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COMMENTARY

Challenging the "Topical Medications-First" Approach to Glaucoma: A Treatment Paradigm in Evolution

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ABSTRACT

Topical glaucoma medications are effective and safe, but they have numerous well-documented limitations that diminish their long-term utility and sustainability. These limitations can include high rates of nonadherence (with associated glaucoma progression), concerning side effects, inconsistent circadian intraocular pressure (IOP) control, complex dosing regimens, difficulty with self-administration, costs, and decreased quality of life. Despite these limitations, topical medications traditionally have been first-line in the glaucoma treatment algorithm, as no other minimally invasive treatment alternatives existed. In recent years, however, novel interventional therapies—including sustained-release drug-delivery platforms, selective laser trabeculoplasty, and micro-invasive glaucoma surgery procedures—have made it possible to intervene earlier without relying on topical medications. As a result, the topical medication-first treatment approach is being reevaluated in an overall shift toward earlier more proactive interventions.

Keywords: Intervention; Treatment; Early; SRDD/sustained release drug delivery; MIGS/micro-invasive glaucoma surgery; Medication; SLT/selective laser trabeculoplasty

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Key Summary Points

Topical medications traditionally have been first-line in the glaucoma treatment paradigm. However, their usage is limited by a host of widespread and impactful downsides, including nonadherence (with associated glaucoma progression), side effects, inconsistent circadian intraocular pressure (IOP) control, complex dosing regimens, difficulty with self-administration, costs, and decreased quality of life.

In the past, the limitations of topical medications were accepted due to the lack of viable alternatives, but this may now no longer be the case.

Novel minimally invasive interventions, including sustained-release drug-delivery platforms, selective laser trabeculoplasty, and micro-invasive glaucoma surgery, are being used earlier in the treatment cascade, including as the first-line therapy.

This shift toward earlier intervention has led to an overall reevaluation of the glaucoma treatment paradigm.

In the coming years, it may be possible and desirable for the topical medication-first approach to be replaced by earlier more interventional therapies that are more effective and less adversely impactful on patients, doctors, and society.

MEDICATIONS FIRST: REEXAMINING AN AGING GLAUCOMA TREATMENT PARADIGM

For more than 150 years—since the discovery of physostigmine isolated from the Calabar bean [1]—topical medical therapy has been the preferred first-line treatment for primary open-angle glaucoma. Other drugs followed, including pilocarpine and epinephrine, and the era of modern glaucoma pharmacology commenced with the development of timolol in the 1970s [2]. The 1990s saw a rapid expansion of medical options for glaucoma, including the first prostaglandin analogue (latanoprost), the first topical carbonic anhydrase inhibitor (dorzolamide), and the first alpha adrenergic agonist (brimonidine) [2]. The first-line utilization of medications has been validated in numerous multicentered clinical trials designed to evaluate its efficacy and safety in the primary treatment of open-angle glaucoma (OAG) or ocular hypertension (OHT) [3–7]. As recently as 2020, the American Academy of Ophthalmology recommended topical medications as the preferred first-line therapy for newly diagnosed POAG or OHT over other treatment modalities for most patients [8].

Topical medical therapy for the treatment of glaucoma is generally considered safe and effective as commonly utilized medications are required to undergo a series of clinical trials to achieve regulatory approval around the world. There is no question that the approved compounds considered foundational therapy are highly effective in reducing intraocular pressure to control glaucoma progression when appropriately instilled. However, topical medication use has critical limitations, among them high rates of therapeutic nonadherence that increase the risk of disease progression, side effects that can be sight-threatening, suboptimal circadian efficacy effects, the need for complex regimens of multiple drugs administered multiple times per day, difficulty with self-administration of topical medications, and others. Despite these significant and well-documented limitations, topical medical therapy remains the established first-line treatment for primary open-angle glaucoma (POAG) and ocular hypertension (OHT) because no meaningful safe and effective alternative therapies existed.

Given the well-documented limitations of topical therapy, coupled with significant advances in alternate approaches to glaucoma management, reliance on a medication-first

approach may no longer be necessary. The 21st century has seen significant development of innovative interventional glaucoma therapies that do not require topical self-dosing one or more times daily and that obviate patient adherence. These include sustained-release drug-delivery platforms, selective laser trabeculoplasty (SLT), and minimally invasive glaucoma surgeries (MIGS), all of which lower IOP and reduce or eliminate the need for chronic medical therapy. The widespread availability of these therapies, coupled with high-quality evidence supporting their efficacy and safety, prompt a reexamination of the traditional topical medication-first approach and consideration of a more proactive, targeted, and earlier patient-centric interventional approach to glaucoma management.

LIMITATIONS OF TOPICAL MEDICAL THERAPY

Nonadherence

Rates of nonadherence to glaucoma therapy range from 30% to 80% in published studies [9–13] and adherence worsens over time [14]. In turn, topical medication nonadherence increases the risk of glaucoma progression [9, 10, 14, 15], which in turn leads to more invasive interventions at increased risk and cost. Underlying causes and contributors to nonadherence are multiple and complex and have been extensively reviewed [16–18]. Unfortunately, intentional nonadherence—purposefully not taking medications as prescribed—can be difficult to detect in the clinical setting since patients may take their medications only in the days leading up to a scheduled office visit. Unintentional nonadherence can often be more easily detected and remedied.

Common causes of unintentional nonadherence include cognitive factors, physical factors, regimen complexity, and difficulty with drop administration [19]. Cognitive factors contributing to glaucoma medication nonadherence can range from forgetfulness [20, 21] to dementia [22, 23], which are particularly relevant given the demographics of the glaucoma population. For example, Alzheimer's disease is a leading cause of dementia in older individuals and is more common in glaucoma patients than in the general population [24–26]. Physical factors may include hand pain and/or weakness attributable to arthritis [23] or tremor [27], both of which make self-dosing with topical ophthalmic therapy difficult [28–30]. The complexity of the medical regimen also affects adherence, with nonadherence being more likely as regimen complexity increases [31]; this can affect a substantial proportion of patients (40–50%) who require a multi-medication regimen for disease control [3, 32–36].

Difficulty with self-dosing can also adversely affect adherence. Correctly administering eye drops is a complex, multistep process involving hygiene, dexterity, proprioception, coordination, and visual acuity. Most patients never receive any training in proper instillation techniques and instead are left to learn on their own [37, 38]. Perhaps not surprisingly, most patients make one or more mistakes when self-dosing [37, 39–41], which consequently increase the risk of glaucoma progression [42] as well as dosing-related adverse events [43, 44]. Examples of common mistakes during eye drop instillation include difficulty aiming the bottle over the eye [30], difficulty squeezing the bottle [30], contaminating the dropper bottle through contact with the lid or ocular surface [37, 38, 40, 41, 45–48], and either dispensing more than one drop [40, 47–50] or missing the eye entirely [38, 40, 45, 47].

Engaging newly diagnosed glaucoma patients to accept responsibility for self-administering topical medical treatment can be challenging. In its mild and moderate stages, glaucoma is typically asymptomatic. There are no bothersome symptoms that therapy relieves to motivate adherence. Often, the only symptoms that medically well-controlled glaucoma patients are likely to experience in their lifetimes are the side effects of topical medical therapy. Even if glaucoma therapy did provide the incentive of symptomatic relief or some other immediate tangible benefit, it is uncertain that adherence would improve: for example, only 33% of patients with cluster headache (also called suicide headache due to their

intensity) adhere to preventive therapy [51], and nearly 30% of patients who have received a kidney transplant fail to adhere to their anti-rejection drug regimen even while knowing that such behavior increases the risk of organ rejection [52]. In fact, rather than providing motivation to adhere, topical medical therapy for glaucoma is associated with numerous safety and tolerability issues that provide substantial deterrence to adherence, as discussed below.

Therapeutic nonadherence in glaucoma increases the risk of disease progression [9, 10, 14, 15] and can lead to a vicious cycle. Nonadherence can lead to disease progression, prompting the addition of more medications, which can further worsen adherence, leading to more progression and the need for more invasive therapies such as incisional surgery. Glaucoma progression is not uncommon among treated patients but can be prevented with effective therapy. In the era before topical beta-blockers, the 20-year cumulative risk of progression from glaucoma diagnosis to blindness in at least one eye was 27% among treated glaucoma patients [53]. After the development of beta-blockers but before prostaglandin analogues, the 20-year risk of blindness in the same population dropped by half to 13.5% [54]. In another study, the 15-year risk of blindness in at least one eye was 14.6% and nonadherence with therapy was a significant risk factor [55]. In a Swedish study, the 10- and 20-year risks of blindness from treated glaucoma in at least one eye were 26.5 and 38.1%, respectively [56]; these higher estimates may be related to the high prevalence of exfoliation glaucoma in Sweden [57], which generally has a more severe course than POAG. These and other studies of progression to blindness in eyes with treated glaucoma [58] underscore the need for a new approach to glaucoma therapy.

Side Effects

Perhaps the most obvious contributor to nonadherence with topical medical therapy is that all medications have side effects, and these side effects are common. For example, while latanoprost is widely considered to be among the safest of topical glaucoma medications, the rate of non-serious ocular adverse events with latanoprost in its US phase 3 registry trial was 10% and the rate of ocular events not graded as adverse events (examples include burning/stinging, tearing, foreign body sensation, etc.) was 48% [59]. Thus, more than 50% of patients receiving latanoprost exhibited one or more unwanted ocular symptoms while on therapy. Additionally, in the United Kingdom Glaucoma Treatment Study (UKGTS), latanoprost only slowed visual field progression by 58% more than placebo, indicating that even first-line standard of care therapy has limitations [60].

In general, the side effects associated with topical glaucoma medications fall into one of three categories: those related to mild or transient discomfort or disturbance, those associated with cosmetic alterations, and those that are safety-related. Numerous topical medications are associated with transient bothersome side effects that may not represent true safety issues. For instance, dorzolamide and the dorzolamide-timolol fixed combination often sting upon instillation because they are formulated as acidic solutions (pH $\sim$ 5.6 to 5.7) to solubilize the carbonic anhydrase inhibitor (CAI) component [61, 62]. The insoluble CAI brinzolamide, in contrast, is formulated as a suspension, avoiding the low-pH stinging but instead causing transient formulation-related blurring of vision that is severe enough to impair driving [63]. Both CAI options are known to cause taste perturbations. Other drugs have other characteristics that are similarly undesirable. For example, 18% of patients using brimonidine tartrate 0.2% will develop a type IV hypersensitivity allergy within 12 months that will cause significant irritation and require cessation of the medication [64]. While these events pose no health-related safety concerns, they can incentivize adverse behaviors such as skipping doses or immediate post-dose use of artificial tears (thereby washing out the active drug before optimal absorption) that reduce therapeutic efficacy.

Side effects that alter patients' appearance can be more problematic. The prostaglandin analogues—the most commonly used class of topical glaucoma medications—are well known

to cause numerous cosmetic alterations. These include common side effects such as conjunctival hyperemia as well as lengthening, thickening, and darkening of eye lashes; and less common effects such as growth of vellus hairs and hyperpigmentation of periorbital skin as well as permanent iris hyperpigmentation [65]. These undesirable cosmetic issues can be more obvious and more unacceptable to patients with unilateral use, rendering the drug class relatively contraindicated for just one eye. As these drugs became available, patients had to tolerate these cosmetic side effects to reap their therapeutic efficacy. New and emerging therapies offer freedom from these adverse cosmetic events. Glaucoma patients today do not have to choose between how they look and how they see.

Some side effects can represent true safety issues. In the first 7 years after the commercialization of topical timolol, before its systemic safety issues were fully recognized, the topical glaucoma drug was suspected as the cause of 32 deaths reported to the United States Food and Drug Administration (FDA) [66], and topical beta-blockers have a substantial list of contraindications related to their systemic side effects [67]. Topical medical therapy was also associated with a higher risk of cataract surgery in both the Ocular Hypertension Treatment Study (OHTS, versus no treatment) [68] and the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT, versus SLT) [69]. Topical prostaglandin analogues have been associated with several safety issues, including intraocular inflammation [70, 71], cystoid macular edema [71], and periorbital fat atrophy [72–74]. The latter is part of a syndrome called prostaglandin-associated periorbitopathy (PAP) characterized by dermatochalasia, blepharoptosis, deepening of orbital sulci, and flattening of lower eyelid fat pads [75]. PAP has also been associated with topical prostaglandin analogues commercialized for over-the-counter use as lash lengtheners [76]. Initially considered a cosmetic side effect, PAP has come to be considered a safety issue: its presence compromises outcomes of trabeculectomy [77] and affects surgical planning for oculoplastics procedures [78].

Perhaps the most impactful adverse effect of topical glaucoma therapy is its association with ocular surface toxicity. Multiple prospective studies have found that the prevalence of ocular surface disease (OSD) in patients using topical glaucoma medications ranges from 30% to 70% [79–85] and is much higher than in the general population (5–30% [86]). Commercial formulations of topical glaucoma medications contain both active and inactive ingredients, and while the active ingredients can have adverse effects on ocular surface health, most of the damage to the ocular surface is attributable to inactive ingredients, specifically preservatives, most commonly the preservative benzalkonium chloride (BAK).

BAK is present in about 70% of all ophthalmic formulations [87, 88] and its cytotoxic effects on ocular surface cells have been well characterized [89–91]. In laboratory and animal studies, BAK has been demonstrated to injure and/or reduce survival of corneal [92–95], conjunctival [93, 96], trabecular meshwork (TM) [97, 98], and ciliary epithelial [97] cells, to promote ocular tissue inflammation [95, 99], to delay corneal wound healing [100], to induce corneal epithelial cell apoptosis [101], and to alter gene expression in TM cells through DNA fragmentation and oxidative stress [98]. The clinical manifestations of BAK-induced ocular surface toxicity are numerous and include symptoms such as pain/discomfort [102, 103] and tearing [103] as well as signs including increased ocular surface staining [104–106], worsened Schirmer test scores [103, 105], and decreased tear break-up time [104, 107, 108]. Together these result in a higher prevalence of punctate keratitis [107, 109] and overall worsening of Ocular Surface Disease Index scores [104, 110]. These adverse events are dose-dependent, worsening with increasing exposure to BAK via multiple medications, multiple drops per day, and duration of therapy [79–85]. BAK-related ocular toxicity is associated with diminished quality of life [111, 112]. Perhaps most insidiously of all, the ocular surface damage caused by long-term use of BAK-preserved medications reduces the success of subsequent glaucoma filtration surgery [88, 113, 114]. Negative effects of first-line therapy on the

outcomes of subsequent interventions alone warrant a reevaluation of the current medications-first approach, as this could be a set-up for long-term treatment failure in some patients.

Efficacy

Topical medical therapy has demonstrated effectiveness in reducing or preventing progression in multiple landmark clinical trials [3, 5, 6]. However, topical medical therapy—even when increased to multiple medications to achieve target pressures—does not always prevent progression. In OHTS, 4.4% of topical medication-treated patients developed POAG within 5 years [3]. In the Collaborative Initial Glaucoma Treatment Study (CIGTS), 25% of topical medication-treated patients progressed within 8 years [6]. In the LiGHT trial, 27% of topical medication-treated patients progressed within 6 years [69]. Coupled with the population data on blindness risks among treated glaucoma patients described above, it is clear that a substantial proportion of glaucoma patients will require more than topical medical therapy for disease control in their lifetime.

As discussed above, nonadherence is one of the factors contributing to the failure of medical therapy to control glaucoma. As former Surgeon General C. Everett Koop, MD, once said, "Drugs don't work in patients who don't take them." [115]. However, even topical medications that are taken as directed have shortcomings in terms of the IOP control they deliver. Many topical medications exhibit peak and trough efficacy related to their pharmacokinetics and dosing schedules. For example, topical timolol dosed twice daily exhibits a roughly 33% loss of effect between 1-h peak and 12-h trough [116]. In its phase 3 registry trials, brimonidine demonstrated an approximately 50% loss of effect from peak to trough with three-times-daily dosing [117]. Also, both timolol and brimonidine have been shown to lower IOP poorly or not at all in the nocturnal period [118, 119]. This is problematic given that IOP tends to be highest at night when blood pressure is at its lowest [120, 121], and the nocturnal period has been identified as a time when glaucoma progression is most likely to occur. These shortcomings of topical medical therapy may partially explain the blindness rates among treated patients described above.

An additional limitation of topical medication efficacy is that many patients require IOP reduction beyond the capacity of single-agent therapy. In OHTS, for example, only 60% of patients achieved target IOP (20% reduction from baseline) using a single medication at 5 years [3]. In CIGTS, only 56% of patients were still at target IOP (determined using a study-specific formula) using one medication only 3 months into the study [34]. In LiGHT, only 43% of medication-first eyes were still at target IOP (20–30% depending on diagnosis and stage of disease) using a single medication at 6 years [69]. Unfortunately, the need for multiple medications for IOP control exposes patients to additive side effect profiles and reduces adherence [31]. Furthermore, as the number of medications required for IOP control increases, the law of diminishing returns comes into play: the medication selected as fourth-line therapy is utilized late in the treatment cascade because its efficacy and/or safety is inferior to the three drugs used before it, and thus it is unlikely to deliver IOP control when better medications have failed to do so. In fact, multiple studies have shown that the addition of a second, third, or fourth medication typically results in only a 10–15% incremental IOP reduction [35, 122, 123], and the addition of a 3rd or 4th medication carries only a 14% chance of successfully controlling IOP after 12 months [35].

Cost

Topical glaucoma medications are expensive. In 2017, Medicare spent USD $1.09 billion on prostaglandin analogues alone [124]. This does not include medications from other drug classes, drugs covered by non-Medicare insurers, nor uncovered medications purchased out-of-pocket by patients. The overall cost to the US healthcare system attributable directly to glaucoma care exceeds USD $9 billion annually [125]. There are also indirect costs to medical therapy borne by physician, the patient, and

the patient's caregiver(s). Physician costs include the time spent educating patients about side effects, teaching proper drop instillation, and prescribing/refilling medications, none of which are billable services. Patient costs include the time spent instilling drops (which can be 5–10 min several times per day for patients on multiple medications), driving to/from the pharmacy to get the medications, and coordinating complex dosing regimens and medication availability. These time costs often also extend to caregivers who may invest time in assisting with daily topical medication dosing, retrieving medications from the pharmacy, and accompanying patients with transportation to doctor visits. The combined nonmedical out-of-pocket costs to patients and caregivers for expenses such as travel and lost wages has been estimated at approximately $100 per patient per year [126]. If insurers decline to cover a prescribed medication (a common occurrence with new medications not yet added to insurers' formularies), there are additional time costs to both patients and physicians when patients call the office seeking prior authorizations or alternate medications. In addition, cost can affect adherence. For example, before the implementation of the Medicare Part D drug benefit, 8.2% of beneficiaries reported skipping doses of glaucoma medications due to cost; after implementation, this dropped to 2.8% [127]. All treatment options have associated costs. Emerging evidence suggests that more interventional approaches to glaucoma—such as SLT or MIGS—may be more cost-effective strategies for long-term glaucoma care [69, 128–131].

Quality of Life

Quality of life is a complex construct defined by the World Health Organization as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." [132]. Health-related quality of life is informed by perceived physical and mental health over time. The glaucoma disease itself affects quality of life both physically and psychologically. At the time of diagnosis, the fear of blindness has a significant detrimental effect on quality of life that dissipates over time as patients become acclimated to and educated about the disease and its prognosis [133]. As glaucoma progresses, deterioration of the visual field decreases quality of life by imposing a series of daily life challenges, including difficulty driving, reading, and recognizing faces [134]. Recent evidence suggests early impairment of vision-related quality of life may manifest even before measurable visual field loss has occurred [135].

The side effects of topical medical treatment for glaucoma can also impact quality of life, including both physical and psychological well-being. Tearing, redness, and burning/stinging associated with topical glaucoma therapy have been shown to decrease quality of life [136]. The development of ocular surface disease from topical glaucoma medications—occurring in 30–70% of patients [79–85]—has also been demonstrated to reduce quality of life [111, 112]. Difficulty self-administering drops also decreases quality of life [137]. Additionally, the treatment burden includes the time to instill drops—which can take 5–10 min multiple times per day if spaced correctly for patients on multiple medications—and the need for dosing away from the privacy of home (at work, at social events, etc.), all of which can affect treatment satisfaction and quality of life.

It is therefore surprising that well-designed studies evaluating quality of life have shown mixed outcomes. For example, in the pivotal trial of the trabecular micro-bypass iStent inject, greater reduction of medication dependence in the iStent inject group versus cataract surgery alone resulted in greater improvement in quality of life using several validated instruments [138]. In another study, improvement in quality of life after cataract surgery combined with various MIGS procedures was related to medication reductions [139, 140]. In another, combined cataract surgery with a trabecular micro-bypass significantly reduced topical medication use and improved ocular surface health, a key determinant of quality of life in glaucoma patients [111, 112]. In contrast, several of the landmark glaucoma trials—including OHTS [141], the Early Manifest Glaucoma Trial

(EMGT) [142], the UKGTS [143], and the LiGHT study [69]—have not consistently shown significant adverse effects of topical medical therapy on quality of life.

It is unlikely that topical medical therapy for glaucoma has no adverse effect on quality of life. Rather, it is likely that the instruments used in these studies are not sensitive or specific enough to detect these differences. Most of the instruments used in these studies were designed to assess the effect of general health, or vision function, or the presence of glaucoma, on quality of life. In each of these studies, patients in all treatment arms were balanced by randomization in terms of diagnosis, visual function status, and general health status, so it is unsurprising that instruments designed to measure effects of these variables found no differences between the balanced treatment groups in these studies. Most instruments are not designed to measure the effects of glaucoma *treatment* on quality of life [144]. Given the interest in early use of sustained-release drug-delivery platforms, SLT, and minimally invasive glaucoma surgery to reduce or eliminate the need for topical medical therapy, there remains significant unmet need for an instrument that assesses the effect of glaucoma treatment on quality of life, as such data will inform clinicians and payors regarding the relative utility of these treatments in improving patient well-being, which will be essential for effecting paradigm change.

DISCUSSION: BEYOND MEDICATIONS: A MODERN INTERVENTIONAL GLAUCOMA TREATMENT PARADIGM

There are considerable limitations of topical medical therapy outlined above, many of which can directly or indirectly increase the risk of disease progression and vision loss, and reduce patient quality of life. Given these limitations, now may be the appropriate time to reexamine the current conventional step-wise treatment approach, in which topical medications are often automatically and universally used as first-line therapy. By broadening the glaucoma treatment algorithm to include various less-invasive surgical interventions in addition to topical medications, doctors and patients are better equipped to design patient-centric treatment plans that span all disease severities and individual needs.

Indeed, the glaucoma treatment landscape has modernized and evolved, providing an opportunity to be more interventional in our approach–utilizing advanced therapies such as SLT, MIGS, and sustained-release drug-delivery systems—all with the common goal of preserving vision and improving patient quality of life. Although change can often be incremental and difficult to detect, there is growing evidence that the glaucoma treatment paradigm is evolving away from topical medications as first-line therapy. Following years of increasing rates of topical medication prescriptions for glaucoma in Australia [145], new data show prescription-writing on the decline in favor of SLT and MIGS procedures [146]. Likewise, based on data emerging from the LiGHT trial of first-line SLT versus topical medications for newly diagnosed glaucoma, the United Kingdom's National Institute for Care and Health Excellence has recommended that SLT be the preferred first-line treatment for patients in the National Health Service [147]. Similarly, the European Glaucoma Society and the American Academy of Ophthalmology have recently updated their glaucoma management guidelines to recommend SLT as first-line therapy [8, 148]. Furthermore, a multicenter trial funded by the US National Institutes of Health/National Eye Institute—the Clarifying the Optimal Application of SLT Therapy (COAST) trial—is currently investigating the role of annual low-energy SLT compared to standard-energy SLT performed as needed in keeping newly diagnosed OAG and OHTN patients off medications for as long as possible [149]. From an economic perspective, compared to topical medical therapy, SLT has been shown to be more cost-effective [69, 130, 150–152].

Similar to laser procedures, the advent of the MIGS family of glaucoma procedures has opened the door for earlier surgical intervention. Designed as safer and more physiologic

alternatives to traditional trabeculectomy and tube-shunt procedures, these procedures collectively offer more modest IOP reductions for patients who would benefit from surgery but whose treatment goals may not justify the risk of traditional surgery [153–155]. Accordingly, the notion of employing surgery earlier in the treatment cascade, rather than saving it as a last resort, has been raised [156, 157]. Given that the trabecular meshwork is the primary site of histopathological changes related to elevated IOP [158], targeting the meshwork early in the disease process is a logical approach, and several studies have suggested a beneficial disease-modifying effect of early intervention that may not be fully explained by IOP reduction alone [159, 160]. Various MIGS procedures combined with cataract surgery have been shown to be cost-effective compared to cataract surgery alone [128, 129, 161], and also compared to topical medication therapy. Relatedly, there have been calls to unbundle some glaucoma procedures from the often-required concomitant cataract surgery and allow them as standalone procedures so patients who might benefit have more than a one-moment-in-time opportunity to receive them at the time of cataract surgery [156].

Following upon SLT and MIGS, SRDD's are the newest entry into the glaucoma treatment space. As a class they aim to provide the benefits of medication without the drawbacks of topical administration or reliance on patient adherence. SRDD's include FDA-approved bimatoprost sustained-release (Durysta, Allergan), as well as several implants in various stages of development and with different routes of administration. These SRDD's include, for example: ocular surface devices (e.g., gel-forming eyedrops, drug-delivery devices, medicated contact lenses, ocular ring inserts, collagen shields); punctal plug depots (e.g., travoprost ophthalmic insert, latanoprost punctal plug delivery system); subconjunctival injections (e.g., of latanoprost or dorzolamide-loaded polymer microparticles); and intracameral implants (providing sustained release of a medication such as travoprost, latanoprost, or omidenepag isopropyl [OMDI]). Although SRDD's are the newest addition to the glaucoma treatment algorithm and many are still in development, they ultimately may offer additional topical-medication-free alternatives within the glaucoma treatment paradigm.

In summary, topical medications for glaucoma have a long history of effectiveness and safety, but newer treatment options may offer meaningful clinical benefits over topical medical therapy. The glaucoma treatment paradigm is in evolution, and novel interventional treatments—including sustained-release drug-delivery platforms, SLT, and MIGS procedures—are increasingly being considered earlier in the treatment cascade, including as first-line therapy. As data continue to emerge from clinical trials and clinical practice, the default topical medication-first approach to glaucoma care may be replaced by a more individualized, patient-centric approach that leverages the wider variety of interventional therapies now available—interventions that may be more effective, safer, and less adversely impactful on patients, doctors, and society at large.

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