HHS Public Access

Author manuscript

Expert Rev Ophthalmol. Author manuscript; available in PMC 2024 April 12.

Published in final edited form as:

Expert Rev Ophthalmol. 2023 ; 18(2): 101–111. doi:10.1080/17469899.2023.2199981.

Emerging glaucoma treatments: are we seeing an improvement in adherence?

Andrew P Droste[1], **Paula Anne Newman-Casey**[1]

[1]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI, USA

Abstract

Introduction: Non-adherence to glaucoma medication and poor follow-up is a global health concern.

Areas covered: Glaucoma remains one of the largest causes of irreversible blindness worldwide. Traditional treatment guidelines suggest topical eye drop medication as first line therapy followed by addition of supplementary medications before proceeding to more invasive glaucoma surgeries. Unfortunately, poor glaucoma self-management remains high, leading to disease progression and blindness. Recent advancements in the field of pharmacotherapies, surgeries, and behavioral approaches have taken aim at increasing support for glaucoma self-management. We review the current and emerging approaches towards glaucoma management, with the exception of bleb-based surgical approaches, to investigate if they have had an impact on adherence. Literature searches were conducted via MEDLINE (PubMed), Embase (Elsevier), Cochrane Library (Wiley), and Preprints from January 1st, 2018, to January 26th, 2023.

Expert opinion: The ability to offer patients a multitude of choices enables patients to tailor their glaucoma treatment to their values and lifestyle. Offering personalized patient education and coaching to support chronic glaucoma self-management would better enable patient engagement in whichever treatment path is chosen. Currently, literature regarding the impact of these new advancements on treatment engagement is lacking; this field is ripe for additional intervention and assessment.

Keywords

Hydrus; Glaucoma; intracameral implants; iStent; Latanoprostene bunod; medication adherence; micro invasive glaucoma surgery (MIGS); nanotechnology

1.0 Introduction

Non-adherence to medical therapies is a global health concern both to individual patients and the healthcare system as a whole [1]. In 2015, The World Health Organization (WHO) estimated that within developed countries, 50% of people with chronic conditions regularly take their medical therapies [2].

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Glaucoma, one of many chronic conditions plagued by poor treatment adherence, is an irreversible, vision-threatening disease of the optic nerve that impacts an estimated 76 million individuals worldwide. Primary Open Angle Glaucoma (POAG) is the most common subtype of glaucoma and remains the leading cause of irreversible blindness [3]. Lowering intraocular pressure (IOP) is the proven method to reduce both the development and the progression of glaucoma [4,5]. The first line treatments for lowering IOP are topical ophthalmic medications [5] with 89% of glaucoma patients taking these medications for disease control [6].

Taking greater than or equal to 80% of prescribed doses has been the benchmark for glaucoma medication adherence as those who take less than 80% of their prescribed doses have been shown to have more severe visual field loss [7]. As the former Surgeon General C. Everett Koop stated: “Drugs don’t work in patients who don’t take them” [8]. Numerous studies have demonstrated that adherence to topical eye drop therapy has much room for improvement. In one study, Dr. Nordstrom and colleagues demonstrated that less than 50% of newly diagnosed glaucoma patients persisted in taking their glaucoma medications one year after they were diagnosed, with persistence continuing to decline after 12 months [9]. For patients using an electronic monitoring system and receiving free medication, 45% of subjects were found to have adherence below 75% [10]. An additional study used claims data to show that those taking prostaglandin analogues for glaucoma treatment only had enough medicine on hand to cover 37% of the 12-month period [11].

The reasons that people have difficulties taking topical glaucoma medications on time every day, is multifactorial and highly individual. There are socio-economic and geographic barriers to obtaining the prescribed medications. People report difficulties with side effects, mistrust of the physician or healthcare system, life stressors and competing demands, difficulty with a complex medication schedule, not believing that a disease that is asymptomatic for so long will truly lead to blindness, or that the prescribed medications will help mitigate that fact [12]. In one study, 61% of study participants with glaucoma cited many of the aforementioned barriers – not just one - as issues keeping them from optimally self-managing their glaucoma [12]. Additionally, we know that 20% of patients cannot instill an eye drop properly due to having physical barriers to instillation, such as having additional chronic comorbidities such as arthritis or Parkinson’s [13-15]. Unfortunately, poor adherence leads to disease progression with a dose-response type effect – the more doses of medication a person misses, the more visual field progression is evident [16].

Attempts to improve glaucoma control by offering alternatives to the current mainstay of treatment – topical ocular hypotensives – have blossomed over the past two decades with advancements in the fields of pharmacology, nanotechnology, and surgical technique. These developments have led to drug eluting implants, surgical technique improvements within the minimally invasive glaucoma surgeries (MIGS), drug eluting contact lenses, among others, whose purpose is to lessen the burden of multiple times-per-day eye drop use. There have been additional emerging investigations on how to better support glaucoma patient self-management that include individualized patient education and coaching alongside devices to aid in eye drop instillation, which is an additional perspective on how to lessen the burden of daily eye drop use. Here we aim to provide an updated review and discussion of the most

recent glaucoma therapies, with the exception of bleb-based surgeries, and their impact on adherence.

2.0 Methods

Comprehensive literature searches were conducted via MEDLINE (PubMed), Embase (Elsevier), Cochrane Library (Wiley), and Preprints from January 1st, 2018, to January 26th, 2023. Medical subject headings (MeSH) of “glaucoma” “drug delivery systems” and “medication adherence” were used in conjunction with text word variations including *topical pharmacotherapies, intracameral implants, stents, adherence, glaucoma, nanotechnology,* and *MIGS*. In total, literature searches resulted in 447 titles. Of the titles, 116 met the inclusion criteria of “emerging therapies for glaucoma and/or treatment adherence.” Of the 116 abstracts reviewed, 48 articles met the inclusion criteria, and the full text was obtained and reviewed. Titles, abstracts, and full articles were reviewed by APD with expert consultation from PANC.

3.0 Emerging glaucoma treatments

3.1 Topical pharmacologics

The American Academy of Ophthalmology Preferred Practice Guidelines states that glaucoma is optimally managed by reducing IOP by 25%, which can be obtained individually or by a combination of medical treatment, laser therapy, or incisional glaucoma surgery [17]. Despite the multitude of options, medical therapy is the most common form of treatment, with 89% of patients utilizing this treatment modality [17,18]. The European Glaucoma Society recently published its 5th edition of guidelines for glaucoma management, and it recommends topical therapy with prostaglandin analogues for first line treatment [19]. Many people require more than a single ocular hypotensive medication to control their intraocular pressure and prevent disease progression. Second line therapy consists of trying alternative medication classes or adding a combination of medication classes that result in patients needing to take multiple topical doses of medication each day [18]. The greater the daily drop burden, in terms of both numbers of medication dispensed at each time point throughout the day and the number of time points during the day where medication is dosed, the greater the issues patients face with perfectly adhering to the regimen.

Pharmaceutical companies have responded to this issue by combining multiple medications into one formula in an effort to increase the ease of the medication regimen [20,21]. Barnebey et al., 2017 compared adherence between combined travoprost 0.004%/timolol 0.5% versus an unfixed combination, using the aid of a drop dispense recorder to measure adherence. The combined medication led to a 12-month adherence of 60% (Standard deviation (SD) 28%) compared to 43% (SD 27%) adherence for the two medications separately, demonstrating that combining the medications into one formula can dramatically increase adherence [20]. Another group in Japan found similar results where patients prescribed a combined prostaglandin analogue and beta-blocker had an adherence rate of 79.1% (SD 32.1%) compared to an adherence rate of 62.2% (SD 38.0%) for those prescribed the two medications separately ($P < 0.0001$). Twelve-month persistence rates remained higher in the combined group 47.6% (95% Confidence Interval (CI): 41.9-53.0)

compared to the separately dispensed medication group at 24.9% (95% CI: 20.4-29.7), concluding that fixed combination therapies can contribute to increased adherence.

3.2 Schlemm's canal-based minimally invasive glaucoma surgeries

2.2.1 Trabecular meshwork stents—Another approach to glaucoma treatment comes in the form of bypassing the eye's trabecular meshwork. In order for aqueous humor to return to the venous system, it must pass through the trabecular meshwork, which can be divided into three distinct regions: the uveal meshwork, the corneoscleral meshwork, and the juxtacanalicular tissue [22]. The juxtacanalicular meshwork has the greatest resistance to aqueous outflow. Minimally invasive glaucoma surgery (MIGS) aims to bypass this area of meshwork and direct aqueous flow into Schlemm's canal [22]. We will discuss the impact various MIGS surgeries have on reducing the number of medications patients require to control their glaucoma. We will only include the MIGS surgeries that utilize a Schlemm's canal-based approach, are performed ab interno, and do not result in bleb formation. These techniques give the MIGS treatments a high safety profile, which in turn, gives the surgeons recommending them, the confidence that these options are a safe alternative to topical medications. Though the safety profile is high, as these options are still surgical, adverse events still do occur and will be detailed with each surgical approach.

Currently there are three trabecular meshwork bypass stents available on the market in the United States that are implanted into the anterior chamber as part of an extended cataract operation or as a standalone procedure. The first stent device approved was the iStent in 2012 from Glaukos Corporation (San Clemente, California). iStent is a heparin coated, titanium stent that is non-ferromagnetic, making it compatible with magnetic resonance imaging devices. The second generation iStent, the iStent Inject, is the smallest of all the available micro-stents and came to market in 2018. The iStent injects differ from the original iStent in that two iStent injects are placed nasally 30-60 degrees apart from one another within the trabecular meshwork [23]. The third option is the Hydrus stent developed by Ivantis Inc (Irvine, California). The Hydrus is a crescent shaped stent with three openings. It is made of nitinol and is inserted into Schlemm's canal along the nasal or inferior quadrant via a clear corneal incision. Upon insertion, the stent dilates allowing the aqueous humor the bypass the trabecular meshwork [24,25]. These stents can be used as standalone therapy or coupled with the continuation of topical medications. A recent meta-analysis of the efficacy and adverse event profile of iStents found that 22.5% of eyes that received iStents had some type of adverse event, which included IOP elevation, stent blockage, stent malposition and hyphema [26].

The purpose of the trabecular bypass stents is to reduce medication burden while lowering intraocular pressure. A randomized controlled trial assessing IOP and medication burden reduction compared the iStent combined with phacoemulsification to phacoemulsification alone. Subjects were separated into primary IOP baselines of less than (<) 26mmHg and greater than or equal to (≥) 26mmHg. Among participants with lower baseline IOPs, mean baseline medication use was 1.03 ± 0.19 and 1.32 ± 0.55 in the phacoemulsification alone and phacoemulsification plus iStent groups respectively and at 24 months post operative follow up was found to have decreased to 0.76 ± 0.69 (P = 0.095) in the phacoemulsification

alone group and 0.32 ± 0.55 (P = 0.05) for those with phacoemulsification plus iStent [27]. In the higher baseline IOP group, medication use was 1.86 ± 0.69 and 2.50 ± 0.89 at baseline in the phacoemulsification alone and phacoemulsification plus iStent groups respectively with a baseline medication reduction to 1.29 ± 0.76 in the phacoemulsification group (P = 0.095) and 0.88 ± 1.26 in the phacoemulsification plus iStent group (P = 0.05) at the 24 month post operative follow up [27].

The HORIZON study, a randomized controlled trial of 369 eyes, compared the Hydrus micro-stent plus phacoemulsification to phacoemulsification alone. Conclusions at the 24-month mark showed a medication reduction from a baseline of 1.7 ± 0.9 to 0.3 ± 0.8 in the treatment group versus 0.7 ± 0.9 in the control group [28]. The five-year results confirm this reduction in medication burden as the Hydrus group had an average of 0.5 ± 0.9 medications and the phacoemulsification group had an average of 0.9 ± 0.9 (P < 0.001) [29]. In this study, in terms of serious adverse events, 0.27% of participants had mild-moderate corneal edema after one month and 1.63% had retinal complications in the Hydrus arm compared to 0% with mild-moderate corneal edema and 2.14% with retinal complications in the phacoemulsification alone arm. In terms of adverse events, non-persistent anterior uveitis occurred in 5.15%, device obstruction in 7.32%, peripheral anterior synechiae in 7.32% of those randomized to the Hydrus arm compared to 1.60% with uveitis, 0% with device obstruction and 0% with peripheral anterior synechiae among those participants randomized to the phacoemulsification alone group.

The COMPARE study, a prospective randomized control trial, compared the Hydrus micro-stent (n=74) to 2 iStent implantations (n=76) as standalone treatment. Among participants randomized to the Hydrus micro-stent arm, 22.6% more individuals were medication-free at 12 months (P = 0.0057). Baseline mean antiglaucoma medications were 2.5 ± 0.7 in the Hydrus group and 2.7 ± 0.8 in the iStent groups, decreasing 1.6 ± 1.2 and 1.0 ± 1.2 respectively at 12 month postoperative follow up (P < 0.001) [30]. In terms of adverse events, in the Hydrus arm, two participants (2.7%) had a > 2-line decrease in best-corrected visual acuity (BCVA), 3 participants (4.1%) had an IOP spike of >10 mmHg, and 2 participants (2.6%) developed a new cataract. In the two implant iStent group, one participant (1.3%) had a > 2 line decrease in BCVA, 4 participants (5.2%) experienced an IOP spike of > 10 mmHg, and 1 participant (1.3 %) developed a new cataract [30]. Device obstruction occurred at similar rates between the two groups with 9 cases (12.8%) and 10 cases (13.2 %) in the Hydrus and 2 iStent groups respectively. [30]. A 2-year comparative analysis of 344 eyes of the Hydrus plus phacoemulsification versus iStent inject plus phacoemulsification found no significant difference between the two stent types in IOP reduction or mean medication reduction, with a mean medication reduction of 1.0 (95% CI: −1.3 – −0.7) for the iStent inject versus 0.5 (95% CI: −1.1-0.0) for the Hydrus (P = 0.081) [31], though this was not a randomized controlled trial.

3.2.2 Non-stent based canal procedures—The Kahook Dual Blade, from New World Medical (Rancho Cucamonga, California) is a single-use, disposable instrument blade that came to the US market in 2015. The Kahook Dual Blade is inserted ab interno and used to remove trabecular meshwork [32]. Twelve-month results from a randomized control trial of 42 eyes comparing the Kahook dual blade combined with

phacoemulsification to phacoemulsification standalone showed no significant difference in medication reduction between the two groups (P = 0.47) [33]. The Kahook dual blade cohort (N = 21) experienced one case of significant endothelial cell count loss reduction, ultimately experiencing decompensation and requiring a Descemet's stripping automated endothelial keratoplasty (DSAEK). Another eye developed transient macular edema but experienced a full recovery at 6 months post intravitreal steroid injection. No cases of hyphema, hypotony, endophthalmitis or other serious adverse event was reported [33]. In comparison to iStent implantation plus phacoemulsification, there was no significant difference in IOP reduction (P = 0.24) or decrease in medication burden (P = 0.17) in the arm randomized to Kahook Dual Blade plus phacoemulsification in a trial with 164 eyes [34]. When defining surgical success as a 20% IOP reduction, 93.7% of those randomized to the Kahook Dual Blade plus phacoemulsification group achieved this metric compared to 83.3% of those randomized to the iStent plus phacoemulsification group (P = 0.04) [34].

OMNI 360, developed by Sight Sciences, (Menlo Park, California) is a single-use trabeculotomy device that uses viscoelastic to dilate Schlemm's canal and the distal collector channels with or without completing a trabeculotomy [35]. Currently, the OMNI Surgical System is being evaluated for efficacy and safety, NCT05044793, and is set to finish its study in 2023. The OMNI device can be used as a standalone procedure or combined with phacoemulsification as well. As a standalone procedure in a retrospective case series in Germany, 38 eyes were followed for 12 months and were found to have a medication reduction from 1.9 medications (SD 0.7) at baseline to 0.5 (SD 0.7) medications (P < 0.001) with one hundred percent of eyes achieving an IOP reduction of greater than 20% (P < 0.0001) [36]. The ROMEO study incorporated 12-month post-surgical outcomes of the OMNI system with phacoemulsification, including 81 patients stratified into two groups. Group 1 comprised subjects who's IOPs were greater than 18 mmHg while group 2 was comprised of subjects with IOPs less than 18 mmHg. Mean IOP was reduced from 21.9 mmHg to 15.1 mmHg in group 1 (P < 0.001) and 14.1 mmHg to 13.4 mmHg in group 2 (P = .3177) [37]. Overall medication reduction was 2.0 ± 1.3 to 1.1 ± 1.1 in group 1 (P < 0.001) and 1.6 ± 1.3 to 0.9 ± 1.2 in group 2 (P < 0.001) [37]. Adverse events from the OMNI 360 included mild inflammation (11%), IOP elevation (5%), hyphema (4%), and secondary surgical intervention (5%) [37].

Trabectome from NeoMedix (Tustin, California) is a single-use hand piece used for trabeculotomy. Using an ab interno approach, the trabectome uses an electrosurgical approach to remove a portion of the trabecular meshwork and inner wall of Schlemm's canal [35]. According to a recent Cochrane review of the literature examining the efficacy of the trabectome, there has only been one RCT published evaluating combined phacoemulsification and trabectome to combined phacoemulsification and trabeculectomy that stopped enrollment early at 19 participants and is at high risk of bias in its results. A case series of 80 eyes in Japanese glaucoma patients assessed the safety of stand-alone Trabectome surgery. There were no serious adverse events such as endothelial cell count loss, choroidal effusion, hemorrhage, or infection noted. Thirteen (16.3%) cases required surgical reintervention and a single case had new onset cataract [38]. Our review identified a second RCT that is currently recruiting subjects and is comparing the trabectome to the Kahook Dual Blade (NCT03894631) but has not yet reported results [39].

The last technique we will discuss in this section, the ab interno canaloplasty (ABiC) from Ellex iScience (Fremont, California), is a microcatheter equipped with a light that is used to viscodilate Schlemm's Canal [35]. ABiC has only been evaluated in retrospective case series and in one series of 25 eyes, medication was reduced from 1.92 ± 1.04 to 0.05 ± 0.023 at 48-month follow up [40]. Five eyes (20%) experienced hyphema and one eye (4%) had a peripheral detachment of Descemet's membrane [40].

Especially when paired with cataract surgery, where a patient is already undergoing a surgical procedure, these minimally invasive glaucoma surgeries with their high safety profile offer patients a way to potentially reduce their daily drop burden. As they are still surgeries, they are not free from adverse events; patients still need to be interested in, and willing to undertake this small but real risk in their treatment. Additionally, as these procedures remain relatively new, the long-term efficacy over the course of a lifetime is yet to be determined and larger, longer-term randomized control studies are still needed. Thus, it remains imperative for patients to remain engaged in their glaucoma treatment and return for recommended follow-up to assess if and when additional interventions are needed.

3.3 Intracameral implants

Intravitreal injections have become the gold standard for treating many retinal diseases including neovascular age related macular degeneration, diabetic retinopathy, and retinal vein occlusions with anti-vascular endothelial growth factor medications [41]. Intravitreal injections of biodegradable medications have also been used to treat uveitis for nearly two decades [42]. The clinical success of these modalities has paved the way for intracameral injections to be used as a new treatment modality for patients with glaucoma.

The bimatoprost sustained release (SR) from Allergan pharmaceuticals, now a subsidiary of AbbVie (North Chicago, Illinois), is a biodegradable implant marketed as Durysta and was the only FDA approved implant to treat glaucoma at the time of this review. The implant is inserted under aseptic conditions via a 28-gauge needle injector, once the cornea is pierced, the implant is then released into the anterior chamber [43].

The Phase III clinical studies, ARTEMIS 1&2, which enrolled 1,122 participants, demonstrated non-inferiority of either 10μg or 15μg Durysta implants to twice daily timolol; however, there was concern that the higher dose (15μg) had a high level of endothelial cell loss and greater adverse events [44]. The implant was administered every four months for a total of three doses during the study. After the three doses, IOP was found to be well controlled for 12 months in 81.8% in the 10μg group and 77.8% in the 15μg group, without need for rescue (non-study IOP lowering medications) [44]. The majority of adverse events from the Durysta implant occurred within two days of treatment and were mild or moderate in 62.3% of patients in the 10μg group and 80.7% of patients in the 15μg group. The most common mild adverse event was conjunctival hyperemia, affecting 20.6% and 31.8% in the 10μg and 15μg groups, respectively. Conjunctival hemorrhage was noted in 9.1% of patients in the 10μg and 6.8 % in the 15μg group, and foreign body sensation was noted in 7.4 % and 8.0% of patients in the 10μg and 15μg groups. In both groups, the most common serious adverse event was significant endothelial cell loss, which was reported in 3.4% of participants in the 10μg group and 7.4% of participants in 15μg group [44].

Currently, Durysta is only FDA approved to be used one time, [43] though there are three ongoing studies measuring long-term safety and efficacy (NCT04647214, NCT05338606, NCT03891446) [45-48].

Sustained drug release enabling continuous medical IOP control via implantable, biodegradable, biocompatible devices is an exciting breakthrough in glaucoma treatment. When FDA approval is granted for continuous implantation of a sustained drug release implant, it will become highly important to ensure that patients who receive the implant understand that the implant will not "cure" their glaucoma and will stop controlling their disease at a time point that is not the same for each individual. Thus, it is imperative that patients who receive the implant return for follow-up care to have their intraocular pressure monitored so that the patient and physician know when additional treatment is needed.

3.4 Selective laser trabeculoplasty

Selective laser trabeculoplasty (SLT), which uses low energy laser pulses to treat the trabecular meshwork and improve aqueous outflow, has been FDA approved for the treatment of glaucoma since 2001. SLT incites less tissue destruction when compared to its predecessor, argon laser trabeculoplasty (ALT), which was first introduced in 1979 [49,50]. In 2019, the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial data was published which demonstrated that SLT was as effective as medication in lowering IOP. The LiGHT trial was the first prospective, randomized controlled trial to test this hypothesis and took place across 6 hospitals in the United Kingdom [51]. When comparing SLT to topical eye drop medications, after 3 years, SLT provided IOP control without medication for 78.2% of patients [52]. Eyes randomized to the topical medical therapy arm had more rapid visual field (VF) progression compared to the eyes that were first treated with SLT, which may be because people's varied adherence to topical glaucoma medications reduces the efficacy of the eye drop in stopping visual field progression [53]. At 6 years, no sight-threatening complications were reported with SLT providing drop-free IOP control for 70% of participants, only a slight decrease from 78% at 3 years [54]. Doctor Gazzard and colleagues who ran the LiGHT trial have hypothesized that additional SLT treatment may prolong the period of time during which patients could remain free of topical glaucoma medications [54].

The results from these trials have changed international treatment guidelines from both the European Glaucoma Society and the American Academy of Ophthalmology, and SLT is now offered as a first-line therapy alongside topical glaucoma medications [55-57]. Similar, to issues with implantable sustained release medications, SLT may leave a patient feeling that they are "cured." Patient education and counseling regarding the chronic nature of the disease and the need for long-term monitoring to determine the need for additional treatments with SLT, medications, or surgical intervention remain critical in mitigating vision loss over a person's lifetime.

3.5 Behavioral approaches to support glaucoma self-management

"Adherence," or the extent to which a person follows the physician's recommendations, applies not only to medication use but also to returning for continuous monitoring and

disease management in the office. Poor follow-up adherence to glaucoma treatment is known to worsen disease outcomes and is associated with higher glaucomatous disease severity [58]. In a retrospective cohort study of 2,206 patients with eye related emergency department visits, 74% of patients completed recommended follow-up with an eye care provider within 2 months. Those who did not follow up with an eye care provider were significantly more likely to return to the emergency department for an eye complaint within the next 4 months compared to those who did see the recommended eye care provider ($P < 0.001$) [59]. In a large community-based eye disease screening program, 41% of those initially screened and provided a scheduled appointment for further evaluation did not follow-up with eye care providers for definitive screening. Of those who defaulted on the first appointment, 71% scheduled another visit however, 62% of these individuals failed to appear for the second scheduled visit [60]. For those who screened positive for glaucoma, 29% failed to return to the clinic and 43% of those who were given eye drops did not return [60]. Reasons given for not attending the appointment with the eye care provider included not having an appointment, a lack of transportation, and a lack of insurance coverage [60]. A study out of the Canadian health system investigated whether giving ED patients who needed follow-up with an ophthalmologist a pre-scheduled appointment time before they were discharged would increase adherence to recommended follow-up. This technique led to an adherence of 98%, demonstrating that having the health care system secure a convenient appointment time for people before going home may alleviate part of the scheduling barriers to accessing follow-up care [61].

New trials have demonstrated the importance of behavioral support alongside medical and surgical treatment to optimally engage patients in their glaucoma care. Engagement in glaucoma care includes engagement both in returning for follow-up visits with the ophthalmologist and in using prescribed medications. A recent systematic review in 2022 by Buehne et al., analyzed 42 studies addressing glaucoma medication adherence. Studies were categorized based off on the content of their behavioral intervention: Reminder systems, medication regimen simplifications, coaching programs, provider focused education, patient focused education, provider and caregiver focused approaches, and alternate engagement strategies [62]. In eighteen of the studies, multifaceted interventions were used. The outcome, medication adherence, was separated by method of assessment into patient self-report, electronic monitoring, pharmacy record data abstraction, chart review, and physical measurement of eye drop bottle weight. Of the 42 studies reviewed, 26 approaches were found to increase adherence by one or more of these outcomes assessment techniques. The authors determined that having multifaceted approaches towards treatment adherence increased adherence compared to single interventions [62]. These findings were corroborated in a network meta-analysis of 19 randomized controlled trials of interventions to improve glaucoma medication adherence, where multifaceted approaches including individualized care plans, tailored care and face-to-face needs assessments were found to increase adherence [63].

In 2022, Dr. Muir and colleagues published the results of their Medication Adherence in Glaucoma to Improve Care (MAGIC) trial which demonstrated that participants randomized to the multifaceted behavioral intervention had a mean proportion of doses of medication taken of 0.85 compared to 0.62 for those participants randomized to the general eye health

education plus usual care group. Their multifaceted behavioral intervention included a face-to-face needs assessment, teaching eye drop instillation and assessing for the need of a drop instillation aid, receiving personal disease management suggestions and glaucoma disease education from a trained ophthalmic technician alongside medication reminder aids [64]. In our group's pilot study of our multifaceted behavioral intervention called the Support, Educate, Empower (SEE) personalized glaucoma coaching program, we found that adherence improved from 60% at baseline to 81% after program completion [65]. The multi-faceted approach in this intervention included using automated medication reminders, three in-person coaching sessions based in motivational-interviewing alongside glaucoma education tailored on a person's type of glaucoma, recommended treatments, testing results and barriers to adherence. The intervention was delivered by a trained health educator or ophthalmic technician. The SEE program is currently being tested in a randomized controlled clinical trial compared to standard care (NCT04735653).

To address the issue of poor adherence to recommended eye care follow-up, Dr. Hark lead a randomized controlled trial from the Wills Eye Hospital. Her team assessed the effectiveness of a patient navigator and social worker intervention on adherence to follow-up care recommendations after a community glaucoma screening program compared to usual care. 74% of those randomized to the patient navigator/social worker intervention attended their recommended follow-up appointment with an eye care provider compared to 39% in the usual care group ($P < 0.001$), representing a clinically meaningful effect size [66].

In both the MAGIC, SEE, and Wills Eye Hospital multifaceted behavioral interventions, adherence was noted to wane after the interventions ceased. At the 6-month mark in the MAGIC trial, the mean proportion of prescribed doses taken on time was 0.85 in the intervention group compared to 0.62 in the control group with adherence in both groups noted to wane over time ($P < 0.0001$) [64]. Similarly, in the SEE pilot study, adherence prior to the intervention was a mean of 60%, increased to 81% after completing the intervention and decreased to 67% one year after the intervention [65]. In the Wills Eye Hospital intervention, yearly attendance at recommended follow-up appointments with the eye care provider stayed similar in the intervention group at 18.6%, 20.9%, and 20.0% for these 3 years compared to those randomized to the usual care group in which attendance dropped over time from 8.1% in Year 1 to 6.4% in Year 2 to 4.0% for Year 3 [62].

These data highlight the importance of continued self-management support for people with glaucoma as glaucoma is a life-long disease that requires life-long adherence to treatment and follow-up recommendations to optimize disease outcomes. A pathway towards reimbursement for provision of chronic disease self-management support has already been established with the G0108/G0109 CPT codes for insurance payment for diabetes self-management support. Data from such trials as MAGIC and SEE may help enable insurance payment for glaucoma self-management support services through a similar mechanism. Additional interventions and trials are needed to identify ways to increase adherence to follow-up recommendations for patients treated with the full spectrum of glaucoma treatment modalities from topical medications to SLT to MIGS to sustained release drugs.

3.6 On the horizon sustained release therapies under clinical investigation

The past few decades have led to great strides in the ways in which we can monitor and manage glaucoma. This section serves as a review of the technologies currently in development.

3.6.1 Nanotechnology—Nanotechnology and nanomedicine comprise devices designed on a nanoscale that incorporate drugs or diagnostic molecules into the body to aid in the ability to target specific tissues and cells [67]. This field has enormous potential in modulating pathologies such as cancers, immunological disorders, genetic diseases, and has also showed promising early results in the management of glaucoma. Nanotechnology has been used to develop two main approaches to prototypes for drug delivery systems for glaucoma treatment: nanofibers and hydrogels.

Nanofiber patches (122-174 nm in diameter) containing timolol maleate have been created for insertion into the conjunctival cul-de-sac to enable preservative-free sustained release of medication [68]. This product has been tested with animals and was found to be safe; it also demonstrated proof of concept with initial IOP lowering of 5 mmHg over a 6-day period in animal studies [68]. Nanotechnology has also been used to create nano-sized drug particles suspended in nano-sized polymeric hydrogels with more than one class of drug included in the gel [69]. The gel is transparent and sits in the conjunctival cul-de-sac, with studies assessing both single-dose testing as well as 7-day daily testing. Daily administration had a cumulative IOP lowering effect that was four-fold greater than the control group ($p < 0.014$) [69]. The invention of a nano-in-nano hydrogel enables a less burdensome dosing schedule that is more potent and able deliver multiple classes of topical glaucoma medications simultaneously.

3.6.2 Contact lens drug delivery—There are approximately 125 million individuals currently using contact lenses globally [70]. Leonardo da Vinci first imagined a contact lens in 1508 to improve vision but it was not until the 1800s when the first glass contact “lens” became a reality [71,72]. Since then, the contact as we know it today has undergone numerous re-inventions and has become a promising modality for sustained drug delivery when coupled with innovations in nanotechnology [73-75].

Traditional topical eye drop therapeutics are hindered by the normal anatomy and physiology of the eye, where a single topical drop administration results in a drug bioavailability of 1-5% leading to the need for multiple administrations of eye drops throughout the day [68,69,73]. This has made contact lenses a promising alternative to topical therapeutics. However, a common problem that has previously hindered the use of contact lenses for sustained release medication use is the relatively low drug loading capacity and the high burst of drug release when the contact is first placed on the ocular surface [73,74]. In 2022, Dang et al. developed a novel PEGylated solid lipid nanoparticle to increase the latanoprost carrying load within a contact lens, limit the burst release of the drug, and provide sustained drug concentration for 96 hours [74]. The Sustained Innovative Glaucoma and Ocular Hypertension Treatment (SIGHT-1, NCT04747808) initial tolerability and safety study of a bimatoprost-eluting contact lens was completed in 5 human subjects

who had never worn contact lenses before and recorded no serious adverse events over 7 days. Dosing and efficacy studies are planned in future studies [76].

Currently, it is not clear when the efficacy of the drug-eluting contact lens would wane before needing to be changed. Additionally, one of the more serious issues contact lens wearers face is infectious keratitis, which is often caused by poor lens hygiene and overnight lens wear [70]. Lens overuse also leads to corneal hypoxia which is a risk factor for infection and corneal scarring, and these are two areas of concern using this modality. Though technology has advanced to incorporate more oxygen-penetrable lenses, corneal oxygen requirements still vary individual to individual and so regular follow-up for those who choose to use drug-eluting contact lenses will be important as this technology becomes available on the market. Incorporating individualized patient education about proper lens hygiene into the treatment paradigm for drug-eluting contact lenses will also help enhance the safety profile of this novel treatment modality.

3.6.3 iDose trabecular meshwork implant—iDose, from Glaukos Corporation (San Clemente, California) is a removable, titanium implant with a reservoir, that is implanted ab interno into the trabecular meshwork and is designed to release micro doses of a novel formulation of travoprost into the anterior chamber [73,77,78]. The iDose has shown initial promise with IOP reduction that is non-inferior to 0.5% timolol dosed twice daily with 81% of participants treated with iDose remaining medication free at 12 months [77]. Glaukos released additional data in a recent press release [79] regarding the safety of the surgical exchange procedure within subjects who had previously received iDose. Thirty-three individuals from the original cohort were found to have an average exchange period of 4.2 years from the time of first implantation to the need for additional ex-plantation and re-implantation [79]. Over the mean of 5.2 years of observation for this cohort, no participant underwent greater than 30% corneal endothelial cell loss [79]. Glaukos intends to submit their New Drug Application (NDA) to the FDA first quarter of 2023.

3.6.4 Optejet MicroProst microdose delivery system—The Optejet microdose delivery system from Eyenovia Pharmaceuticals (New York, New York) uses a horizontal, directional mist, called microdose array print (MAP) for topical delivery, ensuring an even coating of 8μL of drug to the ocular surface for those in a seated or standing position [80]. MicroProst is a micro dose of latanoprost administered by the Optejet device. The Optejet device is a “smart device” that connects to the patient’s phone to deliver medication reminders, track medication adherence, and share dosing information with the glaucoma specialists [80]. Currently, the Optejet device is in various clinical trials for presbyopia and mydriasis treatment (NCT05114486, NCT04657172, NCT03751098, NCT03751631) and is under study for administering anti-glaucoma medications. A recent press release highlights the potential of a microdosing system that does not rely on preservatives to maintain sterility to minimize the inflammatory response to topical anti-hypotensives [81].

3.6.5 Travoprost intracameral implants—Ocular Therapeutix (Bedford, Massachusetts) is currently assessing the efficacy and safety of a travoprost intracameral implant, named OTX-TIC. Similarly, to other intracameral implants, OTX-TIC is a biodegradable implant that is inserted into the iridocorneal angle via a 26- or 27-guage

needle [82]. Phase 1 results were promising with sustained IOP control over seven months without any serious adverse events [83]. OTX-TIC is currently undergoing a Phase 2 clinical trial, NCT05335122. Envisia Therapeutics (Morrisville, North Carolina) finished Phase 2 testing of a travoprost implant, ENV515 (NCT02371746) for 28 days duration at various dosages of 28.2μg, 42.3μg, 42.5μg, and 85.0μg [84]. Preliminary results showed all dosages were found to decrease IOP, with the 42.3μg implant having the greatest overall effect of 6.65mmHg reduction (SD 2.076), though this dose group also had the only recorded serious adverse event of corneal endothelial cell loss [84]. At this time, the ENV515 trial concluded in 2019 and there have been no additional updates on phase 3 status. Similar to the bimatoprost intracameral injection, it will remain crucial that patients who receive the travoprost implants continue to have their intraocular pressure monitored to assess treatment efficacy over time.

3.6.6 Punctal plug delivery systems—Mati Therapeutics (Austin, Texas) has been developing punctal plugs for delivery of different topical therapies including allergy relief, pain relief, and Latanoprost (L-evolute) and Travoprost (T-evolute) punctal plugs for use in sustained glaucoma treatment [85]. In two Phase 2 clinical studies, the Evolute punctal plug system was retained in 96% and 92% of lower puncta over a 12-week period while maintaining a tolerable comfort scores throughout the trial [86]. In 2021, Mati Therapeutics purchased rights related to the Evolute Punctal Plug Delivery System (PPDS) from Novelion Therapeutics, and to date there is no update on Phase 3 studies [87].

4.0 Conclusion

Overall, while there have been many important new tools added to the ophthalmologist's kit to treat glaucoma, the issues of patient engagement in glaucoma self-management, adherence both to daily medical treatment or post-operative treatment, and to recommended follow-up has been relatively under-studied in relation to these new treatments. There have been several studies directly testing interventions whose aim is to improve glaucoma medication adherence, but this patient-centered outcome has not been assessed among the new treatment modalities. It remains important to assess adherence to residual medications and to recommended follow-up among those treated with new treatment modalities such as sustained release medication implants, MIGS and newer technologies such as drug-eluting contact lenses when those become available on the market. It would be fascinating to understand whether being treated with interventions that are seen as "cutting edge" engage individuals further, building upon autonomy in the care of their glaucoma or might these advancements make patients feel that their disease had been "cured" and thus make them feel that further engagement in glaucoma care is not necessary. This classification of data would lend itself to shaping more individualized and nuanced educational and counseling programs for people with glaucoma to further improve our support for people's self-management of this life-long condition.

5.0 Expert opinion

The widespread issue of poor adherence demonstrates the importance of developing technologies, systems, and programs to address this important public health and eye health

issue. Recently, new surgical techniques, more potent pharmaceuticals, and novel drug delivery modalities have been invented in an attempt to lessen the burden of multiple times-per-day eye drop use. Trials of many of the MIGS technologies have demonstrated that these surgeries with a high safety profile can reduce medication burden. Some have even put forth that these new technologies may take adherence out of the patient's hands all together, thereby improving glaucomatous control. We postulate that having multiple ways to control intraocular pressure will serve to give patients more choice, and potentially more autonomy, which may in turn lead to greater engagement in glaucoma care and follow-up, if we as a glaucoma community set the appropriate stage. Even though patients with depot medications or devices may not need to take topical glaucoma medications with as high of frequency, engagement in returning for follow-up care to maintain optimal long-term control of glaucoma remains paramount. Setting the appropriate stage involves facilitating individualized education to enhance engagement in decision-making now that there are multiple ways to control IOP, alongside individualized education and coaching to enhance engagement in chronic glaucoma follow-up care. Measuring adherence to treatment and follow-up recommendations remains an area ripe for inclusion as important patient-centered outcomes in clinical trials of new drugs and devices.

Studying adherence to prescribed medications and to follow-up recommendations is currently resource intensive. Self-reported adherence is relatively easy to obtain, inexpensive, but it is not reliable. Obtaining pharmacy claims data is expensive as it must be purchased through Pharmacy Benefits Managers or third parties. Additionally, it provides only historical information about whether a person filled a prescription in the past as opposed to giving information about adherence to medications in real time, making it more difficult to set up a system to intervene in a salient way. Assessing adherence to recommended follow-up with the current electronic health record structure is also highly resource intensive. The electronic health records are set up to optimize billing but not to optimize data use for clinical purposes. Data from the electronic health record must be systematically extracted and organized by data architects and analysts in order to make it usable, and that also takes time so that the data warehouse is oftentimes a few months behind in data capture. Some electronic health record vendors, include an algorithm to present the no-show rate for each patient, which is a useful marker for general difficulty engaging in health care but is not specific to a particular disease making it difficult to parse if the patient is having trouble with their glaucoma care or their cardiovascular care, for example. Electronically monitoring glaucoma medication use, which is currently considered the gold-standard in assessing medication adherence, remains costly, resulting in a difficult transition out of the research environment and into daily clinical care to inform clinical decision making.

From one perspective, if a physician prescribes a medication but then has no way of supporting the patient in using the medication or in returning for follow up care, this does not seem like a very effective health care intervention. From another perspective, physicians are in short supply and their responsibilities continue to escalate with the aging of the population and the increase in medical knowledge and regulation and they cannot also be expected to personally ensure that each person is taking their prescribed medications and returning for follow-up appointments. A system where ancillary staff are trained to

assist with patient navigation, connect patients to social services when needed, connect patients to transportation resources, and educate and coach patients to support their disease self-management is needed to support a team-based, patient-centered approach to optimal glaucoma management.

With advancements in computer software and artificial intelligence, there is room for the capital equipment and recurrent labor costs of monitoring adherence to treatment and follow-up recommendations to decrease and become more streamlined. Newer technologies that bring down costs for electronically monitoring medication adherence [88] and effortlessly extract and utilize data from the electronic health record [89] represent exciting avenues forward for assessing the impact these new medical and surgical approaches have on glaucoma patient engagement in care and self-management. The behavioral data captured on glaucoma patients' self-management can then inform the support provided by the glaucoma care team. This would personalize the support each patient receives. For a patient who comes for all of their recommended follow-up appointments and takes all of their medications as prescribed, they may need little additional outreach from the glaucoma support team. For a patient who has missed or re-scheduled the last three visits and misses their morning and mid-day doses of medication, they may need more outreach and assistance from the glaucoma support team to navigate treatment choices and care. This paradigm represents the holistic view for improving glaucoma outcomes using a patient-centered approach that not only includes all of the new medical and surgical techniques, but also includes new behavioral approaches for supporting people's autonomy and motivation to pursue their best vision.

Declaration of interest

P. A. N. Casey has received grants from the National Eye Institute R01EY031337, National Institute of Biomedical Imaging and Bioengineering R01EB032328, Centers for Disease Control and Prevention U01 DP006442 and, Research to Prevent Blindness Physician Scientist Award. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Articles of special interest have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. De Geest S, Sabate E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nurs. 2003 Dec;2(4):323. [PubMed: 14667488]
2. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015:217047. [PubMed: 26539470]
3. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. Cureus. 2020 Nov 24;12(11):e11686. [PubMed: 33391921]
4. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet. 2015 Apr 4;385(9975):1295–304. [PubMed: 25533656]
5. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002 Jun;120(6):701–13; discussion 829–30. [PubMed: 12049574]

6. GRF Survey Reveals Glaucoma Has Significant Impact on Patients' and Caregivers' Daily Lives, Well-Being: Glaucoma Research Foundation 2019 [updated October 22, 2021; cited 2023 January 15th, 2023]. Available from: https://glaucoma.org/grf-survey-reveals-glaucoma-has-significant-impact-on-patients-and-caregivers-daily-lives-well-being/
7. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology. 2011 Dec;118(12):2398–402. [PubMed: 21856009]
8. Brody JE. The Cost of Not Taking Your Medicine The New York Times2017 [cited 2023 January 15th, 2023]. Available from: https://www.nytimes.com/2017/04/17/well/the-cost-of-not-taking-your-medicine.html
9. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol. 2005 Oct;140(4):598–606. [PubMed: 16226511]
10. Okeke CO, Quigley HA, Jampel HD, et al. Adherence with topical glaucoma medication monitored electronically the Travatan Dosing Aid study. Ophthalmology. 2009 Feb;116(2):191–9. [PubMed: 19084273]
11. Yeaw J, Benner JS, Walt JG, et al. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm. 2009 Nov-Dec;15(9):728–40. [PubMed: 19954264]
12. Newman-Casey PA, Robin AL, Blachley T, et al. The Most Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey. Ophthalmology. 2015 Jul;122(7):1308–16. [PubMed: 25912144]
13. Hennessy AL, Katz J, Covert D, et al. A video study of drop instillation in both glaucoma and retina patients with visual impairment. Am J Ophthalmol. 2011 Dec;152(6):982–8. [PubMed: 21821228]
14. Hennessy AL, Katz J, Covert D, et al. Videotaped evaluation of eyedrop instillation in glaucoma patients with visual impairment or moderate to severe visual field loss. Ophthalmology. 2010 Dec;117(12):2345–52. [PubMed: 20580092]
15. Stone JL, Robin AL, Novack GD, et al. An objective evaluation of eyedrop instillation in patients with glaucoma. Arch Ophthalmol. 2009 Jun;127(6):732–6. [PubMed: 19506189]
16. Newman-Casey PA, Niziol LM, Gillespie BW, et al. The Association between Medication Adherence and Visual Field Progression in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology. 2020 Apr;127(4):477–483. [PubMed: 31932093]
17. Prum BE Jr., Lim MC, Mansberger SL, et al. Primary Open-Angle Glaucoma Suspect Preferred Practice Pattern((R)) Guidelines. Ophthalmology. 2016 Jan;123(1):P112–51. [PubMed: 26581560]
18. MacIver S, Stout N, Ricci O. New considerations for the clinical efficacy of old and new topical glaucoma medications. Clin Exp Optom. 2021 Apr;104(3):350–366. [PubMed: 33725467]
19. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. Br J Ophthalmol. 2021 Jun;105(Suppl 1):1–169.
20. Barnebey HS, Robin AL. Adherence to Fixed-Combination Versus Unfixed Travoprost 0.004%/Timolol 0.5% for Glaucoma or Ocular Hypertension: A Randomized Trial. Am J Ophthalmol. 2017 Apr;176:61–69. [PubMed: 27993589] * This article highlights the importance of combination medications and dose reduction in increasing adherence.
21. Shirai C, Matsuoka N, Nakazawa T. Comparison of adherence between fixed and unfixed topical combination glaucoma therapies using Japanese healthcare/pharmacy claims database: a retrospective non-interventional cohort study. BMC Ophthalmol. 2021 Jan 21;21(1):52. [PubMed: 33478408]
22. Carreon T, van der Merwe E, Fellman RL, et al. Aqueous outflow - A continuum from trabecular meshwork to episcleral veins. Prog Retin Eye Res. 2017 Mar;57:108–133. [PubMed: 28028002]
23. Voskanyan L, Garcia-Feijoo J, Belda JI, et al. Prospective, unmasked evaluation of the iStent(R) inject system for open-angle glaucoma: synergy trial. Adv Ther. 2014 Feb;31(2):189–201. [PubMed: 24452726]
24. Dick HB, Schultz T, Gerste RD. Miniaturization in Glaucoma Monitoring and Treatment: A Review of New Technologies That Require a Minimal Surgical Approach. Ophthalmol Ther. 2019 Mar;8(1):19–30. [PubMed: 30725339]

25. Stoeckel D, Pelton A, Duerig T. Self-expanding nitinol stents: material and design considerations. Eur Radiol. 2004 Feb;14(2):292–301. [PubMed: 12955452]
26. Popovic M, Campos-Moller X, Saheb H, et al. Efficacy and Adverse Event Profile of the iStent and iStent Inject Trabecular Micro-bypass for Open-angle Glaucoma: A Meta-analysis. J Curr Glaucoma Pract. 2018 May-Aug;12(2):67–84. [PubMed: 30473602]
27. Kozera M, Konopinska J, Mariak Z, et al. Effectiveness of iStent Trabecular Microbypass System Combined with Phacoemulsification versus Phacoemulsification Alone in Patients with Glaucoma and Cataract Depending on the Initial Intraocular Pressure. Ophthalmic Res. 2021;64(2):327–336. [PubMed: 32906138]
28. Samuelson TW, Chang DF, Marquis R, et al. A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract: The HORIZON Study. Ophthalmology. 2019 Jan;126(1):29–37. [PubMed: 29945799]
29. Ahmed IIK, De Francesco T, Rhee D, et al. Long-term Outcomes from the HORIZON Randomized Trial for a Schlemm's Canal Microstent in Combination Cataract and Glaucoma Surgery. Ophthalmology. 2022 Jul;129(7):742–751. [PubMed: 35218867]
30. Ahmed IIK, Fea A, Au L, et al. A Prospective Randomized Trial Comparing Hydrus and iStent Microinvasive Glaucoma Surgery Implants for Standalone Treatment of Open-Angle Glaucoma: The COMPARE Study. Ophthalmology. 2020 Jan;127(1):52–61. [PubMed: 31034856]
31. Holmes DP, Clement CI, Nguyen V, et al. Comparative study of 2-year outcomes for Hydrus or iStent inject microinvasive glaucoma surgery implants with cataract surgery. Clin Exp Ophthalmol. 2022 Apr;50(3):303–311. [PubMed: 35077009]
32. Young CC. Kahook Dual Blade: Ab Interno Trabeculectomy Eye Wiki American Academy of Ophthalmology 2022 [updated December 25th, 2022; cited 2023 January 19th, 2023]. Available from: https://eyewiki.org/Kahook_Dual_Blade:_Ab_Interno_Trabeculectomy
33. Ventura-Abreu N, Garcia-Feijoo J, Pazos M, et al. Twelve-month results of ab interno trabeculectomy with Kahook Dual Blade: an interventional, randomized, controlled clinical study. Graefes Arch Clin Exp Ophthalmol. 2021 Sep;259(9):2771–2781. [PubMed: 33907888]
34. Falkenberry S, Singh IP, Crane CJ, et al. Excisional goniotomy vs trabecular microbypass stent implantation: a prospective randomized clinical trial in eyes with mild to moderate open-angle glaucoma. J Cataract Refract Surg. 2020 Aug;46(8):1165–1171. [PubMed: 32358417]
35. Eliassi-Rad B, Singh V, Aref AA, Tripathy k., Ridha F, Ertel MK, Seibold LK Microinvasive Glaucoma Surgery (MIGS) Eye Wiki: American Academy of Ophthalmology; 2020 [cited 2023 January 19th, 2023]. Available from: https://eyewiki.aao.org/Microinvasive_Glaucoma_Surgery_(MIGS)#Visco_360.2FOMNI
36. Klabe K, Kaymak H. Standalone Trabeculotomy and Viscodilation of Schlemm's Canal and Collector Channels in Open-Angle Glaucoma Using the OMNI Surgical System: 24-Month Outcomes. Clin Ophthalmol. 2021;15:3121–3129. [PubMed: 34321863]
37. Hirsch L, Cotliar J, Vold S, et al. Canaloplasty and trabeculotomy ab interno with the OMNI system combined with cataract surgery in open-angle glaucoma: 12-month outcomes from the ROMEO study. J Cataract Refract Surg. 2021 Jul 1;47(7):907–915. [PubMed: 33315733]
38. Maeda M, Watanabe M, Ichikawa K. Evaluation of trabectome in open-angle glaucoma. J Glaucoma. 2013 Mar;22(3):205–8. [PubMed: 23429629]
39. Nct. Effect of Intra-subject Phaco/Trabectome vs. Phaco/Kahook Dual Blade on Intraocular Pressure. https://clinicaltrialsgov/show/NCT03894631. 2019 [cited. Trial registry record; Clinical trial protocol available at https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01919477/full
40. Kazerounian S, Zimbelmann M, Lortscher M, et al. Canaloplasty ab interno (AbiC) - 2-Year-Results of a Novel Minimally Invasive Glaucoma Surgery (MIGS) Technique. Klin Monbl Augenheilkd. 2021 Oct;238(10):1113–1119. [PubMed: 33202434]
41. Kamjoo SL T; Barash A; Tripathy K; Hsu J; Lim J Intravitreal Injections [Article]. Eye Wiki American Academy of Ophthalmology; 2022 [updated August, 4; cited 2022 12, 05, 2022]. Available from: https://eyewiki.aao.org/Intravitreal_Injections

42. Dong X, Shi W, Yuan G, et al. Intravitreal implantation of the biodegradable cyclosporin A drug delivery system for experimental chronic uveitis. Graefes Arch Clin Exp Ophthalmol. 2006 Apr;244(4):492–7. [PubMed: 16163496]
43. Aref AA. Durysta (Bimatoprost Implant) Eye Wiki American Academy of Ophthalmology 2022 [cited 2022 Dec 17th, 2022]. Available from: https://eyewiki.aao.org/Durysta_(Bimatoprost_Implant)
44. Bacharach J, Tatham A, Ferguson G, et al. Phase 3, Randomized, 20-Month Study of the Efficacy and Safety of Bimatoprost Implant in Patients with Open-Angle Glaucoma and Ocular Hypertension (ARTEMIS 2). Drugs. 2021 Nov;81(17):2017–2033. [PubMed: 34724172]
45. AbbVie. Expanded Access to Bimatoprost (Durysta).
46. AbbVie. Long-term Safety and Efficacy Extension Trial of Bimatoprost SR. 2025.
47. Allergan. 18 Month Prospective Efficacy and Safety Study of Bimatoprost Intracameral Implant (DURYSTA). 2023.
48. Ocular Therapeutix I. A Study to Evaluate the Efficacy and Safety of OTX-TIC (Travoprost) Intracameral Implant for Patients With Open-angle Glaucoma (OAG) or Ocular Hypertension (OHT). 2023.
49. Salim S, Aref A, Albis-Donado O, Moore DB, Morais-Sarmento T, Giaconi J, Seibold LK . Laser Trabeculoplasty: ALT vs SLT EyeWiki American Academy of Ophthalmology; 2022 [updated July 10, 2022; cited 2022 Dec 23,]. Available from: https://eyewiki.org/Laser_Trabeculoplasty:_ALT_vs_SLT
50. Wise JB, Witter SL. Argon laser therapy for open-angle glaucoma. A pilot study. Arch Ophthalmol. 1979 Feb;97(2):319–22. [PubMed: 575877]
51. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre, randomised controlled trial: design and methodology. Br J Ophthalmol. 2018 May;102(5):593–598. [PubMed: 28903966]
52. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. Lancet. 2019 Apr 13;393(10180):1505–1516. [PubMed: 30862377]
53. Wright DM, Konstantakopoulou E, Montesano G, et al. Visual Field Outcomes from the Multicenter, Randomized Controlled Laser in Glaucoma and Ocular Hypertension Trial (LiGHT). Ophthalmology. 2020 Oct;127(10):1313–1321. [PubMed: 32402553]
54. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. LiGHT trial: 6-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension. Ophthalmology. 2022 Sep 16.
55. Excellence NIfHaC. Glaucoma: diagnosis and management: NIH; 2017 [updated January 26, 2022; cited 2022]. Available from: https://www.nice.org.uk/guidance/ng81
56. Ophthalmology AAo. Primary Open-Angle Glaucoma Preferred Practice Pattern 2020 ONE Network American Academy of Ophthalmology 2022 [cited 2022 Dec 23, 2022]. Available from: https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp * This article highlights the AAO's guidline update on incorporating SLT as first line therapy.
57. Society EG. Terminology and guidelines for glaucoma 5th 2020 [cited 2022 Dec 23, 2022]; 5th: [Available from: https://www.eugs.org/eng/guidelines.asp * This article highlights the European guidelines incorporating SLT as first line therapy.
58. Ung C, Murakami Y, Zhang E, et al. The association between compliance with recommended follow-up and glaucomatous disease severity in a county hospital population. Am J Ophthalmol. 2013 Aug;156(2):362–9. [PubMed: 23601654]
59. Chen EM, Ahluwalia A, Parikh R, et al. Ophthalmic Emergency Department Visits: Factors Associated With Loss to Follow-up. Am J Ophthalmol. 2021 Feb;222:126–136. [PubMed: 32882220]
60. Quigley HA, Park CK, Tracey PA, et al. Community screening for eye disease by laypersons: the Hoffberger program. Am J Ophthalmol. 2002 Mar;133(3):386–92. [PubMed: 11860976]
61. Messina FC, McDaniel MA, Trammel AC, et al. Improving specialty care follow-up after an ED visit using a unique referral system. Am J Emerg Med. 2013 Oct;31(10):1495–500. [PubMed: 24035046]

62. Buehne KL, Rosdahl JA, Muir KW. Aiding Adherence to Glaucoma Medications: A Systematic Review. Semin Ophthalmol. 2022 Apr 3;37(3):313–323. [PubMed: 34402384] ** This article is a well-rounded systematic review of all glaucoma treatment attempts aimed at increasing adherence. The review indicates multifaceted approaches have greater success at increasing adherence.

63. Ha A, Jang M, Shim SR, et al. Interventions for Glaucoma Medication Adherence Improvement: A Network Meta-analysis of Randomized Controlled Trials. Ophthalmology. 2022 Nov;129(11):1294–1304. [PubMed: 36028393] ** This article is a meta-analysis of RCTs to improve glaucoma medication adherence and it demonstrated that face-to-face and individualized care increased adherence.

64. Muir KW, Rosdahl JA, Hein AM, et al. Improved Glaucoma Medication Adherence in a Randomized Controlled Trial. Ophthalmol Glaucoma. 2022 Jan-Feb;5(1):40–46. [PubMed: 33892170] ** This study highlights a multifacted, face- to-face and education program resulting in increased glaucoma medication adherence.

65. Newman-Casey PA, Niziol LM, Lee PP, et al. The Impact of the Support, Educate, Empower Personalized Glaucoma Coaching Pilot Study on Glaucoma Medication Adherence. Ophthalmol Glaucoma. 2020 Jul-Aug;3(4):228–237. [PubMed: 33012330] ** This study highlights a multifaceted, highly individualized treatment program that resulted in increased glaucoma medication adherence.

66. Leiby BE, Hegarty SE, Zhan T, et al. A Randomized Trial to Improve Adherence to Follow-up Eye Examinations Among People With Glaucoma. Prev Chronic Dis. 2021 May 20;18:E52. [PubMed: 34014814] ** This article highlights patient navigators playing a previously untapped, but dramatic role in increasing adherence to follow-up recommendations.

67. Nanotechnology in Medicine: Technology Trends Medical Device Network: GlobalData Thematic Research; 2020 [cited 2022 January 9th, 2022]. Available from: https://www.medicaldevice-network.com/comment/nanotechnology-medicine-technology/

68. Mirzaeei S, Faryadras FB, Mehrandish S, et al. Development and evaluation of polycaprolactone-based electrospun nanofibers containing timolol maleate as a sustained-release device for treatment of glaucoma: in vivo evaluation in equine eye. Res Pharm Sci. 2022 Oct;17(5):468–481. [PubMed: 36386485]

69. Wang J, Li B, Huang D, et al. Nano-in-Nano Dendrimer Gel Particles for Efficient Topical Delivery of Antiglaucoma Drugs into the Eye. Chem Eng J. 2021 Dec 1;425.

70. Waghmare SV, Jeria S. A Review of Contact Lens-Related Risk Factors and Complications. Cureus. 2022 Oct;14(10):e30118. [PubMed: 36381898]

71. Hilloowala R. Leonardo da Vinci, visual perspective and the crystalline sphere (lens): if only Leonardo had had a freezer. Vesalius. 2004 Jun;10(1):10–5. [PubMed: 15386876]

72. Moreddu R, Vigolo D, Yetisen AK. Contact Lens Technology: From Fundamentals to Applications. Adv Healthc Mater. 2019 Aug;8(15):e1900368. [PubMed: 31183972]

73. Belamkar A, Harris A, Zukerman R, et al. Sustained release glaucoma therapies: Novel modalities for overcoming key treatment barriers associated with topical medications. Ann Med. 2022 Dec;54(1):343–358. [PubMed: 35076329]

74. Dang H, Dong C, Zhang L. Sustained latanoprost release from PEGylated solid lipid nanoparticle-laden soft contact lens to treat glaucoma. Pharm Dev Technol. 2022 Feb;27(2):127–133. [PubMed: 34704874]

75. Desai AR, Maulvi FA, Desai DM, et al. Multiple drug delivery from the drug-implants-laden silicone contact lens: Addressing the issue of burst drug release. Mater Sci Eng C Mater Biol Appl. 2020 Jul;112:110885. [PubMed: 32409042]

76. Ophthalmics M. MediPrint™ Ophthalmics Announces Successful Completion of Its SIGHT-1 Phase 2a Clinical Study 2021 [cited 2023 January 9th,2023]. Available from: https://mediprintlens.com/mediprint-ophthalmics-announces-successful-completion-of-its-sight-1-phase-2a-clinical-study/

77. Hutton D. Glaukos announces results of two Phase 3 pivotal trials of iDose TR: Ophthalmology Times; 2022 [cited 2023 January 9th, 2023]. Available from: https://www.ophthalmologytimes.com/view/glaukos-announces-results-of-two-phase-3-pivotal-trials-of-idose-tr

78. Ibach M. iDose: An Intraocular Drug-Eluting Delivery Device for Glaucoma The Pipeline: Glaucoma Today; 2020 [cited 2023 January 9th, 2023]. Available from: https://glaucomatoday.com/articles/2020-nov-dec/idose-an-intraocular-drug-eluting-delivery-device-for-glaucoma

79. Glaukos Announces Positive Results for iDose TR Exchange Trial, Highlighting Favorable Safety and Tolerability Eyewire: BMC Vision; 2023 [updated January 11, 2023]. Available from: https://eyewire.news/news/glaukos-announces-positive-results-for-idose-tr-exchange-trial-highlighting-favorable-safety-and-tolerability?c4src=article:infinite-scroll

80. Introducing the Optejet Technology - Eyenovia: Eyenovia 2020 [cited 2023 January 26th, 2023]. Available from: https://eyenovia.com/technology/

81. Hutton D. Eyenovia offers results of study evaluating microdose delivery technology News - Ophthalmology Times: Ophthalmology Times; 2023 [cited 2023 January 26th, 2023]. Available from: https://www.ophthalmologytimes.com/view/eyenovia-offers-results-of-study-evaluating-microdose-delivery-technology

82. Charters L. Travoprost intracameral implant shows efficacy in topical form News - Ophthalmology Times: Ophthalmology Times; 2022 [cited 2023 January 26th, 2023]. Available from: https://www.ophthalmologytimes.com/view/travoprost-intracameral-implant-shows-efficacy-in-topical-form

83. Goldstein MHW T; Goldberg DF; Day D; Braun E; Metzinger JL A Prospective, Multicenter, Open-Label First-in-Human Study to Evaluate the Safety, Tolerability and Efficacy of OTX-TIC (travoprost) Implant in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension: Preliminary Findings [Abstract]. Investigative Ophthalmology & Visual Science. 2019;60:3360.

84. Envisia T. Safety and Efficacy of ENV515 Travoprost Extended Release (XR) in Patients With Bilateral Ocular Hypertension or Primary Open Angle Glaucoma. 2019.

85. Mati Therapeutics selected to present at Ocular Innovation Summit: Pursuing sustained ocular drug delivery programs in inflammation, pain, and glaucoma [Internet]. Ocular Innovation Summit: Mati Therapeutics; 2016. Available from: www.matitherapeutics.com/about/press/ocular-innovation-summit.

86. Utkhede DW R. Improving retention rates for sustained therapeutic delivery through punctal plugs. Investigative Ophthalmology & Visual Science. 2018;59:5675.

87. Mati Therapeutics Announces Purchase of Rights From Novelion Therapeutics Inc. Businesswire: Berkshire Hathaway; 2021 [cited 2023 January 26th, 2023]. Available from: https://www.businesswire.com/news/home/20210201005041/en/Mati-Therapeutics-Announces-Purchase-of-Rights-From-Novelion-Therapeutics-Inc.

88. Payne N, Gangwani R, Barton K, et al. Medication Adherence and Liquid Level Tracking System for Healthcare Provider Feedback. Sensors (Basel). 2020 Apr 24;20(8).

89. Bommakanti NK, Zhou Y, Ehrlich JR, et al. Application of the Sight Outcomes Research Collaborative Ophthalmology Data Repository for Triaging Patients With Glaucoma and Clinic Appointments During Pandemics Such as COVID-19. JAMA Ophthalmol. 2020 Sep 1;138(9):974–980. [PubMed: 32678424]

Article highlights

- Non-adherence to glaucoma treatment remains high both in terms of low rates of medication utilization and low rates of returning for recommended follow-up care.
- Newer medical and surgical technologies aim to decrease medication burden by decreasing the number of daily administration times, but the impact on adherence to medication utilization and recommended follow-up care remains understudied.
- 89% of glaucoma patients use eye drops as treatment. Topical medications continue to play an important role in glaucoma management. Pharmacotherapies that combine medications to decrease dosing improve adherence.
- Minimally invasive glaucoma procedures can decrease the number of medications needed for disease control and offer patients more choices in how they prefer to manage their disease. To enhance the effectiveness of physicians' care, a team-based approach to educating patients about their various options for controlling their glaucoma would likely enhance engagement in care. As glaucoma is a life-long condition and these newer surgeries have only recently become available, additional data regarding efficacy and adverse events over the long term are needed.
- Behavioral approaches supporting glaucoma self-management have shown promising results indicating adherence is modifiable and varies over time. Long-term support is essential for continued adherence to recommended treatments, meaning that for the health care system to support ideal outcomes for glaucoma patients, new team-based approaches to glaucoma self-management support must be created and implemented.