoperative inflammation and infection control into the hands of surgeons would be expected to improve outcomes and patient satisfaction with the postoperative experience. In fact, a paradigm shift to drop-free cataract surgery using PPs for infection and inflammation control is underway [76, 95–98]. Two different sustained-release formulations of the corticosteroid dexamethasone have been developed and are available for use in the United Staes and other global markets. The dexamethasone intracanalicular insert (Dextenza, Ocular Therapeutix) is a rod-shaped depot containing 4 mg of dexamethasone in a resorbable hydrogel polymer matrix that elutes into the tear film for ocular absorption in a tapering fashion over 30 days [99]. Multiple phase 3 trials have demonstrated its efficacy and safety in controlling both postoperative inflammation and pain following cataract surgery [100, 101]. The most common postoperative complication in clinical trials was transient IOP elevation which was equally common in both the insert and the placebo groups. The insert can be placed by an ophthalmologist or optometrist before, during or after surgery for maximal flexibility [102–105]. The dexamethasone intraocular suspension (Dexycu, EyePoint Pharmaceuticals) is a 9% solution injected into the posterior chamber at the end of surgery [106]. The formulation uses proprietary polymer technology that forms a floating sphere measuring approximately 2 mm in diameter [107] that delivers therapeutic drug levels for up to 21 days [108]. In a phase 3 trial, the suspension safely and effectively controlled postoperative inflammation (pain was not an outcome measure); IOP elevation was the most common adverse event and was equally common in the active and placebo arms [108].

Replacing postoperative topical antibiotic therapy—which has not been demonstrated to effectively reduce or prevent the development of postoperative endophthalmitis [109]—with intracamerally administered antibiotics at the time of surgery has been shown in multiple large trials to dramatically reduce or even eliminate the risk of postoperative endophthalmitis. The European Society of Cataract and Refractive Surgeons randomized trial demonstrated a fivefold reduction in endophthalmitis risk with the use of intracameral cefuroxime versus various topical regimens [110]. This finding was confirmed in a series of additional studies [111–113], including a series of over 400,000 surgeries in Iran in which no cases of endophthalmitis occurred in the > 25,000 eyes that received intracameral antibiotics [114]. However, amid concerns for potential safety issues, lack of therapeutics formulated and approved specifically for intracameral use, and absence of any global consensus on protocols for therapy, this promising approach to postoperative infection control has not enjoyed a broad paradigm shift to date [115].

A paradigm shift to a drop-free regimen of anti-inflammatory and antimicrobial therapy after cataract surgery would represent a significant movement away from topical therapy and toward a multi-drug PP approach that would likely improve both clinical outcomes and patient satisfaction. In addition to the abovementioned studies, robust randomized evidence may be needed to fuel such a shift. For example, a recent randomized trial may play a key role in advancing the drop-free approach. In this trial, 41 patients undergoing bilateral sequential cataract surgery randomly received standard topical therapy in one eye (moxifloxacin, ketorolac, and prednisolone acetate) and intracameral moxifloxacin and ketorolac and the intracanalicular

dexamethasone insert in the fellow eye [98]. The primary outcome measure was postoperative pain, with inflammation, patient satisfaction, and safety being secondary outcomes. Assessments were made by study personnel masked to treatment assignment. In the study, the proportion of pain-free eyes was similar in both groups, and inflammation scores were also similar. Visual gains were also comparable between groups. The treatments were equally safe, and interestingly, the out-of-pocket drug cost was lower in the dropless group (mean USD $26) than the topical group (mean USD $184). Importantly, 95% of patients preferred the dropless regimen over topical therapy, likely related in part to the 250+drops required to be instilled over one month in the topical group. This latter finding is important, as patient demand for a new therapy can be a critical driver of paradigm change.

DISCUSSION

Ongoing advances in medical therapy ensure that treatment paradigms are constantly in evolving. Recognizing that topical medications have numerous critical limitations that compromise clinical outcomes and diminish patient satisfaction, there is growing interest in a shift from patient self-administration of therapy to provider-delivered therapy. Several ophthalmic PPs have already been developed and more will continue to emerge for a variety of ocular conditions, with key lessons from glaucoma, retina, and cataract surgery (as discussed in this paper). The adoption of a procedural pharmaceutical approach to medical therapy removes dosing responsibility from patients, thereby improving adherence, leading to better efficacy and safety, and ultimately to better outcomes and greater patient satisfaction. This paradigm shift comes with significant disruption to current clinical care models and will require adaptation and problem-solving. Many modifications have already been assimilated into retina practice and may generalize to other specialty practices; others will require novel solutions to ensure the optimal implementation of provider-based medical therapy. The transition to procedural therapies administered by providers will bring many new challenges to the practice of ophthalmology but is expected to significantly improve patients' vision and lives.

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