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REVIEW

Factors Affecting Glaucoma Medication Adherence and Interventions to Improve Adherence: A Narrative Review

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ABSTRACT

Glaucoma is a leading cause of vision loss. First line therapy for primary open angle glaucoma (POAG) are topical ocular hypotensive drops. Patient adherence with topical therapy for glaucoma is a significant challenge with a reported adherence of 60%. The purpose of this review is to discuss factors associated with glaucoma adherence (including demographic factors, cost, patient education, health beliefs, treatment burden and regimen, and physical limitations) and to explore potential interventions to improve medication adherence. Articles included in this review were found by searching PubMed and Google Scholar using the key words "Glaucoma Treatment Adherence" and "Glaucoma Treatment Compliance." Data from this review demonstrates that higher medication cost, lower patient education/literacy levels, and being of African and Hispanic descent are associated with lower medication adherence rates. The data is inconclusive on whether medication regimen complexity lowers patient medication adherence rates. Interventions that have successfully improved medication adherence rates for minority patients have focused on building trust and addressing fears and false beliefs. For cost, explicit physician communication to patients regarding medication cost is important and can help the physician determine any patient concerns about cost. Outside the USA, adherence has been improved through adherence-contingent rebate systems and government subsidies. Most interventions that aim to increase adherence target patient education and literacy with the following interventions demonstrating efficacy: written instructions targeting glaucoma-specific health literacy, literacy level appropriate glaucoma education videos, and interactive and personalized educational programs. More clinic infrastructure and programs that utilize patient reminder tools and patient educators could help physicians and patients in support of these personalized action plans.

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Key Summary Points

Glaucoma is a leading cause of vision loss and poor adherence with glaucoma topical therapy results in worse outcomes.

Cost is a major barrier to adherence, and clinicians and their staff should proactively mention medication costs, ask about financial obligations, and tailor prescribed medications (generic versus brand name) based on these discussions.

Most interventions to improve adherence target patient education and health literacy. Written instructions targeting glaucoma specific health literacy, literacy level appropriate glaucoma education videos, and interactive and personalized educational programs have been successfully employed.

It remains unclear whether medication regimen complexity is a barrier for patient adherence as studies have shown both improvement in adherence and worsening adherence with increasing medication regimen complexity.

INTRODUCTION

Glaucoma is a leading cause of vision loss, especially in older adults, affecting approximately 3 million Americans [1]. The estimated prevalence of primary open angle glaucoma (POAG), the most common subtype of glaucoma, was estimated to be 64.3 million with projected global increases to 76.0 million and 111.8 million by 2020 and 2040, respectively [2]. Early detection and treatment of glaucoma is critical given the insidious nature of its onset and progression as well as the irreversible nature of associated vision loss.

Poor access to care, initial visual acuity worse than 20/40, and poor control of intraocular pressure (IOP) are major risk factors associated with blindness from POAG [3]. Poor adherence with glaucoma management results in uncontrolled IOP and thus vision loss and blindness [4–7]. A significant challenge with patient medication adherence is that glaucoma is typically asymptomatic in the earlier stages of the disease, thus patients often do not feel the immediate benefit of being adherent with their medications, which they often find onerous. Studies have shown that common barriers to adherence include cost, forgetfulness, side effects, difficulty with eye drop administration, and the need for multiple doses a day [8].

Ocular hypotensive medications are the most common treatment for glaucoma, used by 86% of patients with glaucoma [9]. Ocularhypotensives are very effective, reducing the progression of glaucoma by at least 60% [7, 10, 11]. In general, adherence among patients with chronic conditions varies between 30% and 50% [12]. For glaucoma, many studies have shown 60% as the average estimate of adherence [13–15], with other studies citing adherence varying between 5% and 80% [12]. Researchers attribute the wide variability due to glaucoma adherence being difficult to measure and its measurement having no standardization [16, 17].

This review will discuss factors associated with glaucoma adherence, and explore experimental interventions to improve medication adherence.

Search Strategy

Articles included in this paper were found by searching PubMed, Google Scholar, and Kaiser Permanente Clinical Library using the key words “Glaucoma Treatment Adherence” and “Glaucoma Treatment Compliance.” Articles were limited to English language articles published between 2000 and 2022, with the exception of older articles cited in systematic reviews. From this search 50 papers/abstracts were retrieved and reviewed with only those

falling within the subject matter of this review being further analyzed.

Compliance with Ethic Guidelines

This article is based on previously conducted studies and does not contain any new data with human participants or animals performed by any of the authors.

DEMOGRAPHIC DIFFERENCES IN ADHERENCE

While non-white Americans have a much higher prevalence of glaucoma and thus the greatest burden of disease, they unfortunately have lower medication adherence rates. In the early 1990s, the Baltimore Eye Study established the different prevalence rates of POAG among African Americans and white Americans with the prevalence of POAG approximately four times higher in African Americans than white Americans (4.74% in African Americans versus 1.20% in white Americans) [18]. In 2004, the Los Angeles Latino Eye Study established that prevalence of open angle glaucoma (OAG) in Latinos was also high, measuring at 4.74% [19].

Rees and colleagues sought to determine if there were different adherence rates in white Americans ($n = 133$), African Americans ($n = 58$), white Australians ($n = 107$), and Singaporeans of Chinese descent ($n = 117$) [20]. The study consisted of 475 patients who had used topical eye drops for at least 6 months [20]. Adherence rates were measured via a self-reported Reported Adherence to Medication scale [20]. The authors found that there were significant sociodemographic differences in self-reported adherence rates ($p < 0.001$) [20]. Specifically, white Americans and Australians reported significantly higher adherence (65.4%) than African Americans (56.9%; $p < 0.05$) or Singaporeans (47.5%; $p < 0.05$) [20]; however, Rees and colleagues caution extrapolating their results since the data is self-reported, the studied population is not representative of patients with glaucoma, and most importantly, the disease stage, disease type, or experience of visual symptoms was unknown [20].

A study by Murakami and colleagues on patients with glaucoma from a small hospital in San Francisco, California found that patients of African and Hispanic descent were independently associated with inconsistent follow-up [21]. Data was obtained from an oral questionnaire and patients with glaucoma with inconsistent follow-up were matched 1-to-1 with controls that had consistent follow-up [21]. All in all, factors independently associated with inconsistent follow-up were patients of African descent [adjusted odds ratio (OR) 7.16, 95% confidence interval (CI) 1.64–31.24], patients of Hispanic descent (adjusted OR 4.77, 95% CI 1.12–20.29), unfamiliarity with necessary treatment duration (adjusted OR 3.54, 95% CI 1.26–9.94), unawareness of glaucoma-induced vision loss (adjusted OR 3.09, 95% CI 1.18–8.04), and perception that follow-up visits are not important (adjusted OR 3.54, 95% CI 1.26–9.94) [21].

Dreer and colleagues embarked on a multistudy investigation into topical glaucoma therapy adherence across different racial groups that set to record adherence rates, design a program to increase adherence rates, and implement the program [22]. Adherence was defined in three ways: the proportion of days taking the prescribed number of drops within 3 h of prescribed dosing time, the proportion of days taking any drops within 3 h of prescribed dosing time, and the proportion of days taking any drops within 6 h of the prescribed dosing time [22]. Adherence was measured using an electronic dose monitor (Travatan Dosing Aid) over a 3-month period [22]. It was found that white Americans met the criteria for full treatment adherence on 71.2% of treatment days and African Americans for 53.4% of treatment days [22]. They concluded that race statistically significantly predicted treatment adherence after controlling for age, sex, income, education, number of oral medications, severity of disease, and IOP [22].

In a subsequent design study, Dreer and colleagues sought to construct a culturally informed, health promotion program to improve medication adherence among African

Americans since data historically has been limited on this population. Input for the health promotion program was done by forming focus groups with African American patients with glaucoma [8]. Through these focus groups, the researchers identified five top barriers that impact this patient population: forgetfulness, side effects, cost/affordability, eye drop administration, and the eye drop schedule [8]. Based on these barriers, the Glaucoma Management Optimism for African Americans Living with Glaucoma (GOAL) health promotion program was formed, which consisted of in-person and phone sessions focusing on building trust/rapport, identifying baseline knowledge, discussing barriers, addressing fears and inaccurate perceptions of glaucoma and management through problem solving techniques, and conducting motivational interviewing techniques [8].

In the final study of the multi-study investigation by Dreer and colleagues, the authors implemented the 4-week GOAL program on 11 patients to assess its feasibility, efficacy, and patient acceptability [23]. Results showed statistically significant prepost improvement in medication adherence rates ($p = 0.03$), as well as self-efficacy for glaucoma management ($p = 0.02$), ease of use in administering eye drops ($p = 0.03$), glaucoma treatment satisfaction ($p = 0.05$), and beliefs about the necessity of taking glaucoma medications ($p = 0.05$) [23]. All in all, Dreer and colleagues found that adherence rates in African American patients were lower than their white Americans counterparts and after implementation of a health promotion program, these patients experienced a significant improvement in medication adherence.

The aforementioned studies agree that there is a statistical difference in adherence rates among different race/ethnicity groups. Explanations for these findings range from a patient's perceived need for glaucoma treatment to likely multifactorial and historical contextual considerations, such as the well recognized distrust of the African American community in the medical system [24]; however, studies have shown that adherence rates can improve in this patient demographic by focusing on building trust and addressing fears and false beliefs. Non-white patients with glaucoma are on average younger and may have different socioeconomic barriers related to costs (as they do not qualify for Medicare) and time commitments (as they are not retired), and as such they represent an important demographic in which to improve medication adherence.

COST

A critical factor that affects glaucoma medication adherence is cost. First line management for glaucoma generally begins with pharmacological intervention. Topical medication classes available to lower IOP include beta blockers, alpha-2-agonists, prostaglandin analogs, carbonic anhydrase inhibitors (CAIs), parasympathomimetics, and rho kinase inhibitors [25]. Of these, first line monotherapy commonly utilizes beta blockers or prostaglandins, with alpha-2 agonists and CAIs often added later if additional IOP reduction is needed [25]. Major studies, such as the Advanced Glaucoma Intervention Study (AGIS) showed that the average number of medications prescribed to manage glaucoma was 2.7, and this number has likely gone up since then as the number of topical agents has increased [26]. Rylander and Vold did a cost analysis of glaucoma medications revealing that generic nonselective beta blockers are the least expensive [27]. Specifically, yearly costs for generic beta blockers range from $150.81 to $697.24, and yearly costs for available brand name beta blockers ranged from $203.47 to $657.24 [27]. Generic beta blockers were consistently less expensive than their brand name counterparts [27]. Prostaglandin analogs yearly costs ranged from $427.69 to $577.62 [27]. Generic alpha-2 agonists can cost $352.89 for two times daily dosing or $529.34 for three times daily dosing per year [27]. In contrast, branded alpha-2 agonists can be $559.08 for two times daily dosing per year or as high as $873.98 for three times daily dosing [27]. Glaucoma medications are an added indefinite cost for patients to bear. In the USA, individuals over 65 qualify for Medicare and can enroll in the optional Medicare Part D, which lowers

prescription costs for an additional premium, although it can be a burden for those on a fixed income.

Since the implementation of Medicare Part D in 2006, most adults with glaucoma over the age of 65 have experienced increased rates of prescription drug coverage and thus lower out-of-pocket costs [4]; however, Medicare Part D does not cover adults under 65. Ross and Higginbotham noted that non-Hispanic white patients with glaucoma are more likely to be older than 65 and qualify for Medicare and separately qualify for Medicaid compared with African American and Hispanic patients with glaucoma [28]. Thus, African American and Hispanic patients, who are more likely to get glaucoma at a younger age, are more likely to be impacted by limited prescription drug coverage and high cost of their glaucoma medications [28].

Although many studies have shown that cost affects adherence, it has been difficult to quantify this impact on adherence. In the Glaucoma Adherence and Persistency Study (GAPS) by Friedman and colleagues, 24.7% of patients reported that paying for medications was a significant barrier [29]. Those patients that reported a cost barrier were also more likely to have lower incomes, less educational attainment, be of African American descent, and be female [29]. In the Patient Perspective study by Newman-Casey and colleagues, focus groups of patients with glaucoma were formed to understand their perspective on why glaucoma continues to cause blindness when effective medical treatments are available and what their perceived barriers to effective treatment were [30]. In these focus groups, patients spoke about important systemic barriers, such as cost, specifically the obstacles of insurance companies, authorization for medications, and insurance coverage for their preferred provider [30]. Furthermore, Mansberger and colleagues created a questionnaire, the Glaucoma Treatment Compliance Assessment Tool (GTCAT), which was used to assess glaucoma therapy adherence in focus groups based on the Health Belief Model, and they reported the most cited barrier was cost, followed by forgetfulness and side effects [16].

In an insightful perspective on cost, Tsai and colleagues infer that the role of cost is difficult to remedy by physicians because patients will not: (1) bring up the discussion of medication cost, or (2) inform their physician that they plan to underuse the medication due to cost [5]. They further contend that while cost is an important barrier, it is difficult to pinpoint because there are conflicting reports on: (1) percentage of patients that experience a medication cost barrier, (2) specific medication class and corresponding patient adherence, and (3) varying dosing intervals and corresponding patient adherence [31, 32].

Different strategies have been suggested to combat the impact of cost on patient adherence with glaucoma medications. The Gluaco-Jung study in India suggest that glaucoma medications need to be highly subsidized by government dispensaries, which would improve adherence [33]. A second is a study by Bilger and colleagues examined the impact of offering monthly adherence-contingent rebates to patients who were adherent to all their medications [34]. The study found that patients in the rebate group were more adherent to medications (73.1% of the time after 6 months) compared with patients in the non-rebate group whose adherence was 61.6%, resulting in a statistically significant 12.2 percentage difference after adjusting for baseline differences ($p = 0.027$) [34].

These two studies recognize that cost is a limiting factor for patient adherence but propose different solutions. While the Gluaco-Jung study asserts that implementing government subsidies can improve patient adherence, Bilger and colleagues contend that public subsidies and/or insurance coverage is not sufficient to improve adherence and that patients respond better to a reward system such as an adherence-contingent rebate offer [33, 34]. Although both studies identify financial mechanisms to improve glaucoma adherence, the ideal solution will depend on a number of local factors including insurance programs/coverage as well as patient demographic and cultural factors. Patients with glaucoma living in the USA over 65 have a decreased, but not eliminated, cost burden since most prescription costs are

covered through Medicare and Medicare Part D. A study in 2009 conducted by Blumberg and colleagues compared glaucoma medication cost-related non-adherence pre- and post-Medicare Part D implementation [4]. Data was gathered from the Medicare Current Beneficiary Survey and from in-depth face-to-face patient interviews on filling prescriptions [4]. The authors found that the percentage of patients who did not fill their prescriptions due to cost did not decrease significantly after Medicare Part D implementation ($p = 0.12$), but the percentage of patients with glaucoma who skipped doses or took "smaller doses" did decrease significantly ($p = 0.001$) [4]. Even with the implementation of Medicare Part D for eligible patients, the authors contend that cost-related medication adherence remains an issue, although decreased, and future efforts should aim to further minimize cost related adherence issues in high risk sociodemographic groups [4]. Importantly, this study gathered data from 2004 to 2009 and changes in insurance coverage practices may limit its future generalizability.

A recent study published in 2022 by Delavar and colleagues investigated cost-related barriers to glaucoma adherence stratified by self-reported race and ethnicity with a diverse set of participants gathered from the NIH All of US Research Program [35]. Adherence was measured with seven yes/no questions on why a participant was non-adherent: could not afford prescription medication, skipped medication doses to save money, took less medicine to save money, delayed filling a prescription to save money, asked physician for a lower-cost medication to save money, bought prescription drugs from another country to save money, or used alternative therapies to save money [35]. Delavar and colleagues found that 19.4% of participants asked their physician for a lower-cost medication to save money with the other most common reasons for non-adherence being affordability and delaying filling of the prescription [35]. African American individuals and Hispanic individuals were significantly more likely than non-Hispanic white individuals to report not being able to afford medications, delaying filling medications, and using alternative therapies to save money [35]. Furthermore, African American participants were more likely to report skipping medication and taking less medication [35]. This trend was attenuated but persisted even after controlling for socioeconomic variables, such as income, insurance status, and education [35]. Delavar and colleagues contend that physicians should take a proactive role to discuss cost with all patients because evidence suggests that white patients are more comfortable asking for less expensive medications than their counterparts and patient hesitancy to broach the subject of finances hinders adherence [5, 36]. Although it may be difficult for physicians to consistently broach this subject with their patients in the middle of a busy clinic, incorporating questions about financial concerns as part of ancillary staff patient intake/discharge could serve as a means to inquire about these concerns with patients in a non-judgemental and standardized manner, which could improve adherence.

In review of the Delavar et al. study, other researchers assert that confounding variables need to be considered when discussing cost, such as severity of disease, since patients with severe disease consider cost more as they are likely taking multiple medications, patients greater than 65 in the USA have Medicare to lower cost, and new treatment modalities to decrease IOP such as laser and minimally invasive surgery are more widely available [28].

Cost is a major factor affecting patient adherence to glaucoma medication therapy. To address this barrier, ophthalmologists and their staff should proactively mention medication costs, ask about financial obligations, and tailor prescribed medications (generic versus brand name) based on these discussions [5, 28, 36]. If cost is identified as a significant barrier or concern, physicians may be more inclined to offer non-medical intervention such as selective laser trabeculoplasty (SLT) [28]. Additional studies, including in the USA, should explore if glaucoma medication adherence can be increased by implementing an adherence-contingent rebate system similar to the Bilger and colleagues and/or government subsidies according to Gupta and colleagues [33, 34]. Furthermore, it should be stated that differences in study design and patient population (including country of origin, time, race/ethnicity, health insurance,

and socioeconomic status) should be considered before generalizing findings to other populations.

PATIENT EDUCATION AND HEALTH BELIEFS

A strong association between poor patient health literacy and non-adherence has been previously demonstrated (i.e., missed appointments, missed eye drops, less refills over a 6 month period; $p < 0.001$) [37, 38]. Thus researchers have conducted studies to not only establish areas where practical patient education can improve adherence, such as eye drop instillation, but also to explore broader reasons why patients are non-adherent, such as health beliefs. Gupta and colleagues' proof of concept study on patient eye drop instillation technique found that only 6 out of 70 patients (8.57%) had correct eye drop instillation technique (i.e., one drop into the conjunctival sac without bottle tip contact) [39]. These results indicate that even patients who "take" their ocular hypotensives may not achieve full therapeutic effect because of incorrect instillation technique [39]. Kang and colleagues wanted to assess the relationship between health literacy and successful glaucoma drop administration with veterans receiving care at a Veterans Affair Eye Clinic with the diagnosis of open-angle glaucoma who self-endorsed poor drop adherence [40]. Participants underwent a health literacy evaluation using the Rapid Estimate of Adult Literacy in Medicine (REALM) as well as a qualitative assessment of eye drop administration technique using three different criteria: (1) the drop was instilled in the eye, (2) only one drop was dispensed, and (3) the bottle was not potentially contaminated [40]. A proportion of 78% of the participants read at a high school level (HSL) or higher and 22% read at less than HSL [40]. A greater proportion of participants who read at HSL or higher successfully instilled the drop in the eye compared with those reading at less than HSL (90.6% versus 75.0%; $p = 0.02$) [40]. Criterion 2 and 3, only one drop dispensed and no contamination, were found to not be associated with health literacy level [40]. The researchers believe poor health literacy may be associated with decreased successful eye drop instillation in patients with glaucoma and propose screening for and considering health literacy in developing interventions to improve glaucoma self-management [40].

Kosoko and colleagues conducted a study in an urban resident run glaucoma clinic, where 51% of patients had an educational level of lower than the 12th grade, and found that lower educational attainment was associated with reduced ability to answer questions, such as whether they were informed they had glaucoma, what glaucoma therapy they were currently prescribed, and how often they took glaucoma medication as prescribed during a telephone interview [41]. Specifically, 58% of participants who did not complete high school could not answer questions about their glaucoma medications compared with 21% of participants who did complete high school [41].

A study by Newman-Casey and colleagues, examined the patient perspective on why patients with glaucoma lose vision. A total of 56 patients with glaucoma, 25 with good vision and 31 with poor vision, were interviewed in 9 focus groups and asked about barriers to glaucoma management [30]. A common theme that both patients with good and poor vision agreed upon is that due to glaucoma "being asymptomatic," it is easy to "not prioritize [glaucoma];" however, many patients believed that adhering to medication gave them a sense of "control" over glaucoma and vision loss [30]. The most common barrier to controlling glaucoma that participants identified was the physician–patient relationship, meaning specifically how much time the patient perceived the physician spent with them, elicited their concerns, and actively listened [30]. The second most common barrier was knowledge about glaucoma, with the authors stating this barrier is complex and difficult to assess credibility as some participants preferred to learn about glaucoma through their physician while others preferred to learn through multiple sources (i.e., newspaper, magazine) [30]. The third most commonly cited barrier was having an unsupportive spouse or family to remind the patient to take their drops, as glaucoma is invisible to others as well [30].

Friedman and colleagues contended that adherence to treatment depends on the patients' beliefs about the disease and the benefits of treatment [29]. This study sought to examine how adherence, based on administrative claims data, is impacted by a patient's health-related beliefs and experience with ophthalmologists [29]. Adherence was measured with the medication possession ratio (MPR): the ratio of days of supply medication dispensed divided by the days between pharmacy fulfillments, with higher MPR indicating higher adherence [29]. Eight variables were associated with a lower MPR (lower adherence): doctor-dependent learning about glaucoma, not believing that vision loss is a risk of non-adherence, medication cost, adherence difficulty while traveling, not experiencing adverse effects such as stinging and burning, being non-white, receiving medication samples, and not receiving a phone call visit reminder [29]. Patients were classified as doctor-dependent learners if all of their knowledge about glaucoma came from their doctor [29]. If a patient gained most of their knowledge from a doctor they were classified as a collaborative learner. Conversely, independent learners were patients who learned little to nothing from their doctor [29].

The authors found that doctor-dependent learners had poorer adherence than the collaborative and independent learners ($p < 0.05$) [29]. Additionally, patients who reported receiving phone call visit reminders (with or without postcard reminders) had better adherence to drops than those who received only postcards, received no reminder, or could not recall [29]. Overwhelmingly, 86% (258/300) of interviewed patients did believe that not taking their medications would result in vision loss [29]. On the other hand, the 14% (42/300) of patients who did not believe the sentiment above reported receiving less information, fewer answers to questions, and no demonstration on proper use of eye drops [29]. This culminated in lower MPR (i.e., lower adherence) and the belief that glaucoma would not result in complete vision loss, optic nerve damage, or increased IOP [29]. Interestingly, and perhaps counterintuitively, patients who reported stinging and burning had a higher MPR, potentially because these sensations indicated some medication effect [29]. The GAPS data suggest that a doctor-dependent learning style is associated with less concern about the future effects of glaucoma and the risks of not taking medication [29]. Friedman and colleagues recommend that physicians implement an ask-tell-ask dialog communication strategy detailed below [29]. The thought behind employing this communication strategy is not only to improve education for doctor dependent learners, but it may help physicians overcome some of the health belief-related barriers to adherence aforementioned [29]. All in all, the GAPS study found reasons for non-adherence are multifactorial, including being a doctor-dependent learner, being non-white, and not having a telephone appointment reminder system at their doctor's office [29]. Technology advances in physician–patient communication could be similarly employed in the future including automated reminder text messages and emails. Those patients with the poorest understanding of the consequences of non-adherence had physicians who had not taught them basic information about glaucoma such as how to instill eye drops [29]. Efforts for glaucoma physicians to improve communication and education for their patients would likely have an important impact on improving medication non-adherence. Leveraging ancillary staff such as medical assistants and nurses for basic education, as well as the possibility of group classes, can be further explored as educational avenues.

Interventions and Potential Solutions for Patient Education

Several studies have focused on implementing interventions or multiple simultaneous interventions targeting patient education and measuring their effects on adherence.

Kosoko and colleagues evaluated patients from an urban area and found that after giving written instructions, the ability to accurately answer questions about glaucoma and eye drop management improved both in patients who did and did not graduate high school ($23.36 \pm 30.8\%$ to 88% and $8.46 \pm 21.7\%$ to

96% for participants who did and did not graduate high school, respectively) [41].

One randomized controlled study with a patient population of veterans assessed the number of days without medicine (DWM) after intervention with a glaucoma education video geared toward a patient's literacy level (i.e., adequate, marginal, or inadequate) [42]. Overall, they found the number of DWM was similar for the intervention and control groups over 6 months (63 ± 198 versus 60 ± 198; $p = 0.708$) [42]. While a glaucoma education video alone may not be an effective intervention to improve adherence, the authors suggested that those with lower health literacy may most benefit from educational efforts in the future because this group reported lower self-reported satisfaction with care compared with patients with higher health literacy levels ($p = 0.002$) [42].

Miller and colleagues investigated the effect of their new program—Support, Educate, Empower (SEE)—on medication adherence rates [43]. The SEE program is a personalized coaching intervention that uses customized medication reminders, education, and motivational interviewing [43]. Participants were included if they had an electronically measured adherence $< 80\%$ [43]. The intervention occurred over 7 months [43]. Medication adherence was monitored electronically as the percentage of doses taken correctly [43]. There were 39 participants, 56% of which were male, 44% were white, and 49% were Black [43]. Overall, medication adherence improved from a baseline of 59.9% [standard deviation (SD) 18.5%] to 83.6% (SD 17.5%) [43]. Participants with lower income ($<$ \$25,000 and \$25,000–\$50,000 versus $>$ \$50,000) had lower baseline adherence (48.4% and 64.1% versus 70.4%) but had greater increases in adherence during the first month of medication reminders (19.6% and 21.6% versus 10.2%; $p = 0.05$ and $p = 0.007$, respectively) [43]. Participants taking fewer glaucoma medications also had significantly greater increases in adherence with medication reminders ($p < 0.001$) [43]. All together, the SEE program did improve adherence, especially in lower income groups.

The literature that focuses on improving glaucoma topical medication adherence typically targets interventions at the patient level through education, demonstrating, and understanding the "why;" however, one randomized controlled trial by Cate and colleagues sought to do the same through a Behavior Change Counseling (BCC) intervention and found that their program did not improve adherence nor was it cost effective [44]. BCC is a modified version of Motivational Interviewing that is less time intensive and allows for the exchange of information in addition to asking open ended questions [44]. Improvement in glaucoma adherence was measured using an electronic adherence monitoring device that is able to record the time, date, and number of drops of medication released from the bottle [the Travatan Dosing Aid (TDA)] over an 8-month follow-up period with Travoprost [44]. The TDA data was also used to categorize participants based on baseline adherence behaviors: discontinuation of dosing after a short time interval, adherence $> 97\%$, adherence 80–97%, frequent drug holidays, and variable with frequent missed doses [44]. Patients who received BCC did not have different adherence compared to those who did not receive BCC (77.2% versus 74.8%; $p = 0.471$) [45]. There also was no statistically significant difference in proportion obtaining $> 80\%$ adherence between the intervention and control group (66.7% versus 62.5%; $p = 0.685$) [45]. Similarly, there was no significant difference in IOP reduction (27.6% versus 25.3%; $p = 0.45$) between the intervention and control group [45]. Although the intervention group was more satisfied with information about glaucoma medication due to BCC, the outcomes between groups did not differ and BCC was found to not be cost effective [45].

A systematic review done by Newman-Casey and colleagues in 2014 reviewed eight studies that implemented educational interventions to improve glaucoma medication adherence [46]. The examined studies enacted varying interventions ranging from educational videos about glaucoma treatment, nurse and ophthalmic technician-led individual educational sessions to motivational interviewing, and lectures led by ophthalmologists [46]. Five of the educational intervention strategies produced

significant improvements in glaucoma adherence and three other studies found an improvement that did not reach statistical significance [46]. The strategies that found a statistically significant improvement were: (1) Okeke and colleagues' study (discussed in greater detail below) that implemented glaucoma education, addressed barriers, and created a reminder system, (2) educational slideshow and pamphlet with questions answered by an ophthalmic technician, (3) visit with ophthalmologist or nurse dedicated to glaucoma education, (4) multiple motivational interviews with patients to address barriers, and (5) creation of a glaucoma club with ophthalmologists and patients who interact and learn about glaucoma [46]. Based on these studies, Newman-Casey and colleagues created a conceptual model that included frameworks such as types of barriers to adherence that were categorized into "patient and situation factors" (i.e., lack of understanding, forgetfulness, drop administration difficulty) and "regimen factors" (i.e., cost, side effects, regimen complexity) [46]. They asserted that patient and situation factors can be addressed and improved by educational interventions and advocated for with individually tailored educational material since most of the studies that found a statistically significant improvement used a personalized educational approach [46]. Ultimately, Newman-Casey and colleagues demonstrated that addressing knowledge deficiencies and barriers increased medication adherence.

Waterman and colleagues conducted a systematic review of randomized (or quasi randomized, where the method of allocation is not truly random) controlled trials of interventions for improving adherence to ocular hypotensive therapy, with 16 studies (1565 participants) being included in the review [17]. Of the 16 studies, seven implemented a patient education intervention, 8 studies compared different drug regimens, and the remaining study incorporated a reminder device [17]. Similar to Newman-Casey, Waterman and colleagues detailed three studies that significantly increased ocular hypotensive adherence through incorporation of a complex combination of education and personalized interventions, which are discussed below.

The first study by Gray and colleagues in 2011 involved a multifocal intervention: an assessment of healthcare needs and beliefs about medicine and illness, an educational session, and an interactive training session to learn how to instill eye drops [47]. Adherence was measured using the Reported Adherence to Medication scale, directly asking the participants how often they missed drops using an ordinal scale, and a final questionnaire at the 12-month follow-up [47]. The researchers found that at the final questionnaire, 70% of the intervention group were classified as adherent compared with 43% in the control group [47]. Ultimately, Gray and colleagues surmised that those who received a personally tailored education plan had a better knowledge of glaucoma treatment than those who received standard care ($p < 0.001$) [47]. The second study by Norell and colleagues implemented a 30-min education and tailoring program where participants were first taught about glaucoma treatment through a slideshow and a leaflet [48]. Their knowledge and understanding were then reexamined by an ophthalmic assistant [48]. The ophthalmic assistant also spoke to participants about their daily routines and gave advice on the best times to instill their eye drops [48]. To measure adherence, a medication monitor device that replaced the eye dropper cap and was able to tell whether the bottle has been opened during the last hour [48]. The authors found that participants in the intervention group significantly improved adherence measured by decreased number of missed doses and the proportion of time that exceeded the 8-h dose interval ($p = 0.004$ and $p \sim 0$, respectively) [48]. The third study by Okeke and colleagues implemented a complex intervention that consisted of a 10-min educational video used to promote the importance of taking regular drops and a discussion with the study coordinator to develop a personalized strategy to improve adherence along with scheduled telephone call reminders that occurred on a weekly basis for 1 month and every other week for 2 months [49]. Okeke and colleagues divided up their participants into baseline adherence rates (i.e., > 75%, 50–74%, and < 50%) and tracked adherence rates at the end of the 3-month study

period, finding that all groups except the 50–74% adherence rate group ($p = 0.57$) had statistically and clinically significantly improvement in adherence rates (> 75% adherence group $p < 0.0001$; < 50% $p = 0.03$) [49]. In brief, the three aforementioned studies have shown that creating an interactive, personalized, and complex intervention for patients can improve adherence.

Hahn and colleagues researched whether changes in physician education could improve patient adherence. Twenty-three ophthalmologists were analyzed before and after a 3-h training course that included teachings of a four-step adherence assessment and use of structured open-ended questions (i.e., ask-tell-ask) [50]. A statistically significant difference was found after the training in the use of open-ended questions ($p = 0.001$), increased discussions of adherence ($p < 0.001$), and ophthalmologists' being able to elicit from patients that they have been non-adherent ($p = 0.03$); however, although the study demonstrated improved interviewing by ophthalmologists it did not determine if there was an impact on patient adherence [50].

Patient education and literacy are well-established factors in glaucoma treatment adherence, with most adherence interventional studies targeting patient education. Various efforts to improve adherence through patient education have demonstrated promising results. Interventions that increased adherence included: written instructions targeting glaucoma-specific health literacy, literacy level appropriate glaucoma education videos, the SEE program, and interactive and personalized educational programs. The Behavior Change Counseling (BCC) intervention did not improve adherence. Lastly, physician training on patient interactions can help physicians elicit information and address non-adherence with patients.

TREATMENT REGIMEN AND PHYSICAL BURDEN

An important consideration in medication treatment adherence is the treatment regimen complexity, associated side effects, and physical limitations to instilling drops. Common side effects seen in all glaucoma eye drop classes are stinging eyes after instillation, red eyes, and blurry vision [51]. One study reported that hyperemia was the most common adverse effect responsible for 63% of their studied patients who experienced an adverse effect that resulted in stopping or switching medications [29]. Other aforementioned studies have detailed patient complaints, such as "it puts little cuts in the corner of your eye [that are] very painful" to difficulty handling the small bottle sizes because of arthritis, demonstrating that side effects, physical limitations, and increased frequency of drops may negatively affect adherence [16, 29, 46]. Currently, the literature on the effect of physical limitations on glaucoma medication adherence is limited and there is a need for more data on this important topic. Although there is limited research that focuses on physical limitations, studies in this review have collected data on chronic health-related conditions that patients have in addition to POAG. Out of the 120 subjects included in the study by Dreer and colleagues, 24% of patients had arthritis, which can inhibit ideal drop administration [22]. Furthermore, physical limitations, such as osteoarthritis, rheumatoid arthritis, and other mobility issues such as neck stiffness can inhibit ideal positioning for drop administration. Patients interviewed on why they have low adherence commonly mention (1) having difficulty with drop administration and (2) the difficult mechanism of the bottle (i.e., when you squeeze the bottle either no drop comes out or too many drops come out) [30]. Lastly, limited studies have investigated the relationship between treatment regimen complexity and adherence and how to improve adherence when regimens are complex.

One study by Gurwitz and colleagues examined the relationship between treatment regimen complexity and adherence in elderly patients newly started on topical therapy for glaucoma [52]. In this study, non-adherence was measured in two ways: (1) glaucoma medications that were not filled and (2) the number of days a participant did not take their glaucoma medication over a 12-months period [52]. Twenty three percent of all study participants

Table 1 Summary of factors affecting glaucoma medication adherence

Barriers to adherence	Effect on adherence
Demographic differences	1. White Americans and Australians reported a higher adherence rate of 65.4% compared with African Americans (56.9%) and Singaporeans (47.5) [20]
	2. Patients of African descent were independently associated with inconsistent follow-up (adjusted OR 7.16) [21]
	3. Patients of Hispanic descent were independently associated with inconsistent follow-up (adjusted OR 4.77) [21]
	4. African American patients met the criteria for full treatment adherence on 53.4% of treatment days compared with 71.2% for white Americans patients [22]
Cost	1. Non-Hispanic white patients with glaucoma more likely to have both Medicare and Medicaid compared with African American and Hispanic patients with glaucoma [28]
	2. Patients reporting a cost barrier more likely to have a lower income, to have less educational attainment, to be of African American descent, and to be female [29]
	3. Cost is affected by insurance companies, medication authorization, and insurance coverage for preferred provider [30]
	4. Cost is a barrier because patients do not bring up cost to their physicians or inform their physician they will underuse medication due to cost [5]
	5. Cost as a barrier is difficult to quantify
	a. Specific medication class and corresponding patient adherence was not a part of data collection [31]
	b. varying dosing intervals and corresponding patient adherence [32]
	6. Patients delay filling a prescription [35]
	7. Patients will ask physicians for a lower cost medication [35]
	8. African American and Hispanic individuals were more likely to report not being able to afford medications, delaying filling medications, and using alternative therapies to save money [35]
	9. African American participants were more likely to report skipping medication and taking less medication [35]
Patient health literacy	1. Strong association between poor patient health literacy and missed appointments, missed eye drops, and less refills [37, 38]
	2. Only 6 out of 70 patients had correct eye drop instillation technique [39]
	3. Association between poor health literacy and decreased successful eye drop instillation [40]
	4. Lower educational attainment associated with reduced ability to answer questions about glaucoma [41]

Table 1 continued

Barriers to adherence	Effect on adherence
Patient health beliefs	1. Glaucoma is easy to not prioritize because it is asymptomatic [30]
	2. The patient–physician relationship and active listening is important for controlling glaucoma [30]
	3. Lower adherence is associated with:
	a. Doctor-dependent learning [29]
	b. Vision loss is not at risk if they do not take their glaucoma medication [29]
	c. Medication cost [29]
	d. Adherence difficulty while traveling [29]
	e. Receiving medication samples [29]
	f. Not receiving a phone call visit reminder [29]
	g. Not experiencing adverse effects such as stinging and burning [29]
	h. Being non-white [29]
Physical burden	1. Limited research on effect of physical limitations on medication adherence
	2. Patients do report difficulty with drop administration and difficult mechanism of the bottle [30]
Treatment regimen complexity	1. One study found higher adherence among patients with multiple glaucoma medications [52]
	2. Two studies found adherence may decrease with addition of a second drug and increased number of doses each day [52, 53]
	3. Medication regimen complexity remains incompletely understood with contrasting results

were non-adherent, which was surprising to the researchers since 25% of all participants were home nursing residents who had assumed supervision by caregivers [52]. The mean number of days participants did not take their glaucoma medication in a year was 112 days [52]. There was no difference in adherence between nursing home and non-nursing home residents [52]. Another unexpected finding was that higher adherence was found in participants started on multiple glaucoma medications, although this is confounded by the fact that more complex regimens are typical in more advanced disease [52]. Proposed reasons for this finding included (1) patients with more advanced, and presumably more symptomatic disease, have complicated regimens and (2) these patients may have had more effective counseling from their physicians [52]. These findings demonstrated that adherence can be high in patients with complex treatment regimens even though higher regiment complexity is typically felt to be a barrier to adherence.

Conversely, two different studies that looked at dosing regimen complexity concluded that when adherence is measured by refill intervals, adherence may decrease with the addition of a second drug and may decrease with the number of doses that have to be administered each day [52, 53].

In summary, side effects have an uncertain role and magnitude of impact on patient

Table 2 Summary of proposed interventions to improve glaucoma medication adherence

Study	Location	Number of participants	Proposed intervention	Impact
Dreer et al. [23]	University of Alabama at Birmingham (UAB)	15	Culturally informed health promotion program	Medication adherence rates improved significantly in African American patients
Gupta et al. [33]	India	500	Government subsidizes glaucoma medications	Positive correlation between medication cost and adherence
Bilger et al. [34]	Singapore	100	Adherence contingent rebates	Patients in the rebate group were more adherent to medications 73.1% of the time after six months compared to 61.6% in non-rebate group
Kosoko et al. [41]	Howard University School of Medicine, Washington, DC	438	Written instructions	Question accuracy about glaucoma and management improved from 23.36 ± 30.8% to 88% in patients who did graduate high school and 8.46 ± 21.7% to 96% in patients who did not graduate high school
Muir et al. [42]	Duke University Eye Center, Durham, NC	127	Literacy level appropriate glaucoma education video	Number of days without medicine (DWM) similar between intervention and control group over 6 months
Miller et al. [43]	University of Michigan Kellogg Eye Center	39	Support, Educate, Empower (SEE) program	Improved medication adherence in lower economic groups (< $50,000)
Cate et al. [44, 45]	Norwich, UK	208	Modified motivational interviewing called Behavior Change Counseling (BCC)	No statistically significant difference in adherence between BCC patients and controls over 8 months

Table 2 continued

Study	Location	Number of participants	Proposed intervention	Impact
Newman-Casey et al. [46]	University of Michigan Medical School	Systematic review	Varying interventions including Educational slideshow, pamphlet, questions answered by ophthalmic technician, education focused office visits, motivational interviews, and glaucoma club	Improved glaucoma medication adherence
Gray et al. [47]	University of Manchester, Manchester, UK	127	Personally tailored education plan	Better knowledge of glaucoma treatment ($p < 0.001$) compared to controls
Norell et al. [48]	Unknown Published 1979	82	Glaucoma education through slideshow and leaflet	Decreased number of missed doses ($p = 0.004$)
Okeke et al. [49]	Scheie Eye Institute, Philadelphia, Pennsylvania	196	Multimodal program with education, addressing barriers, and reminder system	Statistically significant improved adherence rates for patients that at baseline had $< 50\%$ ($p = 0.03$) and $> 75\%$ ($p < 0.0001$) adherence rates
Hahn et al. [50]	Albert Einstein College of Medicine, Bronx, New York	23 Ophthalmologists and 100 patients with glaucoma	Physician communication techniques	Improved interviewing technique by Ophthalmologists

adherence. Physical limitations play a role in non-adherence, specifically the ability to properly administer eye drops. The role of medication regimen complexity on adherence remains incompletely understood with contrasting results, which could be a result of different study populations (i.e., geographic location, demographics, support systems, and patient education/believes). Further studies are needed to determine the role treatment complexity plays in adherence, as well as whether changes in bottle design and administration can improve adherence by reducing physicial barriers to instillation.

CONCLUSION

Improving patient adherence to medications is an ongoing challenge in the field of glaucoma. The reasons behind patient non-adherence are multifactorial and contextual ranging from patient demographics, education, health beliefs, and physical limitations, in addition to treatment cost and complexity (Table 1). Physicians should explicitly communicate with patients about medication cost, have open dialogue with patients about their concerns and beliefs, and develop a personalized action plan with patients to optimize medication

adherence. It may be impractical to expect physicians to provide all the necessary education to patients to improve glaucoma adherence in a single clinic encounter, which is why dedicated educational classes, utilizing ancillary staff, and written/online tools can magnify the impact of educational efforts (Table 2). More clinic infrastructure and programs that utilize patient reminder tools and patient educators could help physicians and patients support these personalized action plans. The focus of this review was adherence with medical therapy for glaucoma, further studies and analysis is needed to investigate adherence around incisional glaucoma surgery. Future research on interventions to improve nonadherence should focus on those at highest risk, including those of African and Hispanic descent, younger populations, and those with lower educational levels.

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Declarations

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