2021

Patterns of Medication Adherence in Glaucoma

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PATTERNS OF MEDICATION ADHERENCE IN GLAUCOMA

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements of degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2021

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ABSTRACT

Over 60 million persons globally are affected by primary open angle glaucoma (POAG)—an optic neuropathy characterized by distinctive patterns of vision loss. Glaucoma is a leading cause of irreversible blindness worldwide, and eye drops that delay vision loss are a common treatment modality. In glaucoma, the proportion of patients with good adherence to recommended therapy is reported to be low. High treatment cost, forgetfulness, and regimen complexity have been identified as key determinants of poor adherence.

However, addressing these factors in the clinic is not as simple, as patient and provider values and priorities may differ. Without concordance, it can be difficult to achieve optimal management of glaucoma. In Aim 1, shared values related to glaucoma treatment were identified among patients and providers. Perceived treatment efficacy, glaucoma knowledge, good quality of life, and good patient-provider relationship were recognized by both groups as critical in maintaining good adherence. Interventions may also target these factors and leverage them in order to improve adherence. However, tailoring of interventions is needed so that they adequately meet the needs of patients who are clinically distinct from each other. In Aim 2, this diversity was quantified by identifying distinct patterns of long-term adherence. Statistical modeling was used to identify four patterns: Near-perfect, Good, Declining, and Poor. Characterizing these

groups could reveal other shared attributes which can be used to improve tailoring of existing interventions and increase their effectiveness.

Tailoring can be a challenge however, as there is a dearth of compelling evidence for the recommendation of any specific interventions. This has been attributed to heterogeneity in intervention design, non-reliance on health theory, and diverse patient needs. Employing an evidence-based approach that incorporates theoretical evidence, patient experience, and provider expertise, a taxonomy of evidence-based strategies for improving medication adherence was developed in Aim 3. Education, reminders, health coaching, and motivational interviewing were identified as being most effective and having the highest utility in maintaining good adherence. A thorough understanding of the factors that impact adherence can guide the development of well-designed interventions that appropriately target these deterministic factors and prevent vision loss.

Keywords: glaucoma, perspectives, adherence, patterns, interventions

DEDICATION

It’s your story that I’m telling. You should be here to read it.

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LIST OF ABBREVIATONS

ABC	Ascertaining Barriers to Compliance
AvePP	Average posterior probability
BAK	Benzalkonium chloride
BDNF	Brain-derived neurotrophic factors
BIC	Bayesian Information Criterion
BIPQ	Brief Illness Perception Questionnaire
BCT	Behavior Change Technique
CAI	Carbonic anhydrase inhibitor
CCT	Central corneal thickness
CEHC	Callahan Eye Hospital and Clinics
CINAHL	Cumulative Index to Nursing & Allied Health
DALY	Disability-adjusted life year
Db	Decibels
DOTS	Directly Observed Therapy

GAPS	Glaucoma Adherence and Persistency Study
GBTM	Group-based trajectory modeling
GERD	Gastroesophageal reflux disease
GTCAT	Glaucoma Treatment Compliance Assessment Tool
HBM	Health Belief Model
HIPAA	Health Insurance Portability and Accountability Act
IMB	Information-Motivation- Behavior Skills model
ICA	Iridocorneal angle
ICTRP	International Clinical Trials Registry Platform
IOP	Intraocular pressure
IQR	Inter-quartile range
LiGHT	Laser in Glaucoma and Ocular Hypertension
LALES	Latino Eye Study
MD	Mean deviation
MEMS	Medication Events Monitoring Systems
MI	Motivational Interviewing

MIGS	Minimally invasive glaucoma surgery
MMAS	Morisky Medication Adherence Scale
mRCT	Meta Register of Controlled Trials
NTG	Normal tension glaucoma
OCC	Odds of correct classification
OHT	Ocular hypertension
OPP	Ocular Perfusion pressure
POAG	Primary Open Angle Glaucoma
PACG	Primary Angle Closure Glaucoma
QoL	Quality of Life
RGC	Retinal Ganglion Cell
SEAMS	Self-Efficacy for Appropriate Medication Use Scale
SCT	Social Cognitive Theory
SD	Standard Deviation
SDT	Self Determination Theory
TDI	Timing Distribution Index
TLPD	Translaminar Pressure Difference
TPB	Theory of Planned Behavior

TM	Trabecular meshwork
TTM	Transtheoretical Model
UAB	University of Alabama at Birmingham
VA	Visual acuity
VF	Visual field
WHO	World Health Organization

INTRODUCTION

Glaucoma is a family of eye diseases characterized by damage to the optic nerve—a bundle of approximately one million nerve fibers that relays visual signals from the retina to the brain. Primary open angle glaucoma (POAG) is the most common form of glaucoma, accounting for approximately four million diagnoses and over two-thirds of cases.[1] Most forms of glaucoma are associated with elevated intraocular pressure (IOP), a major risk factor which, for many patients, is lowered through daily use of hypotensive eye drops. However, poor adherence to prescribed hypotensive therapy can lead to irreversible vision loss. In spite of this, medication adherence is often suboptimal.[2-5]

This introductory chapter will describe medication adherence, as well as how it is affected by major determinants and how these determinants have in turn been addressed through interventions. Additionally, this chapter will explore methods of collecting and quantifying adherence data, and will provide a descriptive account of health theories that have been applied to adherence behavior in glaucoma. The body of this work will address three research topics:

1. Comparative assessment of patient and provider perspectives regarding glaucoma treatment.
2. Characterization of patterns of medication adherence
3. Development of a taxonomy of evidence-based strategies for improving medication adherence.

Secondary Glaucomas

IOP relies on the balance between production and outflow of aqueous fluid. This fluid bathes the anterior segment of the eye before draining through the iridocorneal angle (ICA) and trabecular meshwork (TM) and into the venous system. In POAG, the ICA is not anatomically obstructed, and is described as being "open." The imbalance between aqueous production and outflow is believed to be the main reason for elevated IOP. By contrast, primary angle closure glaucoma involves an anatomical obstruction of this angle by the iris. Secondary open angle glaucoma describes conditions where the ICA is obstructed due to pathology. Pseudoexfoliative glaucoma is one such condition, and is characterized by deposition of extracellular material within the eye. In pigmentary glaucoma, pigment granules from the iris are released throughout the eye, leading to obstruction of the TM and elevated IOP.

POAG may be misdiagnosed as other forms of glaucoma. Patients with normal tension glaucoma (NTG) show characteristics of POAG with the exception of elevated IOP. However, NTG is associated with anomalies in blood circulation and organ perfusion. By contrast, patients with ocular hypertension (OHT) may have elevated IOP with no glaucomatous injury, and distinguishing between OHT and early POAG is often difficult. Before patients are diagnosed with POAG, they may also be considered glaucoma suspects. Glaucoma suspects have either glaucomatous pathology or visual field (VF) defects that are suggestive of glaucoma. Despite the similar etiologies of primary and secondary forms glaucoma, this body of work will focus exclusively on POAG. For simplicity, POAG be referred to as glaucoma in this paper from this point onwards.

Primary Open Angle Glaucoma

Prevalence and Risk Factors

Glaucoma—a progressive optic neuropathy [1, 6]—is the leading cause of irreversible blindness in the United States and globally.[1, 7] In the United States, the estimated prevalence of glaucoma is 1.85%.[8] Globally, however, the prevalence almost doubles to 3.05%,[1] translating into over 76 million cases. The true prevalence of glaucoma is likely to be twice as high, as only 50% of all persons living with the condition are believed to be diagnosed.[9] Underdiagnosis of glaucoma has been attributed to several factors, most notably the asymptomatic nature of the disease in its early stages. Estimates of glaucoma prevalence also vary across population samples. The Rotterdam Eye Study, which was conducted in predominantly White northern Europeans reported a prevalence of 0.80%,[10] while the Barbados Eye Study, which was conducted in predominantly Black West Indians noted a prevalence of 7%.[11] By comparison, the Los Angeles Latino Eye Study (LALES) reported a prevalence of 4.74%.[12]

Several clinical and demographic factors have been associated with increased risk for glaucoma. Age is one such factor. The estimated prevalence increases from 0.68% for persons 40-49 years to 7.74% for persons over 80 years.[8] Overall, the prevalence of glaucoma in the over 40 population is expected to almost double by 2040, translating into roughly 112 million patients.[1] Several other factors have been associated with increased risk of glaucoma, including elevated IOP,[13] reduced ocular perfusion pressure (OPP),[12, 14] central corneal thickness (CCT),[15, 16] and larger vertical and horizontal cup to disc ratios.[16] Vascular abnormalities, impaired autoregulation, and optic disc hemorrhage have also been implicated in glaucoma development.[17, 18]

Due to their concurrence,[19] diabetes mellitus is thought to be related to glaucoma, although there is no compelling evidence to support this. The contribution of genetics is more clear-cut, as positive family history has been documented as a strong risk factor for glaucoma.[11, 20] The Baltimore Eye Study reported that persons with a sibling with glaucoma had a three to seven fold increase in the risk of developing the condition.[20] Although not required for diagnosis, IOP is the primary, and sole modifiable risk factor for glaucoma. For the majority of diagnosed patients, it is lowered through daily hypotensive therapy. However, both glaucoma diagnosis and treatment can impose significant financial and psychological burdens on patients and caregivers.

Impact

Forms of visual impairment induced by glaucoma include decreased visual acuity (VA) and diffuse VF loss. Patients may also develop scotomas, which are localized regions of depressed VF sensitivity. Focal scotomas in early glaucoma may progress to arcuate or wedge-shaped scotomas which occupy larger portions of the VF. Progression occurs through the appearance of new scotomas, deepening of existing scotomas, or enlargement of existing scotomas.[21] In later stages of glaucoma, only a central island of vision may remain as the cells that relay visual information from peripheral parts of the retina die. Loss of vision imposes a significant psychological burden on many patients, and anxiety and depression have been found to be prevalent in glaucoma patients.[22] Shin et al. (2021) reported that VF defect severity was significantly associated with high depression.[23]

Glaucoma also imposes significant medical costs, which exceed $3 billion annually.[6] Newman-Casey et al. (2018) found that glaucoma medications generated the highest total costs of any single category of ophthalmic medications.[24] Medical costs, which may be direct or indirect also increase with disease severity.[25] Direct costs arise from paying for medications, transportation to clinics, insurance premiums, nursing home care, and home help. Indirect costs stem from the consequences of advanced disease such as inability to drive, loss of independence, and reduced earnings due to missed days of work.[26] Indirect costs also encapsulate the productivity costs borne by loved ones who act as caregivers.[6]

Glaucoma is also associated with non-medical costs. Quality of Life (QoL), which describes individuals' perception of their position in life relative to their own goals, may be negatively affected as patients become disenfranchised and socially withdrawn as their glaucoma worsens.[27] Family members may also experience emotional distress as they attempt to cope with their loved one's condition and provide emotional support. When compared with a control group of patients with similar systemic conditions, glaucoma patients were reported as more likely to fall or be involved in vehicular accidents.[28] While the economic and psychological impact of glaucoma is well-documented and agreed upon, consensus has not yet been reached for its physiological impact. Due to its multifactorial nature, no unified theory for glaucoma etiology and pathophysiology exists, resulting in several independent, yet inter-related hypotheses that are discussed below.

Etiology and Pathophysiology

Mechanical hypothesis. Empirical evidence supports a direct relationship between IOP and glaucomatous damage.[13, 29] Elevated IOP leads to increased mechanical force on the lamina cribrosa—a network of collagenous beams through which retinal ganglion cell (RGC) axons traverse. RGCs relay visual signals to the brain through axon bundles known collectively as the optic nerve. However, IOP-induced stress and strain forces lead to bowing of the lamina cribrosa (Figure 1).[30] Deformation of the lamellar beams leads to RGC axon compression,[29] interrupted microvascular blood supply, RGC death, and visual field defects.[31] While elevated IOP is a prominent risk factor for glaucoma, the mechanical hypothesis does not explain the absence of glaucomatous injury in persons with OHT or the presence of glaucomatous injury in persons with NTG.[29]

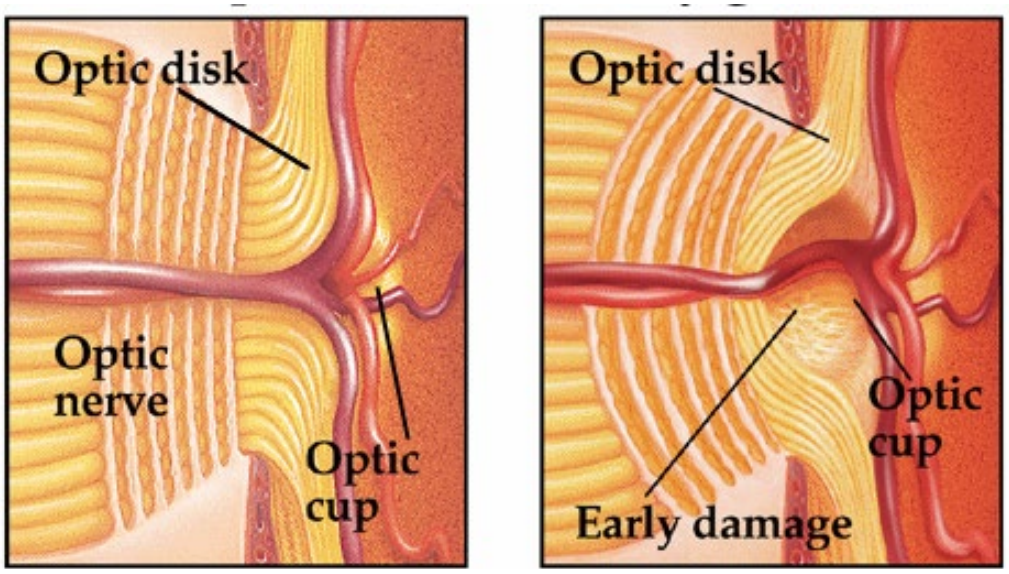

Figure 1. Early glaucomatous damage. Left panel shows a healthy eye. Right panel shows cupping of optic nerve head and lamina cribrosa in glaucoma. Obtained from http://amarilloicare.com/component/content/article/82-patient-education/96-glaucoma

Vascular hypothesis. Optic nerve vasculature and perfusion play an important role in retinal health. Inadequate blood flow impairs oxygen delivery and waste removal,[32] leading to metabolic stress and programmed cell death—apoptosis. Ocular perfusion pressure (OPP) describes the relationship between IOP and systolic and diastolic blood pressure. The LALES study reported an association between low OPP and glaucoma prevalence,[12] and Memarzadeh et al. (2010) reported that patients with either low or elevated blood pressure were at greater risk for glaucoma.[14]

Research also implicates impaired autoregulation in glaucoma etiology.[33] Autoregulation describes local vascular changes in response to changes in perfusion pressure.[34] Elevated IOP and fluctuating blood pressure may impair normal ocular blood flow, resulting in poor autoregulation and ischemic damage to RGCs.[17] The trans-laminar pressure difference (TLPD) also plays a role in glaucoma etiology and pathophysiology.[35] TLPD refers to the difference between intracranial pressure (ICP) and IOP, and researchers have reported a significant negative relationship between TLPD and glaucoma risk.[36] The increasing prevalence of glaucoma in patients with diabetes, hypertension, and other vascular conditions lends further support to the vascular hypothesis.[19]

Neurogenic hypothesis. Several other factors have been associated with glaucoma development. Neurotrophins such as Nerve growth factor (NGF) regulate RGC growth, protection, differentiation, and death. In glaucoma, impaired delivery of these factors due to axonal compression has been linked to RGC death.[37] Elevated neurotransmitter levels

have also been observed in the retinas of glaucomatous patients,[37] and are thought to contribute to excessive neuronal firing, oxidative stress, and apoptosis.[38]

Management

The primary means of managing glaucoma is through use of topical hypotensive drugs. Clinicians often aim for a target IOP that is unique to each patient and is calculated as a 25-30% reduction from baseline IOP. The Collaborative Initial Glaucoma Treatment Study found that hypotensive therapy provided similar levels of IOP reduction and QoL levels as surgical intervention.[39] The Ocular Hypertensive Treatment Study (OHTS) also reported that treatment with ocular hypotensives was effective in delaying the onset of glaucoma in patients with OHT.[16]

Several hypotensive agents are available on the market, including prostaglandin analogs, carbonic anhydrase inhibitors, alpha agonists, adrenergic antagonists (beta blockers) and cholinergic agents. Prostaglandin analogs (e.g., Latanoprost) are among the most commonly prescribed agents. These drugs improve the ease of aqueous fluid drainage, and provide up to 32% IOP reduction. Adrenergic antagonists or beta-blockers (e.g., Timolol) provide similar levels of IOP reduction by decreasing aqueous fluid production. Adrenergic agonists (e.g., Brimonidine) employ a similar mechanism of action to adrenergic antagonists but typically only provide up to 25% IOP reduction. Much like adrenergic agonists and antagonists, carbonic anhydrase inhibitors (CAIs e.g., Dorzolamide) lower IOP by reducing aqueous production. However, CAIs must be instilled up to three times per day due to their shorter duration of action. Despite the

differences in mechanism, efficacy, and side effect profile, hypotensive eyedrops require daily instillation for the duration of patients' lives.

Surgical intervention is pursued by a smaller proportion of patients, but is also effective in managing IOP. The Laser in Glaucoma and Ocular Hypertension Study (LiGHT) reported that patients who had selective laser trabeculoplasty as a first line of treatment were within target IOP at more visits than those using hypotensive eyedrops.[40] For many patients, however, surgical intervention is not the first line of treatment, and may only be indicated when ocular hypotensive therapy has failed to lower IOP to a suitable target. Other commonly performed incisional surgeries include trabeculectomy and tube shunt implantation, which decrease IOP by creating alternative outflow pathways for aqueous fluid. Many surgical procedures carry an elevated risk of complication.[41] As a result, patients may elect to have minimally invasive glaucoma surgery (MIGS). MIGS describes a group of procedures that use microscopic instruments and incisions to limit trauma to the surrounding ocular tissues.

Although neuroprotective agents do not directly reduce IOP, they may provide therapeutic benefit by supporting tissue health and function. Antioxidants and free-radical scavengers such as vitamin E and Coenzyme Q10 reduce apoptosis by decreasing oxidative stress, mitochondrial insult, and nitric oxide production in glial cells, which ultimately supports RGC health and function. Choosing an appropriate course of treatment (pharmacological versus surgical intervention) is an important aspect of care. However, patients who manage their glaucoma through pharmacological intervention must contend with another important facet of glaucoma care—medication adherence.

Medication Adherence

Medication adherence describes the degree to which patients follow recommended guidelines for treatment. Chronic diseases such as cancer, diabetes, and hypertension account for over 65% of the global disease burden [42] and often require daily medication use. Despite the clinical benefit of medicinal therapy, the World Health Organization warns that only 50% of patients are adherent to prescribed therapy.[43] Additionally, poor adherence exacerbates the economic burden of chronic disease by contributing to faster disease progression and over-utilization of medical resources.[44] Poor adherence has also been linked to increased disability-adjusted life years (DALYs),[45] which represent one lost year of "healthy" life.

The actions or behaviors necessary for maintaining optimal adherence vary across conditions, but all require that patients perform them consistently, and with a high level of proficiency. In clinical research and practice, "adherence" has come to replace the more traditional term "compliance." This transition parallels the change from a clinically oriented approach to a more patient-inclusive approach to care, where both patients and providers have proprietorship and involvement in the decision-making process.[46] The term "concordance" has also been introduced into the clinical landscape, and describes the degree to which patient and provider goals, beliefs, and priorities align with each other. Such alignment of treatment goals, values, and expectations is paramount to congenial patient-provider relationships and effective treatment.

ABC Taxonomy: Phases of Medication Adherence

A new conceptual framework for describing behaviors related to adherence was developed by the Ascertaining Barriers to Compliance (ABC) project—an international collaboration of researchers in the field of medication adherence.[47] The taxonomy describes adherence as a process composed of three stages: *Initiation, Implementation and Discontinuation*. *Initiation* occurs when a patient purchases and takes the first dose of a prescribed medication, while *implementation* describes the extent to which actual dosing corresponds to prescribed dosing. *Discontinuation* occurs when the patient stops taking the prescribed medication. The taxonomy also describes a fourth term—*persistence*, which is the duration of time for which the patient follows prescribed therapy. The framework allows for uniformity in both terminology and methodology in adherence research across studies and medical disciplines.

Medication Adherence in Glaucoma

Successful pharmacological management of glaucoma is a complex endeavor that requires that patients perform several behaviors. These include 1) selecting a pharmacy and filling index prescriptions, 2) properly instilling eyedrops at the prescribed dosing time, 3) keeping scheduled clinic visits (visit adherence), and 4) maintaining an adequate supply of medication by refilling prescriptions in a timely manner. Undertaking these actions requires investment from major healthcare stakeholders—namely patients, providers, caregivers and the health system.[48] Patients must have an adequate understanding of the disease, as well as adequate levels of functional and health literacy,

which are necessary for understanding and interpreting clinical information, and making informed decisions about care.

Providers must also ensure that patients understand the rationale for treatment and that the prescribed therapy is effective. Providers themselves should maintain high levels of clinical competence and warmth—two dimensions of care deemed especially important from the patient perspective.[49] Caregivers and loved ones also play an important role by providing emotional, social, and instrumental support. Agents within the health system must work synergistically to develop the resources and policies that facilitate optimal medication adherence and high-quality care.

Measuring Medication Adherence in Glaucoma

One of the most important decisions in adherence research is the determination of appropriate methods for collecting adherence data, as well as appropriate metrics for quantifying these data. Current methods include self-report, journal entries, physician assessment, directly observed therapy (DOT), pharmacy claims, and electronic monitoring. Each method has a unique set of advantages and limitations which influence the degree to which bias can be introduced. Thus, there is no gold standard for measuring adherence. Metrics for quantifying adherence data include adherence rate, medication possession ratio (MPR), dichotomized adherence (adherent versus not adherent), adherence pattern, and measures of nonadherence such as number of missed doses.

Assessment Methods

Assessment methods may be subjective or objective. Subjective methods such as self-report rely on personal judgements and are susceptible to bias, particularly recall bias, response bias, and sampling bias. Objective methods include electronic monitoring, MPR and DOT. These methods may not be influenced by personal perception, but may still be limited by reactivity bias and sampling bias.

Subjective assessment. Self-report is one of the most widely used methods for measuring adherence [50,51] and assessments may be obtained through patient diaries, interviews, or through use of validated survey instrument. Self-report is a simple, low-cost method that often allows patients to provide additional context in which to interpret their adherence e.g., being ill or misunderstanding dosing instructions. However, this method is considered to be the least reliable due to its susceptibility to response bias—a type of reactivity bias that describes the tendency to provide inaccurate responses due to poor recall or intentional misleading.[52, 53, 54]

Questionnaires such as the Morisky Medication Adherence Scale (MMAS),[55] the Glaucoma Treatment Compliance Assessment Tool (GTCAT),[56] the Brief Medication Questionnaire, Glaucoma Medication Self-Efficacy Scale,[57] and the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) aim to reduce bias by standardizing the measurement of self-reported adherence. Nonetheless, these instruments may be difficult to use, particularly for patients with low health literacy levels.[55] This could negatively affect research findings as patients who do not completely understand survey questions may provide responses that introduce noise into the data and obscure potentially

meaningful signals. Sampling bias is another limitation of survey instruments that assess medication adherence through self-report. Patients with higher healthcare engagement may be more likely to participate in clinical research.[58] As a result, data may be skewed towards patients with higher adherence.

Physician assessment is another common approach for measuring adherence, particularly within the clinic. However, it too relies on patient reports and may be limited by response bias as patients have been known to overestimate adherence in order to avoid disapproval from their providers.[59]

Objective assessment. Objective methods for measuring medication adherence include pharmacy claims data, directly observed therapy (DOT), and electronic monitoring. Claims data provide information about prescription refills, and are obtained through review of administrative claims databases. A major advantage of claims databases is that data are unobtrusively collected for as long as patients receive treatment. Thus, these data may be more inclusive of patients with poor adherence and patients who are less inclined to participate in clinical research.[60] Additionally, many patients stop and restart medications, making claims databases an ideal source of data for studying both medication persistence and gaps in therapy.[4] Despite these advantages, claims data are limited by their susceptibility to errors during data input,[52] their inability to capture information about provider-issued drug samples,[4, 61] and their lack of granularity as they provide no information about whether eyedrops are instilled after prescriptions are filled.[4]

Compared to administrative claims data, electronic monitoring is a more robust assessment method. Several devices are available, including Aardex MEMS caps

(Fremont, CA), the Kali drop monitor (Santa Clara, CA),[62] and the AdhereTech Smart Pill Bottle (New York City, NY).[63]Aardex and AdhereTech devices use the "bottle-in-bottle" approach where eyedrops are stored inside containers with electronic caps (Figure 2a). [64] MEMS caps record the precise time that they are unscrewed when patients use the eyedrops stored inside the containers. By comparison, the Kali drop monitor (Figure 2b) [65] contains microsensors that detect changes in the amount of pressure applied to the housing when eyedrops are instilled.[62] Devices may also be equipped with added functionality such as alarms and displays that indicate the number of doses to be instilled. Once recorded, data may be uploaded via near-field wireless readers (MEMS, Travatan dosing aid) or directly into cloud storage (AdhereTech Smart Bottle, Kali drop monitor). Monitors may also incorporate mobile apps for tracking daily adherence.

Electronic monitoring is not without limitations. A notable drawback is their shape, which may make them unsuitable for use with all eyedrop bottles. The Travatan dosing aid is one such device, as it was specifically developed for use with either Travoprost 0.004% or the fixed combination of Timolol 0.5%-Travoprost 0.004%, both of which are manufactured by Alcon Laboratories (Forth Worth, TX, USA). [66] The device accurately reported 93% of instillations,[67] but its use in research (prior to being discontinued) was limited by its incompatibility with other formulations.

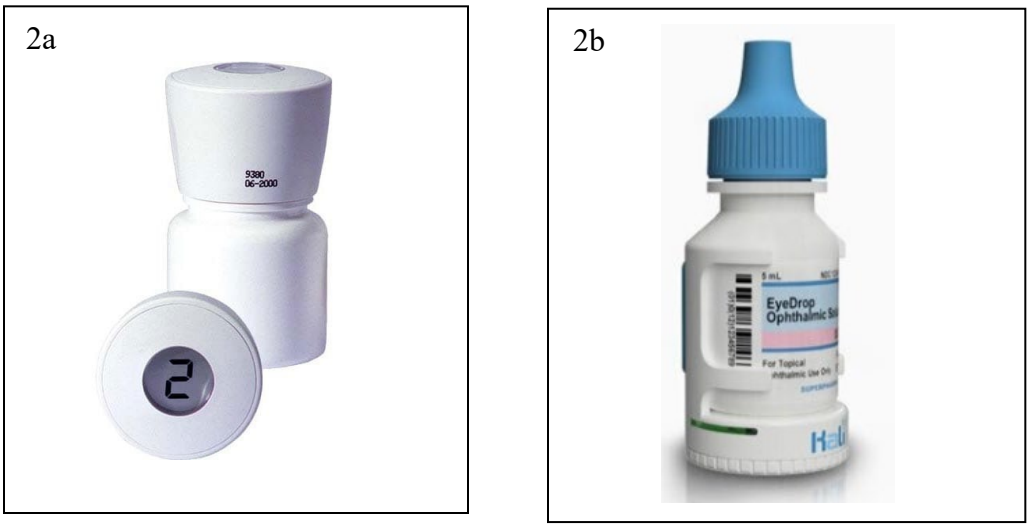

Figure 2. Electronic monitoring devices. MEMS caps (2a) and the Kali drop monitor (2b). Obtained from https://www.westrock.com/products/folding-cartons/memscap Copyright 2021 by WestRock Company. (2a). Obtained from https://www.kali.care/johns-hopkins-post-glaucoma-surgery-study Copyright 2020 by Kali Care (2b).

It is also important to note that electronic monitors do not directly measure whether the eyedrop is instilled into the eye. Therefore, it is possible that patients could deliberately engage with monitors to mask poor adherence.[68] Consistently expending energy to use the devices while not instilling eyedrops is unlikely, but this behavior cannot be wholly discounted. Furthermore, in adherence research, the Hawthorne effect [69] describes patients' tendency to alter their behavior due to the awareness that they are being monitored. A common strategy for addressing this is to discard the first 2-8 weeks of data in order to allow for a return to baseline adherence.[53, 69, 70]

The battery life of monitors is also a limitation, and studies with long follow-up durations may experience high rates of device failure if the devices are not renewed at appropriate intervals. Additionally, the devices may be lost or destroyed, leading to loss

of data if cloud storage were not enabled or possible. A final limitation is that monitors are susceptible to time zone differences. If patients travel with the monitors, the recorded time of instillation may not match the local time, which may affect computed adherence. Despite these constraints, electronic monitors provide more objective and granular data than both pharmacy claims and self-report.

With DOT, adherence is monitored by a trained observer or through video recording. Direct observation of eyedrop instillation captures two critical elements of adherence not well described by other measures—whether appropriate instillation technique was used [71] and whether the eyedrop successfully reached the eye.[69] Poor technique may lead to ocular irritation and infection if bottles are not appropriately stored and come in contact with the eye,[71] and over-instillation of eyedrops can lead to faster depletion of medications and higher out-of-pocket prescription costs.

Additionally, not instilling the proper eyedrop volume may lead to inadequate therapeutic coverage and contribute to uncontrolled IOP. No other assessment methods capture this information, making DOT an invaluable, yet often overlooked assessment method in adherence research. Nonetheless, this method is constrained by its limited practicality in research settings and its susceptibility to the Hawthorne effect.[69] Studies employing DOT may also experience high rates of attrition. Lampert et al. (2019) documented more than 50% attrition during their 6-month intervention for improving eyedrop instillation technique.[71] DOT is a more popular assessment method in conditions with severe outcomes unless patients are adherent, such as HIV and Tuberculosis.

Assessment Metrics

Once collected, quantitative or qualitative metrics may be used to describe adherence. Quantitative metrics provide summary measures of adherence over a designated time period, while qualitative metrics describe patterns of adherence behavior.

Quantitative metrics. The proportion of doses taken each day over a period of time is often expressed as mean adherence (rate or percentage). As a continuous variable, mean adherence provides a robust measure of overall adherence behavior but does not convey information about short-term trends and discrete events. For instance, a patient with ten interspersed days of missed drops may be indistinguishable from a patient with a single ten-day span of missed drops based on mean adherence. As these events may affect therapeutic coverage, it is important to be able to quickly identify and correct them. Mean adherence may also be dichotomized using thresholds of 75%,[72, 73] 80%,[74] or 90% [2] to distinguish between optimal versus suboptimal adherence. There is no universally agreed-upon cutoff, however 80% remains the most common thresholding value.

Researchers may also opt to apply dosing windows and over-utilization penalties during the computation of mean adherence. Dosing windows only encapsulate instillations during a predefined number of hours before or after the specified dosing time. By filtering adherence data in this way, dosing windows capture patients' true therapeutic coverage. For example, patients who are adherent based on the proportion of instilled doses may have such high variability in instillation timing that they may not reap the full therapeutic benefit of eyedrops. The timing distribution index (TDI) provides a measure of the variability in instillation timing, [75] with higher values indicating greater

inter-dose intervals. This measure has also been used to identify distinct dosing patterns.[76] The application of over-utilization penalties also affects computed adherence for patients who instill more than the prescribed number of eyedrops. As previously discussed, over-instillation of eyedrops can lead to faster depletion of medications, more frequent pharmacy visits, and higher out-of-pocket prescription costs, all of which may lead to poor adherence.

The MPR is another quantitative metric that provides a measure of medication availability per prescription period. If a patient refills a 30-day prescription twice within a 3-month period, this results in a MPR of 0.67. MPR is highly flexible, and can be used to compute both medication adherence and persistence. However, MPR has limited granularity as two patients with similar refill rates, but different dosing instructions (monocular versus binocular therapy) cannot be distinguished from each other.[4]

Lastly, adherence may be expressed in terms of non-adherent behavior. Metrics include the proportion of missed doses,[77] the number of days with incorrect number of installations,[78] rate of dosing at incorrect times,[79] drug holiday frequency, and drug holiday duration. Drug holidays are defined as consecutive days of missed doses. There is little consensus on their definition as studies have used a minimum duration of three days while others have used a minimum duration of eight days.[76] Using the eight-day definition, Beckers et al. (2013) reported that patients who took drug holidays had significantly higher IOP compared to patients who did not.[80]

Qualitative metrics. Qualitative metrics are mainly derived by plotting quantitative metrics over time. In such a way, metrics such as MPR can be used to provide a measure of medication persistence over successive prescription periods.[4] Newman-Casey et al. (2015) used group-based trajectory modeling (GBTM) to identify discrete patterns of medication adherence over four years in newly prescribed patients.[81] GBTM is a statistical approach designed to cluster individuals with similar developmental and behavioral trajectories,[82-84] and has been applied in cancer,[85] hypertension,[86] and heart disease.[87] Newman-Casey et al. (2015) identified five patterns in glaucoma: good adherence, moderate adherence, declining adherence, poor adherence, and patients who were non-adherent after the index prescription.

Researchers have also identified distinct patterns of medication adherence through visual inspection of electronically monitored data.[60, 76] A study by Ajit et al. (2010) identified four patterns of adherence: adherence greater than 97%, adherence greater than 80%, adherence below 80% with frequent missed instillations, and adherence below 80% with frequent drug holidays.[76] In work based on these findings, Cate et al. (2013) identified one additional group—patients with adherence between 80 and 97%.[60] A later study categorized adherence according to three groups: near-perfect adherence, moderate adherence, and poor adherence/frequent drug holidays.[80] The researchers found that almost 20% of patients took drug holidays.[80]

The pervasiveness of drug holidays among glaucoma patients is concerning [76] as their impact on disease progression has yet to be quantified. In the short-term, it is not known whether, for instance, an eight-day drug holiday would have a different impact on IOP control than eight interspersed days with missed drops. Exploring patterns of

medication adherence can improve detection of dosing gaps and drug holidays, as well as provide greater insight into the complex interplay of factors that influence adherence.[88]

The way in which adherence is computed requires close attention. The determination of assessment methods and metrics both depend on the research question, the types of bias that can be tolerated, and the resources available to the investigator. A combination of assessment methods and metrics is most ideal. Where this is not feasible, careful consideration of the suitability of each approach should be undertaken.

Adherence to Ocular Hypotensive Therapy

In a 2013 publication, the WHO posited that only half of all patients diagnosed with chronic health conditions were adherent to prescribed therapy.[89] An earlier study in the United States found that poor adherence across health conditions accounted for approximately 10% of all hospital admissions, over 100,000 deaths, and more than $280 billion dollars in medical costs.[90] In glaucoma, poor adherence is associated with worse IOP control and VF defect severity,[91-93] and is a significant challenge. The 2007 Glaucoma Adherence and Persistency Study (GAPS) collected pharmacy claims data from nearly 14, 000 patients and reported mean MPR of 0.64, indicating that patients only had two-thirds of their medication supply.[4] Moreover, a study by Curtis et al. (2009) [94] reported that medication adherence in new glaucoma patients declined more sharply than patients with other chronic conditions (Figure 3).

Among established patients, adherence is often suboptimal.[3] Estimates range from 33% to 97% across assessment methods and metrics.[4, 53, 60, 80, 95, 96] Estimates also vary

across demographic groups, with researchers identifying Black [74] and Hispanic patients [5] to be at greater risk of poor adherence. A survey of 260 patients being treated at a UK ophthalmology clinic revealed that although 77% of patients stated that they were adherent, only 53% were able to correctly name their medication and describe the prescribed frequency of eyedrop instillation.[97] Using a threshold of 75%, Boland et al. (2014) reported that approximately 83% of patients were adherent.[98] Rossi et al. (2011) found that only 33.3% of patients were adherent with a 90% threshold, and that patients with greater than 80% adherence were likely to have a longer history of treatment.[2]

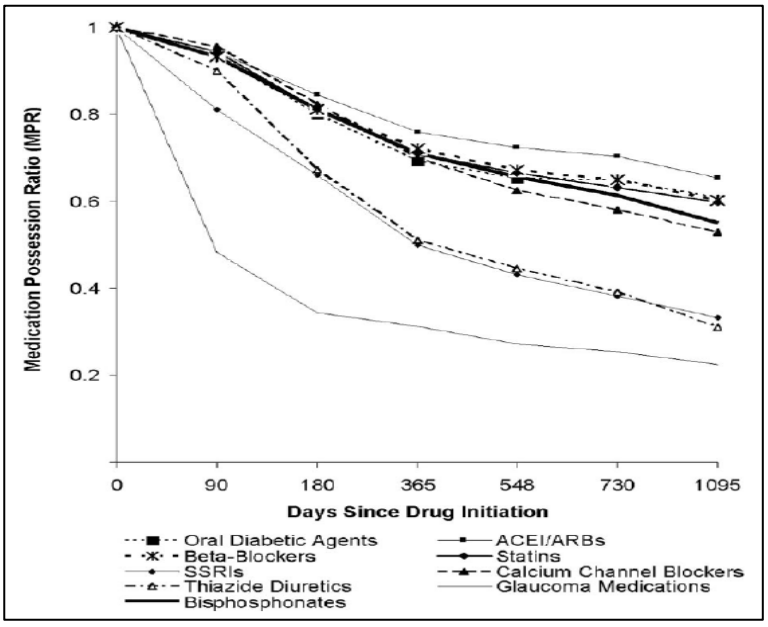

Figure 3. Medication Adherence of Patients Diagnosed with Chronic Diseases During the First Three Years of Treatment. Red trace shows sharpest decline among glaucoma patients.

Note: From "Improving the Prediction of Medication Compliance" by Curtis, R Jeffrey, Juan Xi, Andrew O. Westfall, Hong Cheng, Kenneth Lyles, Kenneth G. Saag, MD, Elizabeth Delzell. 2009. Medical Care 47(3). Copyright 2021 by Wolters Kluwer Health, Inc. Reprinted with permission.

In their analysis of four years of claims data for over 1200 patients, Newman-Casey et al. (2015) reported that moderate adherence (MPR between 0.4 and 0.6) was the most common pattern.[81] In contrast, Ajit et al. (2010) found that Type 2 adherence, defined as having mean adherence above 80% was the most common pattern over three months. The smallest group—patients who prematurely discontinued therapy—only comprised 8% of the sample compared to 16% in the study by Newman-Casey et al.[76]

Determinants of Medication Adherence

The importance of good adherence has been consistently highlighted by the WHO, especially through their assertion that improving adherence to existing treatment could have a greater impact on global health than improvements in any specific medical therapies.[43, 99] As poor adherence is a critical issue in glaucoma, there has been an abundance of studies seeking to identify and target major determinants. Tsai et al. (2007) developed a taxonomy for categorizing over 70 barriers to optimal medication adherence.[100] Categories include patient factors, regimen factors, provider factors, and situational factors, which are discussed below in greater detail.

Patient Factors

Individual beliefs, values, and priorities influence clinical decision-making and important outcomes such as QoL and visual function. Moreover, these factors may change throughout patients' lives.[101] Butow et al. (1997) reported a decline in patients' desire for involvement in decision-making as they became more ill.[102] Another study among cancer patients found that younger and newly diagnosed patients placed more

value on treatment efficacy and survival, while treatment burden and quality of life were more important priorities for older patients and those with more advanced disease.[103] Therefore, it is important that patient perspectives be incorporated into decision-making and that clinical outcomes be defined in terms that are also meaningful to patients.[104]

Education level is also closely related to adherence.[105] Together with disease knowledge and health literacy, education level influences patients' capacity to understand medical information and navigate the healthcare system.[106] In recognition of the important role of education in glaucoma treatment, Davis et al. (2019) invited patients to participate in the design of educational material for improving instillation skill.[107] A systematic review of educational interventions delivered in glaucoma found that successful interventions delivered individualized educational sessions, during which counselors spent time addressing each participant's needs.[108]

Income level is also known to influence adherence.[74] With the median cost per monthly medication supply reported to be $75 (IQR = $102),[24] financial status can significantly limit patients' ability to purchase prescriptions, obtain transportation to the clinic, pay for insurance premiums, and cover the cost of surgery and adjunctive therapy. In fact, patients of lower socioeconomic backgrounds may be less likely to have optimal adherence [74] which may be due to the compounded effect of social and economic barriers to care. Self-reported race is also associated with worse adherence.[74, 109] However, as race has been described as a sociobiological construct,[110] lower adherence in Black patients may also be attributed to the complex interplay of social and economic factors within the context of systemic racial inequality in the United States.

Psychological factors such as self-efficacy may also affect adherence.[111] Self-efficacy describes one's perceived ability to perform an action,[112] and Sleath et al. (2011) found that patients with lower medication adherence self-efficacy were significantly more likely to have worse VF defect severity.[91] Other studies have established a positive relationship between self-efficacy and medication adherence.[112] [113-115] Furthermore, a significant amount of research has been geared towards developing validated instruments for assessing self-efficacy in glaucoma.[57, 116, 117] Patients with higher levels of self-efficacy not only have greater perceived control over their condition, but may also expend more effort to ensure that they are adherent, even during unfavorable or hectic conditions.[46] Self-efficacy is also positively associated with resilience.[118] Racette et al. (2021) reported a positive relationship between medication adherence and resilience during the COVID-19 pandemic,[109] suggesting that resilience may have a protective effect on adherence.

Social and emotional support are also cornerstones to patient wellness.[119] As opposed to instrumental support, which describes physical or tangible assistance e.g., help instilling eyedrops, social support is the perception and actuality that one is cared for. Both types of support are important in glaucoma as patients often experience feelings of disenfranchisement, withdrawal, and depression as their condition worsens.[120] A 2017 study found that glaucoma patients were at elevated risk for depression, worry, anxiety, and other forms of psychological stress compared to patients who did not have glaucoma.[22] Patients with significant vision loss also face the constant challenge of psychologically adjusting to their disability. These patients may adopt new coping strategies, which may be adaptive (healthy and productive) or maladaptive.[121] Freeman et

al. (2016) reported that patients who used denial as a coping strategy after their first glaucoma diagnosis had faster rates of disease progression.[121] As a result, family members and loved ones play a critical role in managing the negative affect and physical burden imposed by glaucoma.

Regimen Factors

Factors directly related to treatment, such as such as complex dosing regimens, perceptions about treatment efficacy, and medication side effects may have a deleterious effect on adherence. Hermann et al. (2011) found that in patients using 0.004% Brimonidine, the number of nonadherent days increased with the number of prescribed drops.[122] Multimorbidity and polypharmacy may also have a similar impact. While medications prescribed for other chronic conditions may not require ocular administration, they may still exert a strain on patients' regimens, finances, and quality of life. As glaucoma prevalence increases with age, there is increased likelihood of patients being burdened by complex treatment regimens across their health conditions.

Frailty and poor dexterity may also be a formidable challenge for elderly patients, who often need physical assistance to instill eyedrops [123, 124] Younger patients may also experience difficulty. A cluster randomized study in German community pharmacies found that while 60% of patients stated that they could properly instill eyedrops, less than 6% were actually able to do so when observed.[71] As opposed to orally administered medications, eyedrop instillation requires strength, skill, and time commitment, particularly in patients with two or more daily instillations.

While not related to the treatment regimen, the asymptomatic nature of glaucoma in its early stages represents a unique challenge.[46] In chronic conditions such as diabetes, symptoms may prompt patients to improve their adherence. However, in glaucoma, the absence of symptoms means that there are fewer cues to spur patients into action. Furthermore, patients may experience little to no therapeutic relief when applying eyedrops,[46] and may instead experience side effects such as keratitis, allergic conjunctivitis, dry eye, hyperemia, sub-conjunctival fibrosis, iris darkening, and orbital fat atrophy when using ocular hypotensives.[125] This creates a major psychological barrier, as patients may have greater ocular discomfort while being adherent versus non-adherent.

Medication persistence is also affected by the perception of side effects. A study by Nordstrom et al. (2005) reported that patients had higher persistence when using prostaglandin analogs, which have a lower side effect profile compared to alpha agonists, CAIs and Beta blockers [126] (Figure 4). Of note though, is that after 36 months, only approximately 30% of patients remained on medication in this sample—a concerningly low proportion. One way of addressing this has been to develop preservative-free eyedrop formulations. The commonly used preservative Benzalkonium chloride (BAK) has been fingered as a major culprit in preservative-induced ocular surface disease.[125]

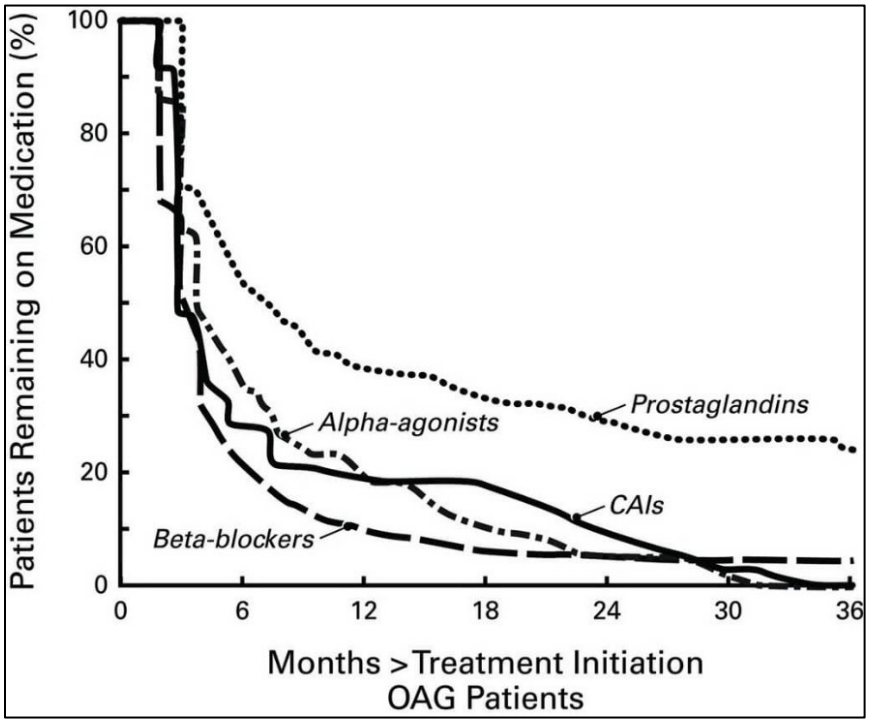

Figure 4. Medication Persistence Over Three Years for Patients Using Prostaglandin analogs, Alpha agonists, Beta-blockers, and Carbonic Anhydrase Inhibitors (CAIs).

Note: From "Persistence and Adherence With Topical Glaucoma Therapy" by Nordstrom, Beth L, Friedman, David S, Mozaffari, Essy, Quigley, Harry A, Walker, Alexander M. 2005. American Journal of Ophthalmology 140(4). Copyright 2021 by Wolters Kluwer Health, Inc. Reprinted with permission.

Provider Factors

Patients' experiences with the pharmaceutical and healthcare systems also shape their adherence. The patient-provider relationship is the vehicle through which these two stakeholders can work synergistically to treat glaucoma and manage eye health. For all its significance however, this relationship is limited by the short duration of the clinic visit secondary to high physician load. The clinic environment can also be highly stressful for patients, and can lead to misunderstanding of clinical information [127] and hesitancy to ask

important questions about treatment. Cultural norms regarding clinical care may also shape patients' perspectives,[128] and by extension, the closeness of the patient-provider relationship. Patients may experience feelings of fear, anxiety, and depression due to their diagnosis, which may be difficult to communicate to providers. Thus, it is important that this relationship be carefully nurtured over the course of treatment.

Historical events such as the Tuskegee Syphilis Study have resulted in a sense of mistrust in the health system, particularly among members of racial and ethnic minorities.[129] In a study on disparities in perceptions of physician trust, Doescher et al. (2000) reported that only Caucasian race was positively associated with trust in providers.[130] This has far-reaching consequences as greater trust is associated with increased adherence.[131] Moreover, lower trust in providers among members of racial and ethnic minority groups may contribute to less representation in clinical research and less emphasis on health priorities specific to these groups.

While not directly related to providers, the healthcare system also influences patient perspectives and decision-making. In the United States, fee-for-service has been the de facto reimbursement model, leading to assumptions of profiteering by clinicians.[132] Patients who hold these assumptions may assume that providers are more interested in generating profit than providing quality care, and may not adequately recognize the need to follow clinical guidelines. Furthermore, treatment has largely been viewed through the lens of clinical relevance, and clinical factors have been prioritized based on the belief that patients and providers share the same values regarding treatment.[133] However, the reality is more nuanced as patients may also prioritize non-clinical support such as health counseling and support groups.

A 2015 study identified access to medication as a potential barrier.[81] The investigators documented both higher medication adherence and medication persistence among patients who had multiple means of refilling medications (in store-pickup and mail order). Expanding mail delivery to patients with limited transportation or patients with strict work schedules may help to minimize the hassle imposed by frequent pharmacy visits. Pharmaceutical companies also indirectly influence adherence through the drug combinations made available for purchase. While they offer similar therapeutic benefit as conventional formulations, preservative-free eyedrops may indirectly lead to improved adherence due to their lower side effect profile. However, these formulations may not be as affordable for patients with lower household income.

Situational Factors

Life events such as weddings and vacations have also been known to interrupt dosing.[134] Patients may forget to bring medications during travel, resulting in extended periods without therapeutic coverage. Individuals in high-demand positions may also struggle to maintain daily dosing, particularly if there are multiple daily instillations.[100] Additionally, health crises such as the Covid-19 pandemic have been reported to affect adherence.[109] In a study by Subathra et al. (2021) 55% of Indian patients indicated that limited access to medication was their principal barrier during the pandemic.[135] Similarly, Racette et al. (2021) documented that medication adherence declined during the Covid-19 pandemic.[109] Personal events such as the death of a loved one or the loss of employment, which both occurred at higher rates during the Covid-19 pandemic may also impose significant levels of psychological stress and may interrupt daily dosing.

Interventions for Improving Medication Adherence

Poor adherence has been addressed through numerous and varied means, ranging from community-based educational programs to web-based personal health record systems. The classification system developed by Tsai et al. (2007) [100] has also been used here to provide a comprehensive account of these interventions.

Patient Factors

Education has proven to be an effective tool for improving adherence.[74, 77, 136] Researchers have identified two critical components for the success of educational interventions, namely knowledge of the potential for future vision loss [137] and knowledge of treatment efficacy.[138] This understanding may boost patients' healthcare engagement and positively impact other closely-related factors such as health literacy. As health literacy has been inversely associated with satisfaction with care,[139] providers have a unique opportunity to improve the patient-provider relationship by targeting this factor.

Other interventions have sought to improve psychological barriers such as low motivation and psychological stress. Motivational interviewing (MI) has emerged as a useful counseling technique for resolving ambivalence and improving adherence in glaucoma.[115, 140-142] Key MI components include a benign and non-judgmental approach by counselors, and use of reflective listening techniques to elicit participants' perceptions about motivators and barriers to adherence.[142] More broadly, health counseling and coaching techniques have been associated with improved disease control [143] and self-perception.[144] While they are not formal interventions, patient focus-groups have been

incorporated into many clinical settings. These gatherings provide opportunities for patients to share valuable knowledge and experience related to treatment. Focus groups also indirectly address the lack of social and emotional support expressed by many patients by fostering peer support networks which can alleviate psychological stress.

Regimen Factors

Interventions addressing regimen factors often incorporate memory aides, dosing aides, and combination drugs. Memory aides have been especially successful.[73, 98, 145] These include calendars, automated and in-person calls, text reminders and MEMS with audible alarms.[78, 146] With increasing number of daily eyedrop instillations, there is also increased likelihood of poor adherence due to forgetfulness, busy schedule, or competing activities.[147] In recognition of the challenges experienced by patients with multiple prescribed daily instillations, researchers have developed a method of computing regimen complexity, which incorporates both number of medications and number of prescribed dosings.[148]

Other approaches involve targeting barriers related to instillation skill and medication side effects.[80, 149] Devices such as the Travatan dosing aid,[80] the Easidrop® guider, and the Eyot® guider [80, 150] have been used with varying degrees of success. It can be difficult to create dosing aides that successfully address the challenge of low dexterity and physical strength in older adults. As a result, dosing aides are likely to play a minimal role in improving adherence for many patients.[46] Within the past decade, many ocular hypotensives have been re-formulated to preservative-free versions or to use modified

preservatives such as sodium chlorite.[151] Preservative-free drug formulations are associated with improved patient satisfaction,[125] IOP control,[152] and ocular health.[153] As patients must no longer contend with side effects, they may become more consistent with eyedrop use.

Reducing the overall number of medications to be instilled may also be a viable approach.[2, 154] Barneby et al. (2017) found that patients who were prescribed fixed combination Travoprost/Timolol were adherent on more days compared to patients with separate containers of Travoprost and Timolol.[154] Gel, spray and single-dose formulations are also commercially available. A study among elderly Finnish patients reported that the single dose units were easier to use,[155] and a 2019 literature review found that preservative-free 0.1% gel Timolol formulations were equally efficacious as higher concentration solutions, and led to improved QoL.

Sustained drug delivery systems using lipid carrier-laden contact lenses have also been developed.[156] Many eye drop solutions are given in high doses due to poor bioavailability, which often leads to ocular and systemic side effects.[157] Sustained-release devices may be beneficial to patients whose condition is poorly controlled by monotherapy or patients suffering from preservative-induced ocular surface disease. However, the incorporation of such formulations may change the optical properties of the lens [158] and future mainstream adoption of such therapies is limited as they may not be affordable for all patients.

Provider Factors

The patient-provider relationship, despite the significance, is difficult to address through interventions and is perhaps best curated through honest communication, a mutual desire for effective treatment, and careful consideration of both shared and unique priorities pertaining to care.[159] Perspectives regarding healthcare differ based on patients' racial and cultural background.[128] Blackhall et al. (1995) found that Korean-American, Mexican-American, African-American and Hispanic patients were more likely to believe that family members should be involved in clinical decision-making, while Caucasian-Americans were more likely to value self-reliance, responsibility and control.[160] Although not an intervention, a patient-centered approach to care may contribute to improved healthcare engagement.[101] In a study by Safran et al. (1998), increased trust in providers was associated with greater patient satisfaction and decreased likelihood of changing physicians.[161]

Many interventions addressing the health system at large have focused on reducing the cost of medications. In a study by Bilger et al., (2019) rebates were offered to patients if they regularly refilled their prescriptions, leading to a significant increase in MPR.[162] Such incentives may be especially effective in patients with less disposable income, who are also more likely to be non-adherent.[74] Clinical intervention through distribution of medication samples may be equally useful. Providing samples is not part of clinicians' regular course of treatment, but go a long way in improving therapeutic coverage during periods when patients are unable to refill medications. However, requesting samples relies on patients' comfort level with their providers and their willingness to ask for assistance.

Situational Factors

Situational factors are often difficult to address due to their stochastic nature. Consequently, interventions that incorporate strategies for improving resilience, self-efficacy, and healthcare engagement may be most useful in overcoming these barriers. Counseling techniques such as MI are often incorporated into other interventions. Contingency planning is another such technique in which health counselors collaborate with patients to anticipate problem scenarios and develop solutions (e.g., keeping back-up medications in the office).

Health Technology

The WHO defines eHealth as the leveraging of health-related information and technology to provide and manage healthcare. Real world applications of eHealth include telemedicine, electronic health record systems, digital applications, patient health portals, and remote monitoring devices. eHealth has become increasingly recognized as an innovative and resource-efficient approach to health education and promotion. Mobile applications such as easyGlaucoma (mHealth Wellness LLC, 2020)[163] aim to improve glaucoma knowledge through daily quizzes and activities, while apps such as the Glaucoma Simulation mobile app (Gazzard, 2021)[164] simulate vision loss and help patients to conceptualize disease progression. Online platforms such as The Glaucoma Community (Responsum Health, 2021)[165] help patients to develop social support networks, and also create avenues through which patients can receive clinically vetted information about glaucoma and learn passively.

Corporate entities have also used technology to improve access to medications. The startup company Pillpak (Amazon pharmacy, 2021),[166] which was recently acquired by Amazon, collaborates with local pharmacies to deliver medications across health conditions. Other entities offering similar services include Capsule (Capsule Corporation , 2021),[167] which promises to deliver medications within two hours of prescriptions being issued, and NowRx (NowRx Inc., 2021)[168] an online pharmacy specializing in same-day, same-hour prescription deliveries. These initiatives bypass the need for patients to visit pharmacies to renew prescriptions and could help to eliminate gaps in therapy. As greater facility of medication access is associated with higher adherence,[81] this service may be beneficial to patients with complex regimens and busy schedules, as well as those with limited mobility and lack of transportation.

Telemedicine is a more clinically oriented initiative that allows patients to remotely access medical information and services. Teleglaucoma, a portmanteau of telemedicine and glaucoma, can increase access to care by improving workplace efficiency for clinical staff and reducing the need for long-distance travel for patients.[169] Research has found teleglaucoma to be more cost-effective than in-person examinations for glaucoma screening,[170] and patients participating in teleglaucoma programs reported similar levels of satisfaction compared to those receiving in-person examinations.[171] However, utilization of telemedicine is not yet optimal, as patients with limited access to the internet or smartphones may find it difficult to access telemedicine portals. Additionally, older patients or those with more advanced disease may prefer to have in-person sessions with their providers.

Interventions vary considerably in their design and methodology. However, across designs, their effectiveness can be improved by linking them to health models, which represent the accumulated empirical and real-world knowledge of the mediators of behavior change.

Health Theory Applied in Glaucoma

There has been no shortage of health theories and models seeking to explain the factors influencing adherence behavior. Health theories use research evidence and real-world experience to conceptualize modifiers of behavior, as well as the relationships between them. More importantly, health theories provide a scaffold for the design of complex interventions, and guide the allocation of research and clinic resources. [172] Despite their utility as guides for intervention design and delivery, their incorporation into glaucoma research has not been fully realized.

A subset of health theories such as the Health Belief Model (HBM), Theory of Planned Behavior (TPB), Social Cognitive Theory (SCT), Self-Determination Theory (SDT) and the Transtheoretical Model (TTM) have been applied in glaucoma research. These theories posit that adherence is a complex behavior that takes place within the larger context of individual values, social experiences, and anticipated outcomes.[172] The HBM, TPB, SCT, SDT, and TTM are discussed in greater detail below, as well as their limitations and applications in glaucoma research.

The Health Belief Model

The HBM was developed in 1958 by the Public Health Service in an attempt to improve participation in Tuberculosis screenings.[173] The HBM has seven constructs: *perceived disease severity, perceived disease susceptibility, self-efficacy, perceived treatment barriers, perceived treatment benefits, cues to action,* and *individual factors*. The HBM posits that the perceived severity of a condition, as well as one's perceived susceptibility to that condition provide the basis for the threat level posed by the disease. The model also argues that the value of a health behavior is determined by weighing *perceived barriers* to the behavior against *perceived benefits* of the behavior. Both the threat level of the condition and the value of the target health behavior are in turn shaped by *individual factors* such as disease knowledge, as well as *cues to action*, which are circumstances such as disease symptoms that prompt patients to undertake the behavior of interest. The final construct—*self-efficacy*, has been studied extensively in glaucoma,[57, 117] and is a major determinant of adherence.[112, 116]

The HBM has been widely applied in glaucoma [159, 174] as its constructs represent principal factors associated with treatment. The largely asymptomatic nature of the condition means that there are no symptoms that serve as cues for patients to participate in glaucoma screenings or improve their adherence. Thus, *cues to action*, by virtue of their absence, are important modifiers of adherence in glaucoma. A further barrier to optimal adherence in glaucoma is the lack of perceived treatment benefit when instilling eyedrops.[46] Moreover, many patients experience side effects and ocular irritation as opposed to relief.[125] Thus, the HBM construct of *perceived treatment benefit* represents a unique aspect of glaucoma treatment.

Similarly, *perceived glaucoma severity* plays a central role in helping patients to maintain their adherence, as fear of blindness is one of the strongest motivators for treatment.[159] Interventions may opt to target *perceived glaucoma severity* by providing information about prominent glaucoma risk factors such as family history. The HBM has also been used in the development of survey instruments for assessing patient perspectives [159] and medication adherence.[56]

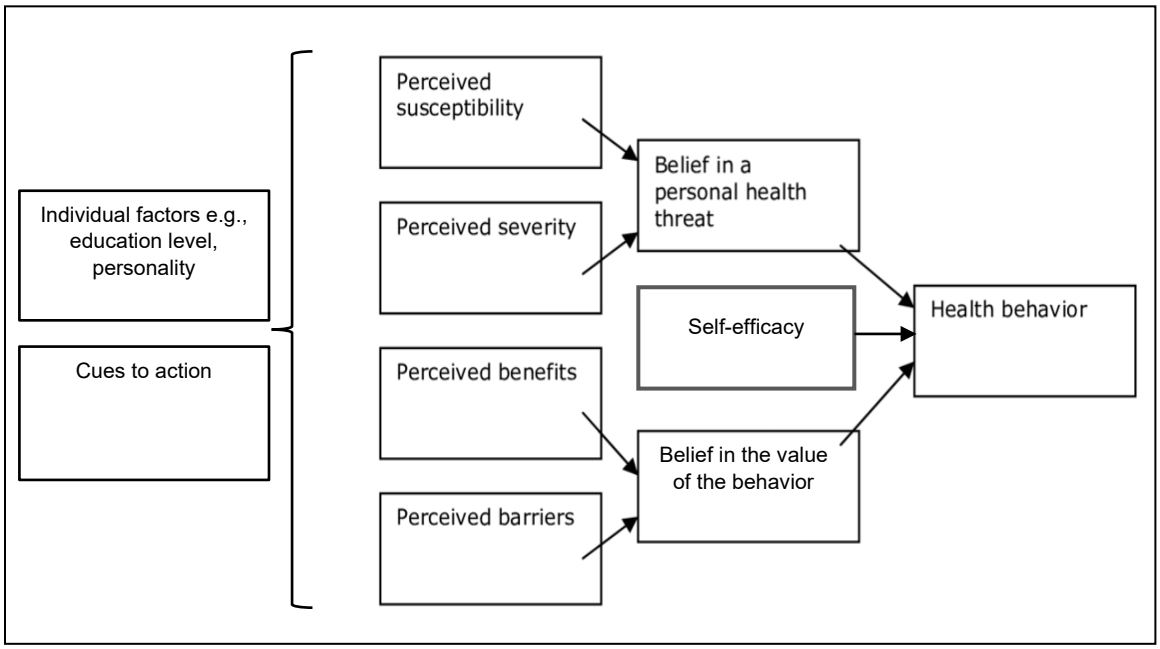

Figure 5. Health Belief Model. Constructs include perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, self-efficacy, and individual factors.

Theory of Planned Behavior

The TPB is an extension of the Theory of Reasoned Action.[175, 176] Both theories posit that an individual's intention to engage in a behavior—their behavioral intention—is predicted by *attitude, subjective norms, social norms, and perceived behavioral control. Attitude* refers to whether the individual sees the behavior as positive or negative, and is influenced by *subjective norms*, which describe the way in which the behavior is seen by friends, family and loved ones. Both *attitude* and *subjective norms* are shaped by *social norms*—the customary codes of behavior. *Perceived behavioral control* describes the facility of undertaking the behavior.

The TPB has been applied in glaucoma to identify principal determinants of adherence.[177] Prior et al. (2012), in a study aiming to identify predictors of behavioral intention for participating in glaucoma screenings, found that *attitude, subjective norm and perceived behavioral control* accounted for two-thirds of the variance in intention scores.[178] Unlike the HBM, the TPB does not acknowledge the role of individual factors such as education. Nor do any of its constructs specifically address elements related to treatment (e.g., perceived treatment benefits etc.). The model instead acknowledges social norms in shaping the value of the target behavior. The relational nature of the TPB may limit the degree to which its constructs can be targeted in research.

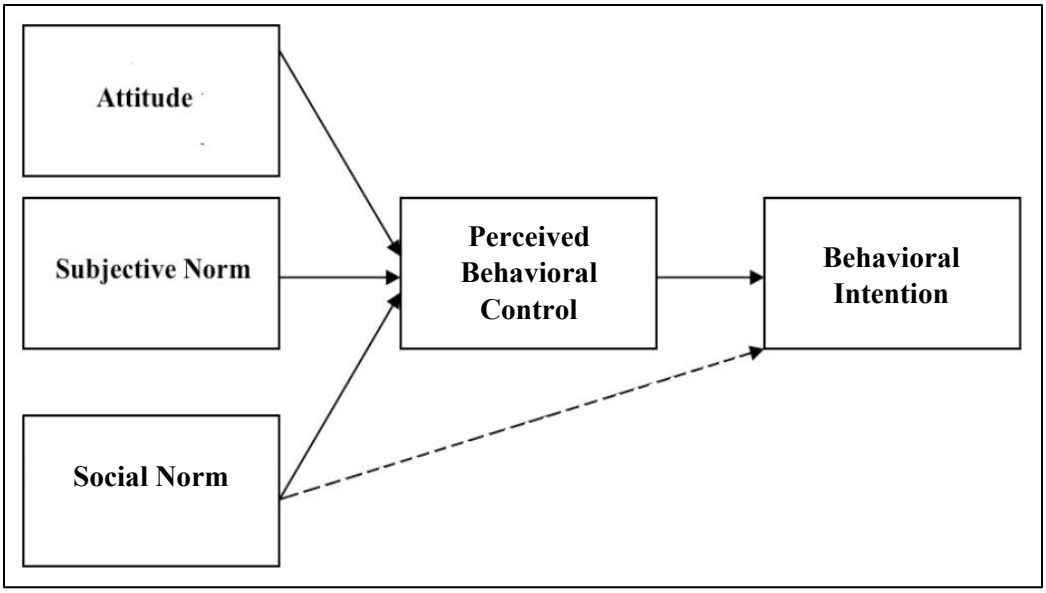

Figure 6. Theory of Planned Behavior. Constructs include attitude, subjective norms, social norms, perceived behavioral control and behavioral intention.

Social Cognitive Theory

SCT was originally developed from the Social Learning Theory,[179] and posits that one's learning process is related to observation of others' experiences. Tenets include *reciprocal determinism, behavioral capability, expectations, self-efficacy, observational learning, reinforcements, self-control,* and *expectancies***.** Reciprocal determinism describes one's attitude towards the action, while *behavioral capability* describes the degree to which one has sufficient knowledge and skill to complete the behavior. *Expectations* and *expectancies* refer to the anticipated outcomes and consequences of the behavior, respectively. Expectancies and outcomes are highly applicable to glaucoma, as patients who believe that eye drops will prevent loss of vision (perceived treatment efficacy) may be more likely to use them consistently.[180]

The final construct, self-control describes individuals' regulation of behavior. In glaucoma, SCT has been used to develop interventions for improving healthcare engagement [181] and medication adherence.[182] However, the theory has several limitations that constrain its use in research, chief among them being that SCT constructs can be too broad reaching to operationalize in their entirety. In addition, the model presents behavior change as being almost entirely socially driven. It does not emphasize the role of external factors such as income level and access to care, which are important in glaucoma.

Self Determination Theory

SDT is a theory of human motivation first developed by Deci and Ryan.[183] SDT incorporates individuals' personal growth and psychological needs, while emphasizing the extent to which human behavior is self-determined. The central tenets of SDT include *autonomy, competence,* and *relatedness.* Competence describes individuals' perceived ability to perform a behavior while *autonomy* describes perceived control of one's circumstances. Relatedness on the other hand, refers to individuals' will to interact with others. *Competence* and *autonomy* are closely related to self-efficacy. In glaucoma, the need to instill eyedrops for the duration of patients' lives poses a formidable challenge, and successful treatment requires high levels of confidence in one's ability to maintain good adherence under different circumstances. SDT has been incorporated in the development of personalized interventions for improving medication adherence.[184] Health counseling techniques such as MI that have been especially effective in glaucoma are consistent with the theoretical framework of SDT, which postulates that individuals must be intrinsically motivated to change or adopt a new health behavior.[185]

The Transtheoretical Model

The transtheoretical model of change (TTM) is a meta-theory developed by Prochaska and DiClemente [186, 187] that incorporates tenets of other established theories. The TTM evolved from studies comparing smokers who quit on their own to those who received smoking cessation therapy.[188] Constructs include *stage of change, process of change, decisional balance, self-efficacy,* and *temptation*. *Stage of change* is perhaps the most well-known construct, and represents different levels of readiness for behavior change including *precontemplation*—where one is not considering undertaking the target behavior, *contemplation*—where one is now considering undertaking the behavior, *preparation*—making plans to undertake the behavior, *action*—undertaking the behavior, and *maintenance*—continuation of the behavior for at least 6 months.

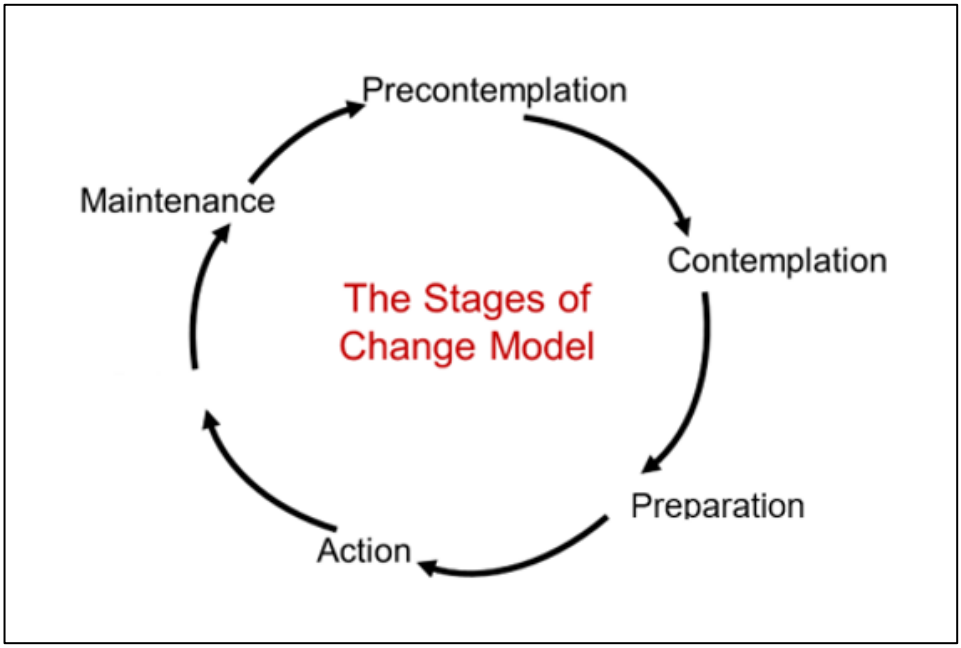

Figure 7. Stages of Change Construct of the TTM. Stages include 1. Precontemplation, 2. Contemplations, 3. Preparation, 4. Action, 5. Maintenance

In glaucoma, the TTM has been used to evaluate readiness for behavior change [134] and in the development of instruments for assessing adherence.[189] However, the model has been criticized for being too rigid due to its application of timelines to the stages of change. Furthermore, researchers have argued that the *precontemplation* and *contemplation* stages may be better suited to addictive behaviors such as alcohol abuse, as opposed to as instillation of eyedrops.[56] The second TTM construct—*process of change*—describes ten behavioral and psychological strategies that facilitate progress through the stages of change.

Processes of change include strategies such as consciousness raising (increasing awareness about the effects of poor adherence), helping relationships (establishing supportive relationships that facilitate better adherence), and stimulus control (re-engineering the environment to incorporate cues that encourage optimal adherence e.g., placing drops near the bathroom sink). Several of these processes have been formally incorporated into taxonomies of strategies for effecting behavior change.[190] Hahn et al. (2009) developed one such taxonomy in glaucoma by linking *stages of change* with *processes of change* that may help patients to improve their adherence over time. [191]

Decisional balance represents the pros and cons of behavior change. A mathematical relationship between *stage of change* and *decisional balance* was reported by Prochaska and DiClemente.[187] Progress from *precontemplation* to *action* was associated with approximately one standard deviation (SD) increase in the pros of behavior change and a 0.5 SD decrease in the cons of changing. This suggests that eliminating barriers to optimal adherence such as regimen complexity and medication side effects may be more effective than increasing perceived benefits of treatment. The

final two constructs are *temptation*—the intensity of circumstances that encourage cessation of the target behavior, and *self-efficacy*. The construct of *temptation* is an aspect of the TTM that is not well-suited for application in glaucoma.

Incorporating Health Theory Into Intervention Design

It is necessary to couch interventions in theoretical frameworks as this allows determinants of change to be appropriately identified and targeted.[190] However, solely applying health theory will not guarantee success. Researchers warn that without standardized design and reporting of the techniques used to effect behavior change (Behavior Change Techniques; BCTs), reproducing them can be difficult.[190]

Standardizing Interventions

Optimizing research through the incorporation of health models requires a comprehensive set of determinations. Amico et al. (2017) [172] describe several steps for ensuring that health theories are appropriately incorporated into intervention design. These include model selection, model tailoring, model operationalization, and model implementation.

It is important to identify which models are most appropriate for studying a specific health behavior. The strongest evidence for or against the application of a model is the concordance between its constructs and the major determinants of the target behavior.[172] Models identify the core processes that facilitate behavior change but often lack details about the nature of these factors for specific populations. Thus, it is also important to be well-informed about the target population so that the health model and

the intervention can be tailored to fit the social context. Rees et al. (2014) showed that Black glaucoma patients were more concerned about the prospect of blindness compared to White and South Asian patients.[128] Incorporating a component that addresses this priority during intervention design may lead to improved relevance, uptake, and effectiveness.

Operationalizing the model constructs that will be targeted through interventions helps to guide the allocation of resources, allowing them to be utilized more efficiently, especially where material or personnel resources may be limited. Theory-informed approaches also allow researchers to better conceptualize the antecedents of behavior, as well as identify gaps in their conceptualization of the relationships between antecedents and the target behavior.[172] Successful implementation of interventions also requires adherence to proposed methodology, as well as sufficient flexibility to account for contingencies.

Model implementation cannot be assessed without evaluation, and it is equally important that the appropriate outcomes, assessment metrics, and assessment methods be selected. For instance, objective methods such as claims data and electronically monitored data provide more reliable and valid data relative to subjective methods. However, if patterns of medication adherence over several years were the outcome of interest, then using claims data may be more feasible and advantageous. If instead, researchers were interested in gathering rich qualitative data about patients' experience with glaucoma, then self-report may be most appropriate.

It is also important that interventions be thoroughly described in published reports. Davidson et al. (2003) proposed that several elements be reported, including the

characteristics of those delivering the intervention, characteristics of recipients, the mode of delivery (online, in-person etc.), the intensity of delivery (e.g., duration of contact time), an account of any health theories which were incorporated into the intervention, and adherence intervention delivery protocols.[192] Organizing BCTs and intervention characteristics into taxonomies can accelerate the identification of the factors that most proximally effect behavior change.[193]

Tailoring Interventions

Medication adherence is a complex behavior. As such, it is important to develop a thorough understanding of the clinical, social, and psychological factors that influence it. It is important to tailor interventions that address these deterministic factors as patients are diverse, and their treatment beliefs, values, and priorities vary considerably.

Studies have identified several discrete patterns of medication adherence, and patients following similar patterns have been found to share several other important characteristics. Further investigation into patterns of adherence behavior may elucidate whether these shared attributes can be successfully leveraged as intervention targets for improving adherence. For instance, patients with poor or declining adherence may primarily be challenged by feelings of psychological stress and low motivation. These patients may be better served by interventions that combat feelings of ambivalence, despondency, and self-doubt. By contrast, patients with moderate adherence may struggle with busy schedules, forgetfulness, or competing activities, and may benefit more from reminders and routines.

A large HMO-based study that used the TTM to assess readiness for behavior change across 15 different behaviors [187] found that approximately 40% of participants were in *precontemplation*, 40% were in *contemplation*, and 20% were in *preparation* for behavior change. The GAPS study reported that 14% of patients of surveyed patients were not concerned that nonadherence could lead to vision loss. These patients can be considered to be in the precontemplation phase of behavior change and may reap greater benefit from processes of change such as consciousness raising.[4] These findings highlight the need to tailor interventions so that they not only meet patients' treatment needs, but also coincide with patients' level of readiness for change.

Glaucoma: A Unique Condition

Glaucoma is only one of several chronic conditions in which patients must use medication for the duration of their lives. However, it is unique in three important respects: the ocular route of administration (which complicates dosing), the absence of early symptoms which would otherwise prompt patients to take action through screenings or exams, and medication side effects which, together with the absence of symptoms, imposes a formidable psychological barrier to adherence behavior. Furthermore, unlike other conditions where medication provides relief from symptoms, glaucoma patients must hang their hopes on the future. Thus, glaucoma presents an apt disease model in which to study adherence as patients must overcome unique obstacles in order to maintain their adherence. By virtue of the uniqueness of this condition, interventions that have demonstrated success may have similar or greater levels of success in other conditions in which these factors are absent.

PATIENT AND PROVIDER PERSPECTIVES ON GLAUCOMA TREATMENT ADHERENCE: A DELPHI STUDY IN URBAN ALABAMA

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Optometry & Vision Science, Sep 2021, 98(9):1085-1093

Abstract

Significance: Glaucoma patients and providers recognized perceived treatment efficacy, patient-provider relationship, psychological stress, instillation skill, good quality of life and forgetfulness as key determinants of glaucoma adherence. This shared insight could help shape the development of clinical and behavioral interventions for addressing treatment barriers and improving adherence.

Purpose: Despite their impact on adherence in glaucoma, sociobehavioral factors may not be adequately explored during clinical consultations. We aimed to elicit consensus between patients and providers around key determinants of adherence, and hypothesized that patients would place greater emphasis on sociobehavioral factors compared to providers.

Methods: A two-round Delphi survey was used to assess treatment beliefs, barriers, facilitators, motivators, and needs among 18 glaucoma patients and providers. In *Round 1*, agreement with 46 statements was scored on a 5-point Strongly Disagree to Strongly Agree Likert scale. Statements with which 80% or more of panelists agreed reached consensus and advanced to *Round 2,* where participants were asked to prioritize them based on their importance to treatment.

Results: There was consensus regarding the influence of perceived treatment efficacy, good provider relationship, good quality of life, psychological stress, glaucoma knowledge, instillation skill, and forgetfulness on glaucoma adherence. For statements

that failed to reach consensus, Bonferroni-corrected Mann-Whitney U test revealed that the greatest differences between patients and providers pertained to regimen complexity (provider median = 4, IQR= 1; patient median = 1.5, IQR= 1, *P* = .002), instillation skill (providers = 4, IQR= 0.5; patients = 2, IQR= 1, *P* = .001), and low motivation (providers = 3, IQR= 2.25; patients = 1, IQR= 0, *P* = .003).

Conclusion: While patients and providers prioritized sociobehavioral factors as key determinants of adherence, disagreement between these groups were observed in other areas. Continued juxtaposition of patient and provider perspectives could spotlight underexplored areas and guide the development of successful interventions for improving adherence.

Key words: Glaucoma, Adherence, Patients, Providers, Perspectives

INTRODUCTION

Over 60 million people worldwide are affected by primary open angle glaucoma (POAG)[1-3]— a progressive optic neuropathy characterized by retinal ganglion cell death and distinctive patterns of vision loss. Although daunting, this figure is likely to be an underestimation, as only half of all persons living with glaucoma are believed to be diagnosed.[4] Glaucoma is a leading cause of irreversible blindness in the United States,[2, 5] and eye drops that lower intraocular pressure (IOP) and delay glaucomatous progression accounted for over 50% of Medicare part D prescribing costs in 2013.[6] Despite extensive prescribing, the proportion of patients with good adherence to recommended therapy is reported to be as low as 20%.[7] Although later studies have reported higher rates,[8-10] adherence in glaucoma remains suboptimal. High treatment cost, low education level, forgetfulness, and regimen complexity have been identified as key sociodemographic and clinical determinants of poor adherence.[11] However, many interventions based on these variables have demonstrated variable degrees of success, suggesting the possible influence of social, psychological, and behavioral factors on adherence to glaucoma therapy.

Sociobehavioral factors such as poor patient-provider relationship,[12] low self-efficacy,[13] and psychological stress[14] have been found to affect adherence in glaucoma. A study in diabetes also reported that patients were intentionally non-adherent in social settings due to embarrassment and public perception.[15] Despite their influence, providers

may have a limited ability to address sociobehavioral factors due to disparate perspectives and experiences relative to patients.[16] A 2005 study reported that poor communication between patients and providers led to nearly one in five patients using the wrong regimen.[17] It is vital that patients and providers improve their understanding of each other as this is the basis for shared decision making and effective treatment. We aimed to elicit consensus between patients and providers around key determinants of adherence using Delphi surveys. We used a mixed methods approach to assess treatment perspectives, and hypothesized that patients would place greater emphasis on sociobehavioral factors compared to providers.

METHODS

Participant Selection and Recruitment

This research was reviewed by an independent ethical review board and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research. Additionally, all research adhered to the Health Insurance Portability and Accountability Act (HIPAA), as well as the tenets of the Declaration of Helsinki. Optometrists and ophthalmologists with at least 2 years of experience treating glaucoma, and patients diagnosed with POAG for at least two years were recruited to participate in the Delphi survey. Patients also had to be above age 40, have best-corrected visual acuity better than 20/40, have been using hypotensive eye drops for at least 3 months, and have at least 2 reliable visual field tests (false positive rates < 33% and fixation loss rates < 20%).

Providers were recruited from Callahan Eye Hospital and Clinics (CEHC), the University of Alabama at Birmingham (UAB) School of Optometry Eyecare clinic, and community-based practices within Jefferson county. All patients were recruited from CEHC. Visual field tests were obtained from patients' clinical charts and used to determine disease severity. Based on perimetric research, we accepted visual field tests taken within 6, 12, and 24 months of study commencement for patients with severe, moderate, and mild glaucoma, respectively.[18-20] Regardless of disease severity, 90% of

patients underwent visual field testing within 12 months of study commencement. Disease severity was ascertained according to the Hodapp-Parrish-Anderson criteria.[21]

Delphi Survey Methodology

Delphi surveys use iterative rounds of questionnaires to refine consensus around a topic of interest among diverse respondents. These respondents—referred to as panelists, may represent one or more professional groups. In our study, we employed two professional groups: glaucoma patients and glaucoma eye care providers. In Delphi surveys, panelists complete questionnaires in each round, and items that reach high levels of agreement (consensus) are identified. Responses are summarized and items that fail to reach consensus are excluded from successive rounds of questionnaires.[22] In this way, expert consensus on a specific topic is continuously refined. Delphi surveys lack the limitations of other qualitative methods such as focus groups which provide rich qualitative data but afford little anonymity.

An additional advantage of Delphi surveys is their allowance for meaningful findings using relatively few participants. Sample size determination in Delphi surveys, unlike studies that use inferential statistics, is motivated by the need to maximize the generation of ideas, while minimizing cost and procedural inefficiencies. Panels with 15-25 members are both common and empirically sound in healthcare research.[23] We determined the sample size for our study by referring to Delphi literature recommending 10 to 50 panelists.[24] We determined the size of our patient groups (n=10) and provider groups (n=8) by following recommendations that advise 5-10 panelists per professional

group.[25] We employed the modified, two-round Delphi survey which is appropriate when substantial primary literature exists on the topic under study.[22]

We used purposive, non-random sampling, which in Delphi studies is primarily based upon panelist expertise and experience in the research area.[26-28] Consequently, Delphi panels may, by design, be unrepresentative of the larger population in order to ensure that panelists have expertise and experience relevant to the topic being investigated. In an effort to maximize the expertise of our panel, we oversampled for patients more likely to have difficulty maintaining good adherence, racial and ethnic minorities, patients with severe glaucoma, patients with glaucoma for more than 2 years, and patients with complex regimens. Provider panelists were selected from various backgrounds (e.g., ophthalmology, optometry, tertiary referral centers and community-based clinics). Recruitment letters were mailed to eligible participants and followed with up to 3 phone calls.

Round 1 Data Collection

Prior to study commencement, the interviewer (SP) was trained in qualitative data collection by completing instructional modules from the University of Minnesota[29] and the University of Kansas,[30] and later completed three trial interviews under supervision of study personnel. Modules covered recommendations for conducting focus groups, in-person and telephone interviews, guidance on notetaking and recording during interviews, recommendations for transcribing and reporting qualitative research findings, and guidelines for minimizing bias. In *Round 1*, participants completed the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25),[31] demographic questions, and

a semi-structured Health Belief Model (HBM)-based questionnaire exploring several dimensions of glaucoma treatment.

The HBM predicts the likelihood of a given health behavior by factoring in modifying variables called constructs.[32] Documented determinants of adherence were identified via literature review and mapped onto the HBM constructs they addressed. Five groups of determinants reflecting five HBM constructs were identified: *treatment beliefs, treatment barriers, treatment motivators* (perceived benefits of treatment), and *treatment facilitators* (thoughts and actions that lead to desired behavior). The final group constituted *treatment needs*, which despite being recognized in glaucoma literature, are not included in the HBM. Statements addressing identified determinants were developed, and face validity of each statement was assessed by a panel of optometrists and social scientists.

Participants' level of agreement with each questionnaire statement was scored on a 5-point Likert scale (Strongly Disagree to Strongly Agree), and wording for patient and provider questionnaires was adjusted to reflect their respective perspectives. For instance, providers were asked "*Do you think that the medication you prescribe is effective?*" whereas patients were asked *"Do you believe that the medication prescribed by your doctor is effective?".* In addition to Likert scale-based responses, panelists were encouraged to provide additional context which was audio-recorded with participants' consent to allow transcription. The NEI VFQ-25 was excluded from provider questionnaires as only patients' clinical characteristics were of interest. Patient questionnaires were administered by the interviewer in private rooms at CEHC, while

provider questionnaires were administered at CEHC (n=2) or their practice (n=6). All data were collected from September 2019 to November 2019.

Round 1 Analysis

Likert responses were recoded so that Strongly disagree=1; Disagree=2, Neutral=3; Agree=4; Strongly Agree=5. IBM SPSS Statistics Version 26 (Armonk, NY)[33] was used to perform Bonferroni-corrected Mann-Whitney U tests for significant differences between patient and provider responses. Neutral scores (3) were then omitted for each statement, and remaining scores were dichotomized into two response types: agreement (4 or 5) or disagreement (1 or 2). Disagreement was indicated by negative values, while agreement was indicated by positive values. For example, a statement receiving scores of 4 and 5 from 9/18 panelists had an agreement level of 50% whereas a statement receiving scores of 1 and 2 from 9/18 panelists had an agreement level of -50%. Consensus was defined as an agreement level of 80% or more, and all statements reaching consensus advanced to *Round 2*. This threshold was selected as it was the most conservative threshold reported in similarly-sized Delphi studies.[34]

After quantitative analysis was complete, audio recordings of the questionnaire sessions were transcribed, and qualitative analysis was performed in Nvivo Version 12.[35] A codebook was developed by two researchers (SA, SP) during preliminary review of the transcripts, and codes were assigned to the transcribed text based on content.[36] Per each code, verbal responses were sorted into two groups: *confirmatory (+)*—where panelists agreed that the factors being discussed impacted adherence, and *contradictory (-)*—where

panelists disagreed. A coding comparison between the two researchers was performed, and Cohen's kappa statistic was used to assess inter-coder reliability.

Round 2 Data Collection And Analysis

Once *Round 1* data were analyzed, post-round reports containing individual questionnaire scores and median scores for the entire panel were mailed to all panelists, who were also invited to review the reports and revise their *Round 1* responses if desired. No panelists amended their responses after reviewing *Round 1* reports. In *Round 2*, panelists were asked to prioritize the statements that reached consensus in *Round 1* based on their importance to glaucoma treatment. *Round 2* was conducted from December 2019 to February 2020, and post-round reports were issued to panelists after analysis. No panelists were lost to attrition, and we had a 100% response rate in both Delphi rounds.

RESULTS

Demographic and Clinical Characteristics

Table 1 shows the clinical and demographic characteristics of Delphi panelists. Fifty percent of patient panelists had severe glaucoma (MD worse than -12 dB), while 70% of patients were diagnosed with 3 or more chronic health conditions—the most common of which were hypertension, depression, gastroesophageal reflux disease (GERD), and diabetes. Persons of African descent constituted the largest racial group among patients (70%), followed by persons of European descent (30%). Among providers, persons of European descent constituted the largest racial group (62.5%), followed by persons of African descent (25%), and persons of Asian descent (12.5%). Males constituted 40% of patients compared to 37.5% of providers. All patients were between the ages of 50 and 70, compared to only 37.5% of providers.

Table 1

Clinical and Demographic Characteristics of Patient and Provider Panelists

STUDY VARIABLES	**PATIENTS (N=10)**
Mean acuity (LogMAR)	0.24 (0.14)
Mean Intraocular Pressure (mmHg) OD	14.5 (3.7)
Mean Intraocular Pressure (mmHg) OS	14.5 (4.6)
Median NEI VFQ-25 (general health)	50 (0)
Median NEI VFQ-25 (general vision)	37.5 (25)
Median NEI VFQ-25 (psychological stress)	46.9 (51.6)
Glaucoma severity	**N (%)**
Mild	2 (20)
Moderate	3 (30)

Severe	5 (50)
Number of comorbidities	**N (%)**
0	1 (10)
1-2	2 (20)
3-4	5 (50)
5 or more	2 (20)
Comorbidities	**(%)**
Diabetes	3 (30)
Hypertension	7 (70)
High cholesterol	3 (30)
GERD	4 (40)
Depression	4 (40)
Medication type	**(%)**
Prostaglandin analogs	50
Beta blockers	21.43
Carbonic anhydrase inhibitors	21.43
Alpha agonists	7
Sex	**N (%)**
Male	4 (40)
Female	6 (60)
Age	**N (%)**
50-59 years	4 (40)
60-69 years	4 (40)
70-79 years	2 (20)
Race	**N (%)**
African Descent	7 (70)
European Descent	2 (20)
Multiracial (European and Native American)	1 (10)
Ethnicity	**N (%)**
Hispanic	1 (10)
Income level	**N (%)**
Less than $10, 0000	1 (10)
$10, 000 to $59, 000	6 (60)
$60, 000 to $100, 000	1 (10)
$100, 000 to $149, 000	1 (10)
More than $150, 000	1 (10)
Education level	**N (%)**
Some high school	1 (10)
Some college	6 (60)
Bachelor's degree	2 (20)
Graduate or professional degree	1 (10)
Employment level	**N (%)**
Unemployed/unable to work	1 (10)
Employed full-time	3 (30)
Retired	6 (60)

STUDY VARIABLES	**PROVIDERS (N=8)**
Sex	**N (%)**
Male	3 (37.5)
Female	5 (62.5)

Age	**N (%)**
30-39 years	2 (25)
40-49 years	3 (37.5)
50-59 years	2 (25)
60-69 years	1 (12.5)
Race	**N (%)**
African Descent	2 (25)
Asian Descent	1 (12.5)
European Descent	5 (62.5)
Specialty type	**N (%)**
Optometrists	5 (62.5)
Ophthalmologists (specialists and surgeons)	3 (37.5)
Weekly Patient load	**N (%)**
25-50	5 (62.5)
50-75	1 (12.5)
75-100	1 (12.5)
100-125	1 (12.5)
Method for assessing adherence	**N (%)**
Self-report	6 (75)
Self -report and prescription records	2 (25)

Note: From "Patient and Provider Perspectives on Glaucoma Treatment Adherence: A Delphi Study in Urban Alabama" by Poleon S, Racette L, Fifolt M, Schoenberger-Godwin YM, Abu SL, and Twa MD. 2021. Optometry and Vision Science 98(9), 1085-1093. Copyright 2021 by Wolters Kluwer Health, Inc. Reprinted with permission.

Statements Failing to Reach Consensus

Of the 36 statements that failed to reach consensus, 19 showed opposing responses and are shown in Figure 1. One statement was excluded as patient scores were evenly dichotomized and a majority response type could not be determined (*Reminders and alarms are helpful*). This reduced the number of statements to 46. Relative to providers, patients agreed that they could manage glaucoma without instrumental help (physical assistance). However, patients disagreed that they could manage glaucoma without emotional support or that they could easily detect changes in their vision over time (fig. 1a). Among treatment barriers, patients disagreed with providers that any barriers except for *busy schedule* negatively affected adherence (fig. 1b).

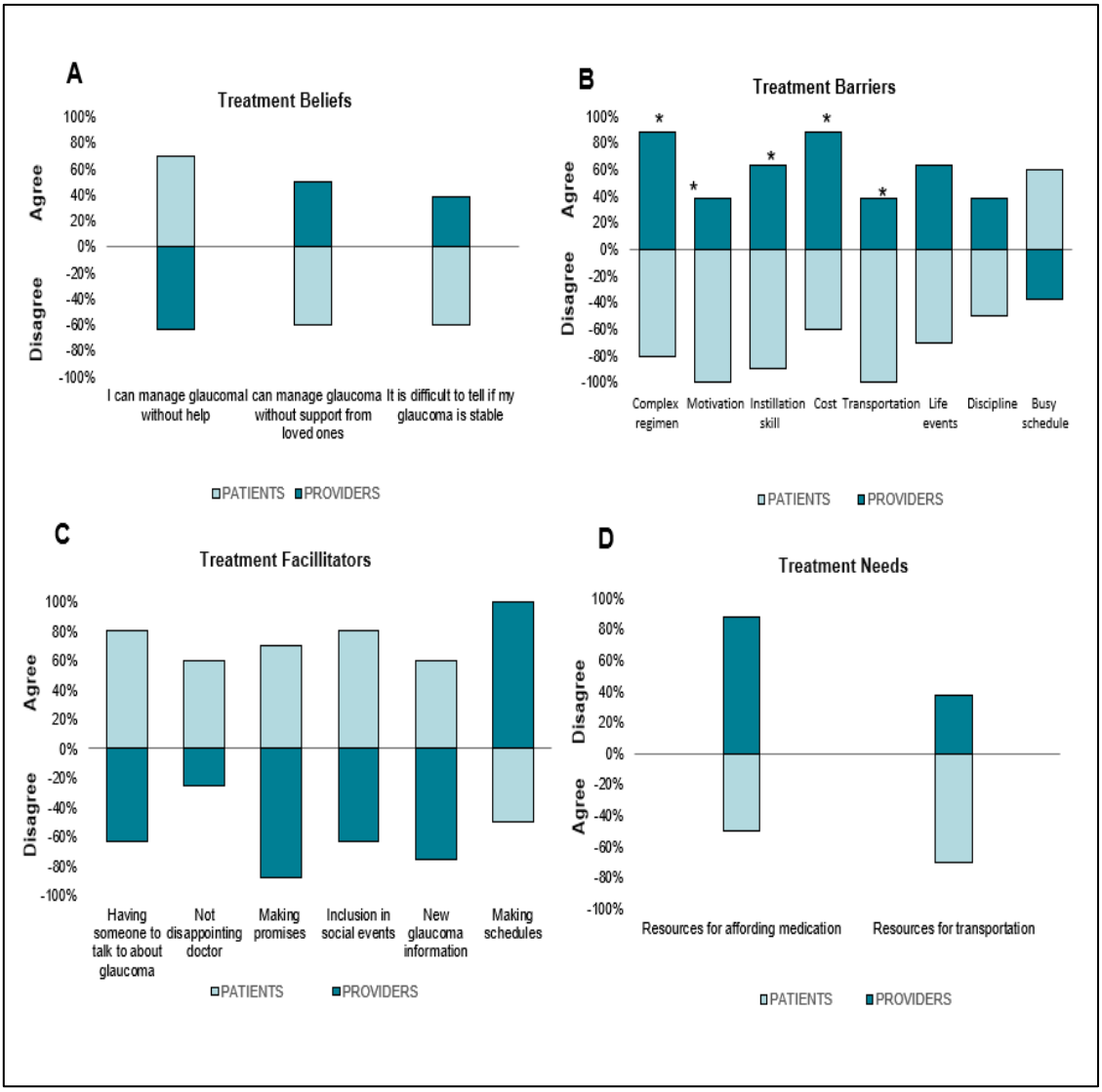

Figure 1. Majority Response Types and Agreement Levels for Statements that did not Reach Consensus. Three treatment beliefs (1a) eight treatment barriers (1b) six treatment motivators (1c) and two treatment needs (1d) failed to reach consensus and showed opposing responses among patients and providers (N=18). Consensus= 80% or more overall agreement. Negative values indicate disagreement with statements, while positive values indicate agreement. *= Statistically significant differences between patient and provider responses detected by Bonferroni-corrected Mann-Whitney U test.

Note: From “Patient and Provider Perspectives on Glaucoma Treatment Adherence: A Delphi Study in Urban Alabama” by Poleon S, Racette L, Fifolt M, Schoenberger-Godwin YM, Abu SL, and Twa MD. 2021. Optometry and Vision Science 98(9), 1085-1093. Copyright 2021 by Wolters Kluwer Health, Inc. Reprinted with permission.

Bonferroni-corrected Mann-Whitney U tests revealed significant differences between patients and providers regarding the influence of regimen complexity (provider median = 4, IQR= 1; patient median = 1.5, IQR= 1, ***P*** = .002), poor instillation skill (providers = 4, IQR= 0.5; patients = 2, IQR= 1, ***P*** = .001), low motivation (providers = 3, IQR= 2.25; patients = 1, IQR= 0, ***P*** = .003), medication cost (providers = 5, IQR= 3; patients = 2, IQR= 0, ***P*** = .002), and transportation (providers = 3, IQR= 2.25; patients = 1, IQR= 0, ***P*** = .001). Patients agreed with providers that all facilitators except for *making schedules* positively impacted adherence (fig. 1c), and disagreed with providers that help was needed with transportation or paying for treatment (fig. 1d).

Statements Reaching Consensus

Figure 2 depicts the agreement levels for statements that reached consensus and advanced to *Round 2*. In Round 2, perceived treatment efficacy (*Prescribed medication is effective; Not using eyedrops affects vision)* was prioritized as the most impactful treatment-related belief, followed by good patient-provider relationship (*I can openly discuss problems with my doctor)*, and adequate glaucoma knowledge (*I have a good understanding of glaucoma*). Also in *Round 2*, *reducing worry about blindness* was prioritized as the strongest motivator for good adherence, followed by *being independent*, *being able to navigate freely,* and *being able to drive*. *Memory aides* were identified as the most pressing treatment need, followed by *guides for instilling drops*.

Qualitative Analysis

Results of our thematic analysis are presented in Table 2. For patients, prominent themes related to good quality of life (13 comments), psychological stress (10 comments), and glaucoma knowledge (9 comments). Among providers, patient-provider relationship (40 comments), glaucoma knowledge (29 comments) and quality of life (16 comments) were the most recurrent themes. Cohen's Kappa was calculated to be 0.62 indicating good inter-rater reliability.[35]

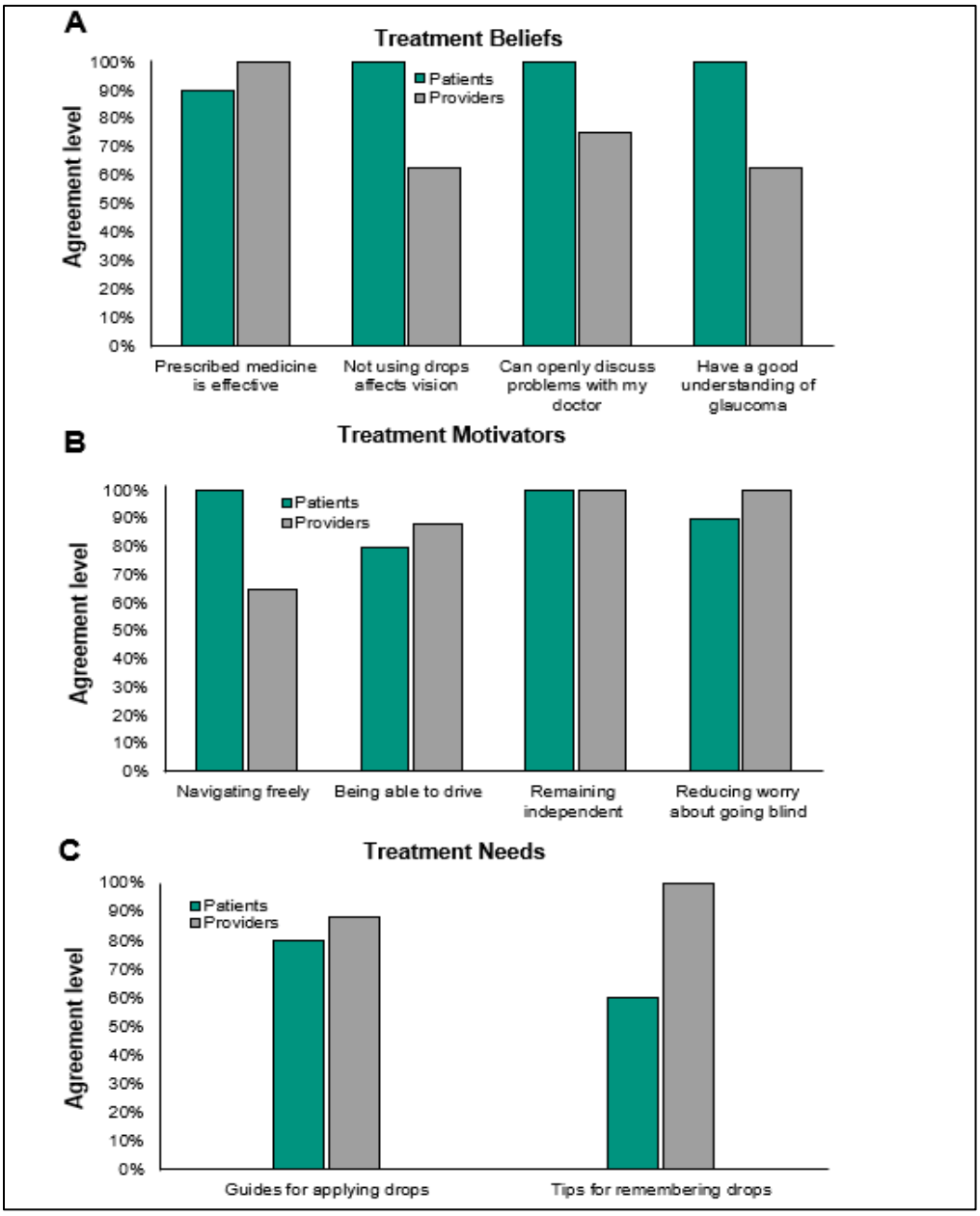

Figure 2. Agreement Levels for Statements that Reached Consensus. Four treatment beliefs (2a), four treatment motivators (2b), and two treatment needs (2c) reached consensus in Round 1. Consensus= 80% or more agreement. No statistically significant differences between patients and providers (N=18) were detected by Bonferroni-corrected Mann-Whitney U test.

Note: From "Patient and Provider Perspectives on Glaucoma Treatment Adherence: A Delphi Study in Urban Alabama" by Poleon S, Racette L, Fifolt M, Schoenberger-Godwin YM, Abu SL, and Twa MD. 2021. Optometry and Vision Science 98(9), 1085-1093. Copyright 2021 by Wolters Kluwer Health, Inc. Reprinted with permission.

Table 2

Median Likert Scores and Majority Response Types for Questionnaire Statements in Round 1

Themes	Patients			Providers		
	Sample quote	(+)	(-)	Sample Quote	(+)	(-)
Health system, Provider relationship	"I don't want to disappoint my doctor because I'm the patient that really does what they say, and they know"	2	2	"Patients want to please the physicians. If they think the physician will be disappointed if they say I'm not taking my drops"	39	1
Treatment cost	"This one we had to get for surgery prep was expensive"	4	2	"Cost of eye drops, that's a big deal"	8	0
Social/emotional support	"I only talk to my daughter about this"	3	1	"Especially for moderate-severe or those having surgery"	10	0
Psychological stress (worry, fear, anxiety)	"I'm embarrassed because other people can read along with subtitles, and I can't even get to it"	7	3	"They become frustrated by that, and you must keep reminding them that the goal is to prevent loss of vision not to get more"	11	6
Instrumental support	"I can't drive or do any of those things, I need help"	3	1	"I would say that most need some type of support system"	14	0
Medication side effects	"The taste, just the taste"	2	1	"Even if effective, it may not be used because of burning, stinging"	6	2
Transportation	"I will have to disagree with that since I can't drive or do any of those things"	1	1	"Lack of reliable transportation-I've had a lot of no shows-IOP check, things like that"	7	1
Instillation Skill and dexterity	"I remember when it was the child top, but now you have to squeeze and line this up."	2	0	"It's got to be 90 percent of patients who would need help with this"	11	1
Glaucoma knowledge and health literacy	"Yes, I teach anatomy and I take the eyes apart in class"	7	2	"We give patients a ton of information and a lot is lost as soon as they hear the diagnosis"	26	3
Treatment efficacy	"I understand if I don't take my medicine, I will be blind"	6	1	"Sometimes it's hard to really tell if it's working"	7	3
Life events and busy schedules	"I take care of people; I take care of my husband"	3	0	"it's just hard when they're on vacation"	4	1

Comorbidities and complex regimens	"I take so much medicine. The drops are the last thing I do at the end of the day"	1	0	"The problem is that there is a balance. After 2, 3 medications, compliance just falls"	11	0
Forgetfulness and reminders	"They gonna call to remind me so I don't even keep up"	4	3	"Reminders, if patients are able to, are incredibly helpful.	14	0
Self-efficacy	"I might miss some here and there"	1	0	"Many of them do need help"	5	0
Motivation	-	0	0	"Motivation is there, but it can wax and wane"	3	1
Quality of Life	"It took me from being independent to being dependent again."	11	2	"Patients want to be independent. If the VF gets tiny and central vision is affected, they won't be"	15	1
Surgical treatment (fear or complications)	"He has to pause from regular medication after surgery, but he is on another one"	1	0	"I'll see people that are teetering on surgery or not. I'll say let's just give it one more month, then they'll come clean"	5	0

Positive signs (+) indicate confirmatory statements where panelists agreed that themes affected adherence. Negative signs (-) indicate contradictory statements where panelists disagreed that themes affected adherence.

Note: From "Patient and Provider Perspectives on Glaucoma Treatment Adherence: A Delphi Study in Urban Alabama" by Poleon S, Racette L, Fifolt M, Schoenberger-Godwin YM, Abu SL, and Twa MD. 2021. Optometry and Vision Science 98(9), 1085-1093.

DISCUSSION

While several studies have explored patient perspectives in glaucoma, a smaller proportion have comparatively assessed patient and provider perspectives.[10, 14, 37] Our study revealed consensus regarding the impact of perceived treatment efficacy, patient-provider relationship, forgetfulness, psychological stress, instillation skill, wanting good quality of life, and glaucoma knowledge. Among these, perceived treatment efficacy, reduced psychological stress, and memory aides were the most highly prioritized treatment beliefs, treatment motivators, and treatment needs, respectively. While both panelist groups identified determinants of socioeconomic and sociobehavioral origin, providers tended to recognize socioeconomic treatment barriers such as cost and transportation. Patients tended to recognize sociobehavioral treatment facilitators such as social support and close patient-provider relationships.

Other prominent differences between patients and providers pertained to the importance of day-to-day support. Relative to providers, patients minimized instrumental support while prioritizing emotional support, suggesting a need for greater emphasis on patients' level of social and emotional wellness. Social support is also closely related to good quality of life[38, 39]—another factor that reached consensus. Both patient and provider panelists recognized the importance of being able to navigate freely, drive, and remain independent, as well as the threat that glaucoma posed to the continuation of these activities. The patient-provider relationship was also spotlighted; patients agreed that not

wanting to disappoint their doctor influenced their adherence behavior whereas providers disagreed. As many clinicians rely on patient-reported adherence, patient overestimation due to provider expectations could skew assessment and misinform treatment decisions.[40] Some providers commented that provider expectations were barriers to honest communication, while others considered them to be facilitators of good adherence if properly leveraged. One patient admitted to deliberately skipping clinic visits during periods of poor compliance as they believed that their doctor would know.

Despite differences in perspectives, several factors reported to be important in adherence literature reached consensus in this study. Both panelist groups recognized the impact of psychological stress—a finding consistent with research indicating that glaucoma patients are up to 12 times more likely to experience depression than persons without glaucoma.[41] In response to such findings, there have been increasing appeals for the adoption of interventions that manage the negative affect associated with glaucoma diagnosis.[42] Panelists also expressed a need for eyedrop instillation guides. Poor instillation skill has been identified as a treatment barrier,[43-45] with as few as 10% of patients correctly instilling eye drops.[46] This is concerning as poor instillation may result in poor IOP control and increased treatment costs, as well as poor treatment efficacy, which was another factor that reached consensus. Unlike many chronic conditions, glaucoma has no overt symptoms that prompt patients to maintain good adherence. This suggests that positive perceptions about the effectiveness of treatment are strong determinants of adherence, as evinced by the continued use of IOP-lowering drops among patients, even when there is no immediate perceived benefit.[47] Providers stated

that they reinforced treatment efficacy with a variety of techniques such as simulations of progression.

Other notable themes included patient motivation and the irreversible nature of glaucoma. As therapy delays progression rather than restoring vision, patients may experience dampened treatment expectations and lower motivation. In recent years, motivational interviewing has become a common strategy for resolving patient ambivalence, and has demonstrated favorable results.[48] Patients also communicated high levels of openness with providers. Research has shown that communication styles and clinical priorities vary across ethnicity, race, and culture[49] and that their incorporation into clinical decision-making is associated with improved outcomes.[50] However, such findings stand in contrast with glaucoma research indicating that patients' views and treatment goals may not be adequately explored.[51] Our results highlight the need for providers to remain vigilant for sociobehavioral determinants, particularly as less observable factors such as psychological stress have been associated with elevated IOP.[52]

In addressing the under-representation of complementary patient and provider perspectives in glaucoma literature, this study revealed areas of consensus regarding the impact of perceived treatment efficacy, provider relationship, psychological stress, glaucoma knowledge, wanting a good quality of life, instillation skill, and forgetfulness. Qualitative analysis revealed the patient-provider relationship to be the most commonly discussed theme, and we believe that it is one of the most proximal and direct determinants of good adherence. Strengths of this study include qualitative analysis, which supported our findings,[53] and panelists' diverse clinical and demographic backgrounds, which provided nuanced perspectives. Although unaware, several patients

and their personal providers participated in the study. This imparted an added layer of granularity to the study as these paired responses directly measured differences and similarities in perspectives. Other strengths include use of an established health model in the development of questionnaires, and the issuance of post-round reports which afforded patient panelists the opportunity to appreciate research findings.

This study is not without limitations, however. The relatively small panel size may limit the generalizability of our findings, as providers' responses were based on experiences with multiple patients while patients' responses were based on experience with a single provider, as well as their unique clinical history. Lastly, all participants were aware that the Delphi panel comprised both patients and providers, and that both groups would receive post-round reports. Despite the data being de-identified, this knowledge could have contributed to responder bias. To our knowledge, this is the first study to comparatively assess treatment perspectives among glaucoma patients and providers using both qualitative and quantitative methods. Our hypothesis was partially supported, as both groups prioritized sociobehavioral factors as key treatment beliefs, barriers, motivators, facilitators, and needs. However, per Delphi studies, the external validity of our findings lies in whether they are substantiated in real-world situations. Continued juxtaposition of patient and provider perspectives could spotlight other underexplored areas and inform the development of successful interventions for improving treatment adherence in glaucoma.

REFERENCES

1. Kapetanakis VV, Chan MP, Foster PJ, et al. Global Variations and Time Trends in the Prevalence of Primary Open Angle Glaucoma (Poag): A Systematic Review and Meta-Analysis. Br J Ophthalmol 2016;100:86-93.
2. Tham YC, Li X, Wong TY, et al. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040: A Systematic Review and Meta-Analysis. Ophthalmology 2014;121:2081-90.
3. Adelson JD, Bourne RRA, Briant PS, et al. Causes of Blindness and Vision Impairment in 2020 and Trends over 30 Years, and Prevalence of Avoidable Blindness in Relation to Vision 2020: The Right to Sight: An Analysis for the Global Burden of Disease Study. The Lancet Global Health 2021;9:e144-e60.
4. Sommer A, Tielsch JM, Katz J, et al. Relationship between Intraocular Pressure and Primary Open Angle Glaucoma among White and Black Americans: The Baltimore Eye Survey. Arch Ophthalmol 1991;109:1090-95.
5. Quigley HA, Broman AT. The Number of People with Glaucoma Worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262-7.
6. Newman-Casey PA, Woodward MA, Niziol LM, et al. Brand Medications and Medicare Part D: How Eye Care Providers' Prescribing Patterns Influence Costs. Ophthalmology 2018;125:332–39.
7. Olthoff C, Schouten J, Borne B, Webers C. Noncompliance with Ocular Hypotensive Treatment in Patients with Glaucoma or Ocular Hypertensionan Evidence-Based Review. Ophthalmology 2005;112:953-61.
8. Cate H, Bhattacharya D, Clark A, et al. Patterns of Adherence Behaviour for Patients with Glaucoma. Eye 2013;27:545-53.
9. Okeke CO, Quigley HA, Jampel HD, et al. Adherence with Topical Glaucoma Medication Monitored Electronically: The Travatan Dosing Aid Study. Ophthalmology 2009;116:191-99.
10. Friedman DS, Quigley HA, Gelb L, et al. Using Pharmacy Claims Data to Study Adherence to Glaucoma Medications: Methodology and Findings of the Glaucoma Adherence and Persistency Study (Gaps). Invest Ophthalmol Vis Sci 2007;48:5052-7.
11. Dreer LE, Girkin C, Mansberger SL. Determinants of Medication Adherence to Topical Glaucoma Therapy. J Glaucoma 2012;21:234-40.
12. Tsai JC. Barriers to Adherence with Glaucoma Therapy: Potential Relationships to Disease Progression. Adv Stud Ophthalmol 2007;4:72-75.
13. Sleath B, Blalock SJ, Carpenter DM, et al. Ophthalmologist-Patient Communication, Self-Efficacy, and Glaucoma Medication Adherence. Ophthalmology 2015;122:748-54.

14. Dietlein TS, Jordan J, Dinslage S, Krieglstein GK. What Do Glaucoma Specialists Know About Their Patients? Graefes Arch Clin Exp Ophthalmol 2006;244:859-62.
15. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin Adherence Behaviours and Barriers in the Multinational Global Attitudes of Patients and Physicians in Insulin Therapy Study. Diabet Med 2012;29:682-9.
16. Addario BJ, Fadich A, Fox J, et al. Patient Value: Perspectives from the Advocacy Community. Health Expect 2017;21:57-63.
17. Buller AJ, Connell B, Spencer AF. Compliance: Clear Communication's Critical. Br J Ophthalmol 2005;89:1370.
18. Chauhan BC, Garway-Heath DF, Goñi FJ, et al. Practical Recommendations for Measuring Rates of Visual Field Change in Glaucoma. The British journal of ophthalmology 2008;92:569-73.
19. Jansonius NM. Progression Detection in Glaucoma Can Be Made More Efficient by Using a Variable Interval between Successive Visual Field Tests. Graefes Arch Clin Exp Ophthalmol 2007;245:1647-51.
20. Wu Z, Saunders LJ, Daga FB, et al. Frequency of Testing to Detect Visual Field Progression Derived Using a Longitudinal Cohort of Glaucoma Patients. Ophthalmology 2017;124:786-92.
21. Chang TC, Ramulu P, Hodapp E, Thanos A. Clinical Decisions in Glaucoma: Second Edition: Ta Chen Chang; 2016.
22. Hsu C-C, Sandford B. The Delphi Technique: Making Sense of Consensus. Pract Assess Res Evaluation 2007;12:1-8.
23. Akins RB, Tolson H, Cole BR. Stability of Response Characteristics of a Delphi Panel: Application of Bootstrap Data Expansion. BMC Med Res Methodol 2005;5.
24. Needham RD, de Loë RC. The Policy Delphi: Purpose, Structure, and Application. The Canadian Geographer / Le Géographe canadien 1990;34:133-42.
25. Delbecq A, Van deVen A, Gustafson D. Group Techniques for Program Planning; a Guide to Nominal Group and Delphi Processes. In. Glenview IL: Scott Foresman and Company; 1975:83-107.
26. Hasson F, Keeney S, McKenna H. Research Guidelines for the Delphi Survey Technique. J Adv Nurs 2000;32:1008-15.
27. Brady SR. Utilizing and Adapting the Delphi Method for Use in Qualitative Research. International Journal of Qualitative Methods 2015;14.
28. Powell C. The Delphi Technique: Myths and Realities. J Adv Nurs 2003;41:376-82.
29. Krueger RA. Designing and Conducting Focus Group Interviews. Available at: https://www.eiu.edu/ihec/Krueger-FocusGroupInterviews.pdf. Accessed: September 30, 2019.
30. Vilela M. Conducting Interviews. [last updated: 2020]. Available at: https://ctb.ku.edu/en/table-of-contents/assessment/assessing-community-needs-and-resources/conduct-interviews/main. Accessed: October 26, 2018.
31. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-List-Item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119:1050-58.

32. Jones CL, Jensen JD, Scherr CL, et al. The Health Belief Model as an Explanatory Framework in Communication Research: Exploring Parallel, Serial, and Moderated Mediation. Health Commun 2015;30:566-76.
33. Spss Statistics for Windows [Computer Program]. Version 26.0. Armonk, NY: IBM Corp 2019.
34. Green RA. The Delphi Technique in Educational Research. Sage Open 2014;4.
35. Nvivo Qualitative Data Analysis Software [Computer Program]. Version 12. QSR International; 2018.
36. Zhang Y, Wildemuth BM. Qualitative Analysis of Content. Human Brain Mapp 2005;30:2197-206.
37. Sleath B, Sayner R, Vitko M, et al. Glaucoma Patient-Provider Communication About Vision Quality-of-Life. Patient Educ Couns 2017;100:703-09.
38. Wang Y, Zhu L, Yuan F, et al. The Relationship between Social Support and Quality of Life: Evidence from a Prospective Study in Chinese Patients with Esophageal Carcinoma. Iran J Public Health 2015;44:1603-12.
39. Wang Y, Zhao Y, Xie S, et al. Resilience Mediates the Relationship between Social Support and Quality of Life in Patients with Primary Glaucoma. Frontiers in Psychiatry 2019;10.
40. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to Therapy with Oral Antineoplastic Agents. J Natl Cancer Inst 2002;94:652-61.
41. Zhang X, Olson DJ, Le P, et al. The Association between Glaucoma, Anxiety, and Depression in a Large Population. American J Ophthalmol 2017;183:37-41.
42. Mendez-Ulrich JL, Sanz A. Psycho-Ophthalmology: Contributions of Health Psychology to the Assessment and Treatment of Glaucoma. Psychol Health 2017;32:330-42.
43. Stone JL, Robin AL, Novack GD, et al. An Objective Evaluation of Eyedrop Instillation in Patients with Glaucoma. Arch Ophthalmol 2009;127:732-6.
44. 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;117:2345-52.
45. 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;152:982-8.
46. Lampert A, Bruckner T, Haefeli W, Seidling H. Improving Eye-Drop Administration Skills of Patients – a Multicenter Parallel-Group Cluster-Randomized Controlled Trial. PLoS ONE 2019;14.
47. Stryker JE, Beck AD, Primo SA, et al. An Exploratory Study of Factors Influencing Glaucoma Treatment Adherence. J Glaucoma 2010;19:66-72.
48. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational Interviewing: A Systematic Review and Meta-Analysis. The British journal of general practice : the journal of the Royal College of General Practitioners 2005;55:305-12.
49. Rees G, Chong XL, Cheung CY, et al. Beliefs and Adherence to Glaucoma Treatment: A Comparison of Patients from Diverse Cultures. J Glaucoma 2014;23:293-8.
50. Kangovi S, Mitra N, Grande D, et al. Patient-Centered Community Health Worker Intervention to Improve Posthospital Outcomes: A Randomized Clinical Trial. JAMA Internal Medicine 2014;174:535-43.

51. Sleath B, Slota C, Blalock SJ, et al. Provider Use of Collaborative Goal Setting with Glaucoma Patients. Optom Vis Sci 2014;91:549-55.
52. Gillmann K, Hoskens K, Mansouri K. Acute Emotional Stress as a Trigger for Intraocular Pressure Elevation in Glaucoma. BMC Ophthalmol 2019;19:69-69.
53. Kennedy HP. Enhancing Delphi Research: Methods and Results. J Adv Nurs 2004;45:504-11.

GROUP-BASED TRAJECTORY MODELING OF PATTERNS OF MEDICATION ADHERENCE IN GLAUCOMA

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In preparation for *Ophthalmology*

Format adapted for dissertation

Abstract

Objective: To identify and characterize patterns of medication adherence in glaucoma.

Design: Prospective cohort study

Participants: Seventy-two patients enrolled in an NIH-funded glaucoma progression study at the University of Alabama at Birmingham were included. Participants were included if they were above age 18, used hypotensive eyedrops, had at least 2 reliable visual field tests, had visual acuity better than 20/40 at baseline, and had at least 14 months of adherence data.

Methods: Daily adherence to hypotensive eyedrops was measured with Medication Event Monitoring Systems (MEMS) and expressed as mean weekly adherence. Mean weekly adherence data were fit with cubic polynomial functions to estimate trajectory models with 2, 3, 4, 5, and 6 adherence trajectory groups.

Main Outcome Measures*:* Longitudinal patterns of medication adherence

Results: We observed 4 trajectory groups: Near-perfect adherence (51.8%) Good adherence (23.2%), Declining adherence (18.1 %), and Poor adherence (6.9%). Higher illness perception scores negatively predicted membership in the Good ($P = 0.044$) and Declining adherence groups ($P = 0.041$). In the logit model, non-Black race positively predicted membership in the Adherent vs non-Adherent group ($P < .001$).

Conclusions: We identified 4 distinct patterns of adherence: Near-perfect, Good, Declining, and Poor. It is important to characterize patterns of medication adherence as this may provide deeper insight into its complex nature. Identified predictors of each

pattern can be used to tailor interventions to the patients in greatest need of and most likely to benefit from them.

Key words: Glaucoma, Adherence, Patterns, MEMS, Medication

INTRODUCTION

In glaucoma—the leading cause of irreversible blindness worldwide[1]—hypotensive eyedrops that lower intraocular pressure (IOP) and delay glaucomatous progression[2] are the preferred treatment modality for a majority of patients. While studies have reported medication adherence rates as high as 97%,[3-7] adherence to prescribed therapy is often suboptimal.[8] Additionally, the use of summary metrics such as mean adherence may not adequately capture the complexity of adherence behavior as important trends such as drug holidays may go undetected. This limitation is evinced by studies identifying discrete patterns of medication adherence through descriptive and statistical analysis.[3, 9] Analyzing patterns of medication adherence is an important area of research as this analysis might reveal shared characteristics among patients who follow similar patterns.

Group-based Trajectory Modeling (GBTM) is a statistical technique for clustering individuals who follow similar developmental or behavioral trajectories.[10-12] GBTM has been applied in conditions such as cancer,[13] hypertension,[14] and heart disease [15] to identify patients with similar treatment outcomes. The technique has also been applied in glaucoma to identify patterns of medication adherence in claims data.[16] Claims data provide information on medication availability and gaps in therapy,[17] but do not provide information about daily utilization of medications. In contrast, electronic monitors

capture this more granular data. In this study, we aimed to identify patterns of medication adherence by performing GBTM in electronically monitored adherence data. We also used GBTM to identify predictors of each adherence pattern. Identifying shared attributes of patients in each adherence group can allow researchers to improve targeting of existing interventions to patients in greatest need of them and most likely to benefit from them.

METHODS

Study Participants

Ancillary adherence data obtained from patients enrolled in an NIH-funded longitudinal study on glaucoma progression (NIH grant EY025756) at the University of Alabama at Birmingham (UAB) were used for analysis. Study approval was obtained from the UAB Institutional Review Board. All aspects of this study followed HIPAA regulations and adhered to the tenets of the Declaration of Helsinki. At baseline, participants in the parent study were required to be above age 18, have a diagnosis of primary open-angle glaucoma, visual acuity better than 20/40, mean deviation (MD) better than -12 dB on a reliable visual field test, and spherical and cylindrical refraction within 5D and 3D, respectively. Visual field testing was performed with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) using the 24-2 pattern and the Swedish Interactive Thresholding Algorithm. Participants with a history of secondary glaucoma, diseases affecting the visual field, intraocular surgery (except uncomplicated cataract or glaucoma surgery), or cognitive impairment were excluded. Additionally, participants had to be using ocular hypotensive eyedrops and had to have at least 14 months of data after their baseline visit be included in the analysis. We analyzed data collected between July 2018 and June 2021.

Medication Adherence

In the parent study, adherence was electronically recorded using Medication Event Monitoring Systems (MEMS) caps manufactured by Aardex (Liège, Belgium). Patients were given one MEMS device for each prescribed eye medication, and were instructed to store their eyedrops inside the MEMS bottle. Patients were informed that the MEMS caps recorded the date and time at which the devices were opened, and were instructed to use their eyedrops as normal. During research visits, data from the MEMS caps were uploaded into MedAmigo—a web platform for data analysis and visualization. The MEMS caps were not equipped with LCD displays, and patients did not receive reminders or feedback on their adherence. Daily adherence was calculated using the formula $\frac{Number\ of\ doses\ taken}{Number\ of\ doses\ prescribed}\ X\ 100\%$. No penalties were applied for overdosing (taking doses that exceed the prescribed number) and extra doses were not included in the calculations. As a result, the minimum and maximum values for adherence were 0.0 and 100, respectively. For patients with multiple eyedrops, a daily rate was calculated per eyedrop and averaged across the total number of eyedrops. Adherence data for the first two months were excluded from analysis as we allowed patients to revert to normal behavior during this time.[17, 18] The remaining 12 months of daily adherence data were averaged over every 7-days to yield 52 datapoints corresponding to 52 weeks.

Trajectory Modeling

In GBTM, trajectories are identified from the underlying data. The probability of belonging to each group is modeled as a multinomial logistic regression and participants

are assigned to the group for which they have the highest probability of belonging.[14] We considered a censored normal (cnorm) trajectory model to be most appropriate as our data were continuous and censored by maxima (100) and minima (0.0). Although the data were not normally distributed, they were best fit by a cnorm model compared to the zero-inflated and logit models, which are better suited to Poisson and Bernoulli distributions, respectively. We used the *traj* command in Stata 16.0 (College Station, TX) to fit 52 data points of mean weekly adherence data with polynomial functions in order to estimate cnorm models with 2, 3, 4, 5, and 6 trajectory groups.[19]

The Bayesian Information Criterion (BIC) is a measure of the trade-off between model fit and model complexity. Improved fit from adding more trajectory groups or higher order polynomial functions is rewarded while increased complexity from these added parameters is simultaneously penalized.[20, 21] Lower BIC absolute values indicate better model fit. We used cubic functions for trajectory modeling as they fit the raw data in the most analytically tractable manner and yielded a small (0.8%) increase in BIC relative to quadratic functions.[22] As dichotomized adherence is clinically useful,[23] we also estimated a Logit model with two adherence trajectories. Based on current literature,[13, 24] we used an 80% threshold to distinguish between adherence (1) and non-adherence (0).

Model Selection

The model with the lowest BIC was preferred. As BIC tends to favor more parsimonious models, an additional metric—Bayes factor—was used to determine what

constituted a meaningful improvement in BIC with the incremental increase in the number of groups.[20] For two models with different numbers of trajectory groups, Bayes factor (B_{10}) is the ratio of the probability that model 0 (two groups) is the correct model to the probability that model 1 (three groups) is the correct model. Based on previous work in GBTM,[12, 25] we did not use the Bayes factor, but used the BIC - log Bayes factor approximation to assess improvements in model fit. Two multiplied by the change in BIC (model 1 BIC - model 0 BIC) approximates twice the natural logarithm of the Bayes factor ($2\ (\Delta BIC) \approx 2 \log_e (B_{10})$). This metric has been found to be valid for testing the number of components in growth mixture modeling.[25] Values greater than 6 indicate strong evidence against the null model (model 0).

Model selection was also moderated by the following criteria: having an average posterior probability of group membership above 0.7 for each group,[10] odds of correct classification above 5, for each group,[20] at least 5% of participants in each group,[12] and having the highest number of clinically meaningful groups.[15] An average posterior probability close to 1 suggests that individuals are assigned to trajectory groups with little ambiguity, and odds of correct classification greater than 1 indicate that the odds of correct group classification are greater than those attained by random chance.[20] To identify the model with the highest number of clinically meaningful groups, we referenced glaucoma literature [3, 9, 16] and sampled a panel of eight optometrists and ophthalmologists with 18.5 ± 9.5 years of experience treating glaucoma.

Covariates

After selecting the optimal model, we added predictors to determine their influence on group membership. Based on documented predictors of adherence,[24, 26-29] we included the following: education level, self-reported race, age, number of comorbidities, marital status, employment level, income level, regimen complexity, medication self-efficacy, eyedrop self-efficacy, and illness perception. Medication self-efficacy and eyedrop self-efficacy were assessed with the Glaucoma Medication Self-Efficacy and Glaucoma Eyedrop Self-Efficacy Scales, respectively.[30] Illness perception was measured with the Brief Illness Perception Scale (BIPQ).[31] We operationalized regimen complexity as the number of daily eyedrop instillations multiplied by the number of prescribed ocular medications.[32] Covariates were modeled separately, and significant covariates were included in the final cnorm and logit trajectory models.

RESULTS

A total of 72 participants were included in our analysis. Patient characteristics are reported in Table 1. Mean age was 68.9 years (95% CI: 67.2 – 70.6) and median adherence was 97% (95% CI: 0.85 – 0.97). The study population was 52.7% female, and 51.5 % of patients self-reported as being White. Median number of comorbidities was 3.0 (95% CI: 2.0 – 3.0), with hypertension (71%), hyperlipidemia (51%), and Type 2 diabetes (28%) being the most common. Median eyedrop self-efficacy score was 18.0 (95% CI: 17.0 – 18.0) (maximum score = 18) and median medication self-efficacy score was 25.5 (95% CI: 23.0 – 27.0) (maximum = 30). Higher scores indicate higher perceived ability. Median glaucoma illness perception score was 30.0 (95% CI: 27.0 – 33.0) (maximum = 80), indicating a less daunting outlook on glaucoma.

Table 1

Demographic and Clinical Characteristics of Participants (N= 72)

Study variable	Mean (95% Confidence Interval)
Age (years)	68.9 (67.2 – 70.6)
Gender	Percentage (%)
Female	52.7
Male	47.3
Comorbidities	Percentage (%)
Hypertension	71
Hyperlipidemia	51
Type 2 diabetes	28
Race	Percentage (%)
Caucasian race (White)	51.5

African race (Black)	47.2
Asian	1.3
Highest education level	Percentage (%)
High school	12.8
Some college (Bachelor's degree)	68.1
Graduate or professional degree	19.1
Employment level	Percentage (%)
Employed	54.2
Unemployed	45.8
Marital status	Percentage (%)
Unmarried	58.3
Married	41.7
Income level	Percentage (%)
Less than $40, 000	21.3
$40-$80, 000	27.7
$80-$99, 000	8.5
More than $100, 000	8.5
Not reported	34
Clinical variables	Median (95% Confidence Interval)
Number of ocular medications	1.0 (1.0 – 2.0)
Regimen complexity	2.0 (1.0 – 4.0)
Number of comorbidities	3.0 (2.0 – 3.0)
Medication self-efficacy score	25.5 (23.0 – 27.0)
Eyedrop self-efficacy score	18.0 (17.0 – 18.0)
Illness perception score	30.0 (27.0 – 33.0)
Median adherence	0.97 (0.85 – 0.97)

Table 2 provides the BIC, Bayes Factor, and group percentages for the cnorm and logit models. Figure 1 (panels A to F) shows the trajectories modeled by the logit and cnorm models. All groups had membership > 5%, odds of correct classification > 5, and average posterior probability > 0.70. The 6-group model had the lowest BIC (-816.9). However, based on research literature,[3, 9, 16] the 4-group model (Fig.1, panel D) was considered to have summarized the data in the most parsimonious and clinically useful way.[3, 9, 16] This model estimated 4 groups which we described as follows: Group 4 (gold trace) – Near-perfect adherence (51.8%), Group 3 (green trace) - Good adherence (23.2%), Group 2 (maroon trace) - Declining adherence (18.1%), and Group 1 (navy trace) - Poor adherence (6.9%). The 2-group logit model (Fig.1, Panel A) estimated the

following: Group 2 - Good adherence (64.6%) and Group 1 - Poor adherence (35.4%). Notably, the majority of clinicians (62.5%) identified the 3-group model as being most clinically useful.

Table 2

Trajectory Model Parameters and Group Percentages

Number of Groups	BIC	Bayes Factor	Group percentages (%)					
			Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
2*	-1649.0	-	35.4	64.6	-	-	-	-
2	-1660.8	-	37.2	62.8	-	-	-	-
3	-1137.7	523.1	9.7	26.3	64	-	-	-
4	-1003.9	133.8	6.9	18.1	23.2	51.8	-	-
5	-882.6	121.3	6.9	18.0	12.4	26.4	36.3	-
6	-816.9	65.7	6.9	12.5	7.3	10.4	26.5	36.4

Logit model*

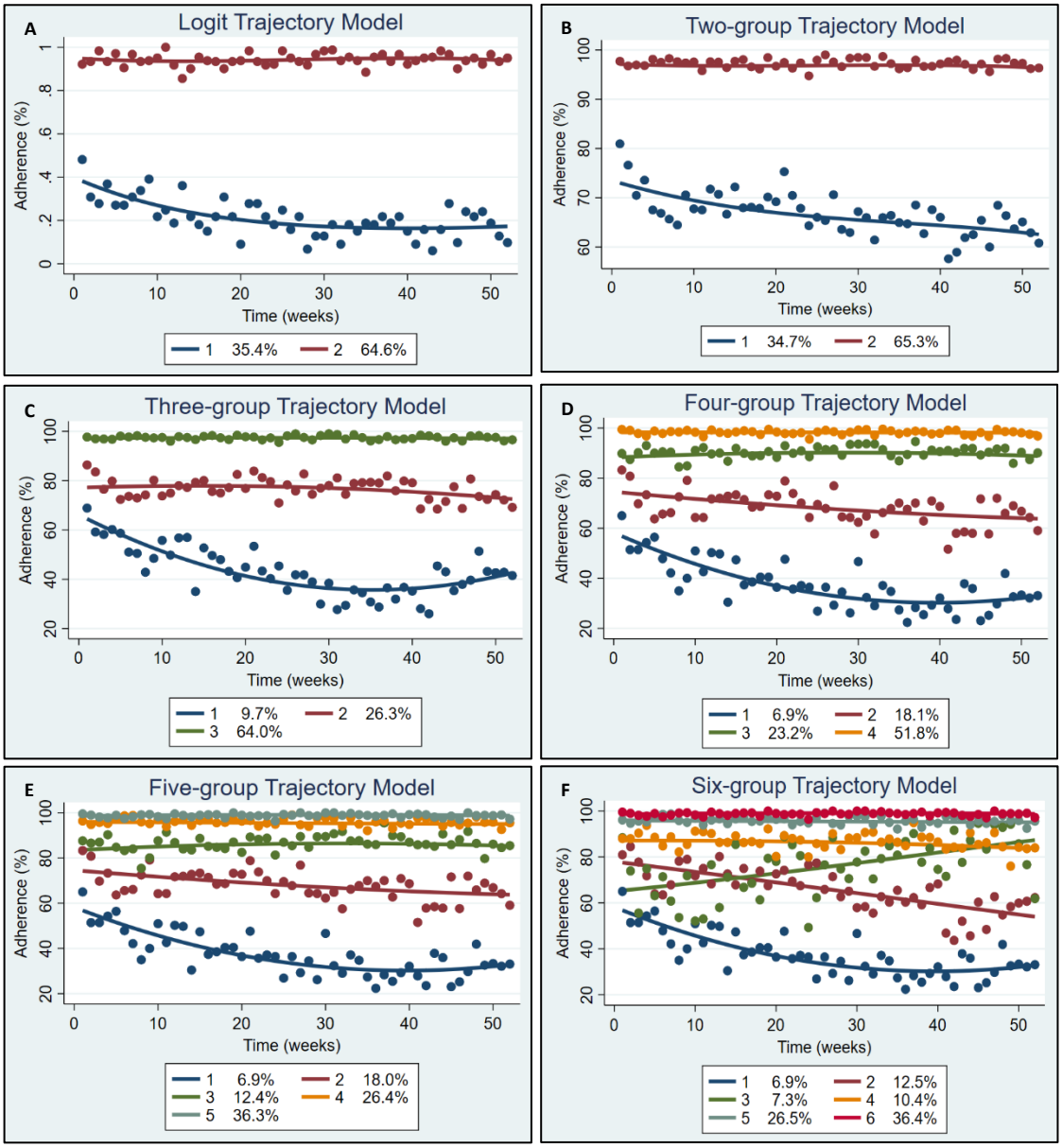

Figure 1**.** Trajectories identified over 52 weeks using GBTM. Logit model (A). Cnorm models (B-F). Percentages indicate group prevalence. 4 = Near-perfect adherence, 3 = Good adherence, 2 = Declining adherence, 1 = Poor adherence

Tables 3 and 4 show the contribution of predictors to group membership in the cnorm and logit models, respectively. Coefficient estimates represent the log-odds of being in each adherence group per unit increase in the value of the risk factor. Higher illness perception scores negatively predicted membership in the Declining (P = 0.041) and Good (P = 0.044) adherence groups. In the logit model, non-Black race positively predicted membership in the Adherent vs non-Adherent group (P < .001).

Table 3

Predictors of Adherence Patterns in the 3-group Cnorm Model

GROUP	VARIABLE	ESTIMATE	STD ERROR	T-VALUE	P-VALUE
2	Constant	6.4304	5.7098	1.126	0.2602
	Education	1.8454	1.8291	1.009	0.3131
	Number of comorbidities	-0.3428	0.5782	-0.593	0.5533
	Illness perception score	**-0.2147**	**0.1051**	**-2.041**	**0.0413**
3	Constant	7.3491	5.6269	1.306	0.1916
	Education	1.4765	1.8042	0.818	0.4132
	Number of comorbidities	-0.3514	0.5666	-0.620	0.5352
	Illness perception score	**-0.2089**	**0.1038**	**-2.012**	**0.0443**
4	Constant	9.0254	5.5217	1.635	0.1022
	Education	1.0538	1.7702	0.595	0.5517
	Number of comorbidities	-0.5590	0.5542	-1.009	0.3132
	Illness perception score	-0.1917	0.1011	-1.895	0.0582

Reference group: Group 1—Poor adherence. Bolded items are significant predictors.

Table 4

Predictors of Adherence Patterns in the 2-group Logit Model

GROUP	VARIABLE	ESTIMATE	STD ERROR	T-VALUE	P-VALUE
2	Constant	-2.3016	0.8294	-2.775	0.0056
	Race	**1.9931**	**0.5640**	**3.534**	**0.0004**

Reference group: Group 1—Non-adherence. Bolded items are significant predictors.

DISCUSSION

We used GBTM to identify patterns of glaucoma medication adherence in a sample of 72 patients with electronically monitored data. We observed four patterns: Near-perfect, Good, Declining, and Poor adherence. Higher illness perception score negatively predicted membership in the Good and Declining adherence groups. In the Logit model, non-black race positively predicted membership in the Adherent versus non-Adherent group. Of note was clinicians' preference for the three-group model (62.5% of votes), which likely reflected their preference for a simple and straightforward system for categorizing adherence behavior.

Our finding that higher illness perception score positively predicted membership in the Poor adherence group was surprising. We hypothesized that a more daunting view of glaucoma would spur patients into action and facilitate higher adherence. We did not find this association in our study. An alternative hypothesis is that patients with a more daunting view of glaucoma may experience greater levels of psychological stress. These patients may use maladaptive coping strategies such as denial, leading to periods of poor adherence. In support of this line of thought, Jiang et al. (2017) reported that illness perception score was negatively associated with medication adherence.[33]

Our finding that non-Black race predicted higher levels of adherence parallels literature in glaucoma identifying persons of Black race as being at greater risk for poor

or non-adherence.[24] Race has been described as a pseudo-variable, with researchers arguing that it is a social construct representing the complex interplay of socioeconomic, psychological, and cultural factors, rather than biological factors.[34] Thus, the effect of Black race on adherence in our study can likely be attributed to the impact of these factors within the context of systemic racial inequality in the United States. A study by Shen et al. (2018) found that Black patients experienced poorer communication quality and clinical decision-making compared to White patients.[35]

The sole other GBTM study in glaucoma plotted MPR over four years and identified five trajectories: Good, Moderate, Declining, Poor, and non-Adherence after index prescription.[16] Compared to this study, we did not identify a Moderate adherence group. This may be due to the subjective descriptions of the adherence patterns. During the monitoring period, a subset of participants had moderate adherence rates (above 50%). However, due to the trend of declining adherence, we opted to define this pattern as Declining. Additionally, we did not identify a "non-Adherent after index prescription" group as no newly diagnosed patients were included in our study.

We identified one group not described in the aforementioned study: Near-perfect adherence. This was likely due to the granularity of electronically monitored data, which facilitated better discrimination between patients with Good and Near-perfect adherence. Studies using electronic monitoring have also identified patient subgroups with near-perfect adherence, defined as "Adherence over 97%." [3, 36] Despite having less granularity than electronic monitoring, pharmacy databases have the advantage of unobtrusively collecting longitudinal data—an advantage in patients with poor adherence who may be

less willing to participate in research. Thus, combining data from multiple sources may provide greater insight into the complex and dynamic nature of medication adherence.

In this study, 22% of patients had some of their data collected during the COVID-19 pandemic. As research indicates that glaucoma medication adherence was affected during the pandemic,[37, 38] we were concerned about how this may have affected the identified trajectories. We performed supplemental analysis on data collected prior to March 13, 2020, as this was the date of the COVID-19 Emergency Declaration. The dataset was truncated at 16 weeks, which was the longest period in which all participants had pre-COVID data. The same trajectories were identified at 16 weeks as those identified using the full follow-up period (Figure 2). Approximately 80% of patients placed in a trajectory group at 16 weeks remained in this group at 52-weeks.

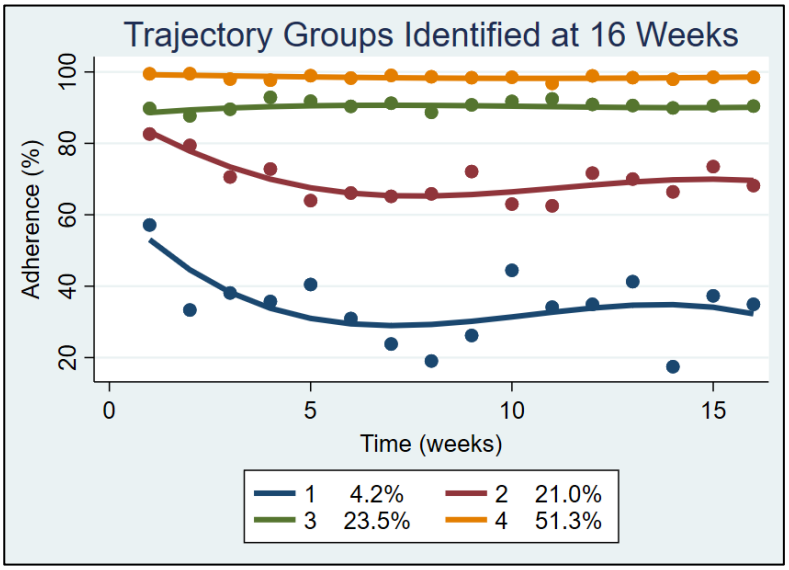

Figure 2. Trajectories identified at 16 weeks. Percentages indicate group prevalence. 4 = Near-perfect, 3 = Good, 2 = Declining, 1 = Poor adherence.

In the GBTM study by Newman-Casey et al. (2015),[16] patients with over 70% adherence during their first year of treatment were less likely to have a significant decline in adherence over the next three years. Taken together with our result, this finding highlights the stability of trajectory groupings as well as the potential utility of GBTM in predicting future adherence based on current trajectories.

Although interventions for improving medication adherence in glaucoma are abundant, identifying a preeminent approach has been difficult, given the diversity of treatment needs and barriers in the patient population.[39] However, characterizing patterns of medication adherence may allow investigators to identify shared treatment needs among patients with similar patterns. For instance, patients with Poor and Declining adherence may primarily be challenged by barriers such as treatment costs or even denial of glaucoma. These patients may be better served by interventions such as motivational interviewing which are designed to combat feelings of ambivalence and self-doubt. Patients with moderate adherence may instead struggle with busy schedules, forgetfulness, or competing activities, and may benefit more from reminders and structured routines. A deeper understanding of how adherence is shaped by social, economic, and behavioral factors may allow clinicians and researchers to proactively introduce interventions to patients with the greatest need for them.

This GBTM study helped to characterize adherence subgroups within the glaucoma population and has several strengths, the foremost being that GBTM was performed on data obtained through objective monitoring, which provides a more proximal measure of adherence behavior. A drawback of this approach is that electronic monitors are susceptible to the Hawthorne effect, where behavior changes when persons

are aware of observation.[17] However, exclusion of the first two months of adherence data likely mitigated this effect. An additional strength was the use of 52 measurements of the outcome variable—mean weekly adherence. As GBTM is best suited to averaged data that change as a smooth function of time, our robust dataset helped to improve model fidelity and prediction accuracy.

However, this study is not without limitations, which include small sample size, and the exclusion of participants with MD worse than -12dB. GBTM has been performed in samples ranging from 41 to 25,000 patients.[14, 15, 40, 41] Larger samples allow the GBTM procedure to better detect subgroups that represent small portions of the population. However, the granularity of the data likely compensated for the small sample size. By contrast, the exclusion of patients with severe visual field damage may have influenced our findings as worse visual field damage has been associated with worse adherence.[29] These patients' adherence patterns were not represented in our sample, potentially affecting the identified trajectories and the proportion of patients placed into each trajectory group.[29] A final limitation inherent to the GBTM procedure itself is that it may identify additional groups in order to accommodate non-normality in the data,[42] although researchers have demonstrated that multi-group models can be determined through the use of the BIC even when the data are not normally distributed, skewed, or kurtotic.[43]

It should be noted that researchers should not automatically assume that trajectory groups have substantive meaning. Nagin and Odgers (2010) caution against the quixotic quest to identify the "true" number of groups as trajectories are mere approximations of a more complex reality.[10] This is the first GBTM study in glaucoma to identify and characterize adherence patterns in electronically monitored data. We identified four

patterns: Near-perfect adherence, Good adherence, Declining adherence, and Poor adherence. Higher illness perception scores negatively predicted membership in groups with higher adherence. Performing this characterization is important, because rather than delivering broad interventions to patients with diverse needs, researchers can use their knowledge about patients to develop targeted interventions that better meet those needs.

REFERENCES

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121(11):2081-90.
2. 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. Archives of Ophthalmology 2002;120(6):701-13.
3. Cate H, Bhattacharya D, Clark A, et al. Patterns of adherence behaviour for patients with glaucoma. Eye (Lond) 2013;27(4):545-53.
4. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). Invest Ophthalmol Vis Sci 2007;48(11):5052-7.
5. Kumar JB, Bosworth HB, Sleath B, et al. Quantifying Glaucoma Medication Adherence: The Relationship Between Self-Report, Electronic Monitoring, and Pharmacy Refill. J Ocul Pharmacol Ther 2016;32(6):346-54.
6. Robin AL, Novack GD, Covert DW, et al. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. Am J Ophthalmol 2007;144(4):533-40.
7. Kass MA, Meltzer DW, Gordon M, et al. Compliance with Topical Pilocarpine Treatment. American Journal of Ophthalmology 1986;101(5):515-23.
8. Olthoff C, Schouten J, Borne B, Webers C. Noncompliance with Ocular Hypotensive Treatment in Patients with Glaucoma or Ocular HypertensionAn Evidence-Based Review. Ophthalmology 2005;112:953-61.
9. Ajit RR, Fenerty CH, Henson DB. Patterns and rate of adherence to glaucoma therapy using an electronic dosing aid. Eye (Lond) 2010;24(8):1338-43.
10. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol 2010;6:109-38.
11. Nagin DS. Group-based trajectory modeling: an overview. Ann Nutr Metab 2014;65(2-3):205-10.
12. Jones BL, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. Sociological Methods & Research 2001;29(3):374-93.
13. Shi Q, Mendoza TR, Gunn GB, et al. Using group-based trajectory modeling to examine heterogeneity of symptom burden in patients with head and neck cancer undergoing aggressive non-surgical therapy. Qual Life Res 2013;22(9):2331-9.
14. Paranjpe R, Johnson ML, Essien EJ, et al. Group-Based Trajectory Modeling to Identify Patterns of Adherence and Its Predictors Among Older Adults on Angiotensin-

Converting Enzyme Inhibitors (ACEIs)/Angiotensin Receptor Blockers (ARBs). Patient Prefer Adherence 2020;14:1935-47.
15. Elmer J, Gianakas JJ, Rittenberger JC, et al. Group-Based Trajectory Modeling of Suppression Ratio After Cardiac Arrest. Neurocrit Care 2016;25(3):415-23.
16. Newman-Casey PA, Blachley T, Lee PP, et al. Patterns of Glaucoma Medication Adherence over Four Years of Follow-Up. Ophthalmology 2015;122(10):2010-21.
17. Muir KW, Lee PP. Glaucoma medication adherence: room for improvement in both performance and measurement. Archives of ophthalmology (Chicago, Ill : 1960) 2011;129(2):243-5.
18. Cook P, Schmiege S, McClean M, et al. Practical and analytic issues in the electronic assessment of adherence. West J Nurs Res 2012;34(5):598-620.
19. Jones BL, Nagin DS. A Stata Plugin for Estimating Group-Based Trajectory Models. 2012.
20. Niyonkuru C, Wagner AK, Ozawa H, et al. Group-based trajectory analysis applications for prognostic biomarker model development in severe TBI: a practical example. J Neurotrauma 2013;30(11):938-45.
21. Schwarz G. Estimating the Dimension of a Model. Ann Statist 1978;6(2):461-4.
22. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. Med Care 2013;51(9):789-96.
23. Jones JP, Fong DS, Fang EN, et al. Characterization of Glaucoma Medication Adherence in Kaiser Permanente Southern California. J Glaucoma 2016;25(1):22-6.
24. Dreer LE, Girkin C, Mansberger SL. Determinants of medication adherence to topical glaucoma therapy. J Glaucoma 2012;21(4):234-40.
25. Kass RE, Raftery AE. Bayes Factors. Journal of the American Statistical Association 1995;90(430):773-95.
26. Sayner R, Carpenter DM, Robin AL, et al. How glaucoma patient characteristics, self-efficacy and patient-provider communication are associated with eye drop technique. The International journal of pharmacy practice 2016;24(2):78-85.
27. Tsai JC. Barriers to Adherence With Glaucoma Therapy: Potential Relationships to Disease Progression. Adv Stud Ophthalmol 2007;4(3):72-5.
28. Rees G, Chong XL, Cheung CY, et al. Beliefs and adherence to glaucoma treatment: a comparison of patients from diverse cultures. J Glaucoma 2014;23(5):293-8.
29. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology 2011;118(12):2398-402.
30. Sleath B, Blalock SJ, Stone JL, et al. Validation of a short version of the glaucoma medication self-efficacy questionnaire. Br J Ophthalmol 2012;96(2):258-62.
31. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006;60(6):631-7.
32. Odegard PS, Carpinito G, Christensen DB. Medication adherence program: Adherence challenges and interventions in type 2 diabetes. J Am Pharm Assoc (2003) 2013;53(3):267-72.
33. Jiang H, Zhao L, Yang L, Cai HY. [Relationships among illness perceptions, medication beliefs and medication adherence in primary angle closure glaucoma patients]. Zhonghua Yan Ke Za Zhi 2017;53(2):109-14.

34. Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. JAMA 2019;322(2):113-4.
35. Shen MJ, Peterson EB, Costas-Muñiz R, et al. The Effects of Race and Racial Concordance on Patient-Physician Communication: A Systematic Review of the Literature. J Racial Ethn Health Disparities 2018;5(1):117-40.
36. Beckers HJ, Webers CA, Busch MJ, et al. Adherence improvement in Dutch glaucoma patients: a randomized controlled trial. Acta Ophthalmol 2013;91(7):610-8.
37. Subathra GN, Rajendrababu SR, Senthilkumar VA, et al. Impact of COVID-19 on follow-up and medication adherence in patients with glaucoma in a tertiary eye care centre in south India. Indian J Ophthalmol 2021;69(5):1264-70.
38. Racette L, Abu SL, Poleon S, et al. The impact of the COVID-19 pandemic on adherence to ocular hypotensive medication in patients with primary open-angle glaucoma. Ophthalmology 2021.
39. Zullig LL, Blalock DV, Dougherty S, et al. The new landscape of medication adherence improvement: where population health science meets precision medicine. Patient Prefer Adherence 2018;12:1225-30.
40. Choi C-W, Stone R, Kim K, et al. Group-Based Trajectory Modeling of Caregiver Psychological Distress Over Time. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 2012;44:73-84.
41. Kenyon CC, Gruschow SM, Quarshie WO, et al. Controller adherence following hospital discharge in high risk children: A pilot randomized trial of text message reminders. J Asthma 2019;56(1):95-103.
42. Muthén B. Latent Variable Analysis: Growth Mixture Modeling and Related Techniques for Longitudinal Data. 2004.
43. Bauer DJ, Curran PJ. Distributional assumptions of growth mixture models: implications for overextraction of latent trajectory classes. Psychol Methods 2003;8(3):338-63.

DEVELOPING A TAXONOMY OF EVIDENCE-BASED STRATEGIES FOR IMPROVING MEDICATION ADHERENCE IN GLAUCOMA

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In Preparation for *Journal of Glaucoma*

Format adapted for dissertation

Abstract

Purpose: Equivocal findings of interventions aiming to improve medication adherence in glaucoma stem in part from heterogeneity in intervention design, and diversity of patient needs and barriers. This ambiguity may be resolved by grounding the behavior change techniques (BCTs) used in adherence interventions in health theory and incorporating patient perspectives into the design of these interventions. In this study, we aim to 1) develop an evidence-based taxonomy of BCTs for improving medication adherence in glaucoma and 2) to assess the utility of the BTCs included in the taxonomy.

Methods: We performed a systematic literature review to identify studies that delivered interventions for improving medication adherence in glaucoma patients. We included only studies that used electronic monitoring and had a minimum follow-up duration of three months. For each study, we assessed risk of bias, effectiveness of the intervention, and the degree to which the intervention was grounded in health theory. We then isolated all BCTs delivered during the intervention, and invited a sample of patients and providers to assess them based on their utility in day-to-day management of glaucoma.

Results: Thirteen studies were included in this review. Study designs included randomized controlled trials (n = 8), prospective studies (n = 4), and one mixed-methods study. Five studies reported a significant improvement in medication adherence. No studies explicitly stated a reliance on health theory during intervention design. BCTs incorporated into the taxonomy included education, reminders, motivational interviewing (MI), health coaching, instillation skill training, and combination therapy vs polytherapy. Education, reminders, MI, and health coaching were most effective BCTs, and were

perceived as having the greatest utility in day-to-day management of glaucoma by patients and providers.

Conclusion: Education, reminders, MI counseling, and health coaching were the most effective and highly-scored BCTs. By being more intentional about use of health theory, researchers can improve the precision with which clinical priorities and major determinants of behavior change are targeted during intervention delivery.

Key words: glaucoma, interventions, adherence, taxonomy, health theory

INTRODUCTION

Primary open-angle glaucoma (POAG) is an optic neuropathy characterized by retinal damage, connective tissue remodeling and visual defects. Over 60 million persons globally live with glaucoma,[1] which is chiefly managed through ocular hypotensive therapy.[2] Due to its association with glaucoma progression,[3, 4] suboptimal adherence to prescribed therapy is a significant concern. In response, there has been a wealth of interventions aiming to improve medication adherence either by reducing barriers such as regimen complexity or by increasing motivators such as perceived treatment benefit. Many such interventions have demonstrated success.[5-9] However, there is a dearth of compelling evidence for the recommendation of any specific strategies.[10]

Interventions for improving adherence employ specific techniques in order to elicit behavior change—known as Behavior Change Techniques (BCTs). BCTs are varied in nature and range from text reminders,[11] to educational sessions [12] and positive affirmations. Interventions may therefore combine several different BCTs (complex interventions) or deliver a single BCT (simple intervention). Abraham and Michie (2008) argue that variability in intervention design may be resolved by linking BCTs to health theory.[13] Bartholomew et al. (2006) further argue that intentional reliance on health theory during intervention design may help to reveal associations in published literature that are obscured by ambiguous findings across interventions.[14] Thus, it is critical that BCTs be both effective and informed by health theory.

We aimed to create a taxonomy of BCTs by performing a systematic literature review of interventions aiming to improve adherence in glaucoma and assessing the degree to which they relied on health theory. As diversity in patient needs and values may also contribute to ambiguity in intervention results across study populations, incorporating patient preferences and provider expertise into intervention design may provide strong experiential support for the selection of techniques that are most effective and relevant to these groups.[15] Therefore, we invited glaucoma patients and providers to assess each BCT that was included in the taxonomy based on its utility in day-to-day management of glaucoma.

METHODS

Eligibility Criteria for Selected Studies

We restricted our review to studies that focused on the implementation phase of adherence, as opposed to the initiation (when patients fill their first prescription) and discontinuation phases (when patients end hypotensive therapy).[16] The implementation phase encompasses the entire period during which patients use prescribed medications, and describes the degree to which patient dosing corresponds to prescribed dosing.

To create the taxonomy, we reviewed literature databases and clinical registers, and identified studies that met our eligibility criteria. We included studies that delivered interventions for improving adherence in glaucoma patients. Studies were not limited to a particular design and the interventions they delivered could be simple or complex. Eligible studies were required to report a change medication adherence as the primary outcome. Additionally, we limited our review to studies that used electronic monitoring as this method provides the most objective assessment of adherence. Use of electronic monitors may initially lead patients to alter their adherence due to the knowledge that they are being monitored.[17] However, research suggests that two months may be sufficient for patients to return to baseline adherence.[18] Therefore, we required studies to have a minimum follow-up duration of three months.

Information Sources

Eligible studies were identified by searching the following registers and databases: Embase, Jstor, PubMed, Directory of Open Access Journals, Scopus, Science Direct, CINAHL, PsychInfo, SAGE journals, Cochrane Central Register of Controlled Trials, Meta Register of Controlled Trials, Clinical Trials.gov, and WHO International Clinical Trials Registry Platform.

Search Strategy

We used hedges to search databases and registers. Hedges are standardized search strategies that employ Boolean operators to improve retrieval of research evidence and clinical concepts related to the search topic. Appropriate hedges were identified from: Hedges - PubMed via LHL - Research Guides at University of Alabama - Birmingham (uab.edu). For databases that did not support advanced search structures, only key words were used. All databases were searched between November 2020 and March 2021, and no time restrictions were applied. Dissertations, abstracts, and gray literature sources (non-academic sources such as government and organizational reports) were excluded from the search.

Abstract Screening

Covidence—a systematic review tool (Veritas Health Innovation, Melbourne, Australia) was used to screen abstracts, perform full-text review, quality assessment, and data extraction. Records identified during literature review were imported into Covidence and duplicates were automatically deleted. Two reviewers (SP and LR) independently

screened abstracts. Any abstracts that did not meet eligibility criteria were not advanced to full-text review. The reference sections of review articles were also searched to identify additional eligible studies, which were then imported into Covidence for abstract screening. During full-text review, ineligible studies were excluded and the reason for their exclusion was documented. Reviewers were not masked to the names of the investigators, their affiliations, or the journal of publication. Disagreements between reviewers were resolved via discussion.

Quality Assessment

Studies were reviewed for risk of bias by two authors (SP and LR) using the Cochrane risk of bias assessment tool.[19] For each study, we assessed the degree to which bias was introduced due to inadequately performing the following:

1. Sequence generation: generating random sequences that specify how participants should be assigned to intervention or control groups.
2. Allocation concealment: preventing participants and trial personnel from knowing forthcoming group allocations.
3. Blinding of participants and personnel: ensuring that participants and trial personnel are unaware of current group allocation.
4. Blinding of outcome assessors: ensuring that individuals reporting and assessing study outcomes are unaware of group allocation.

We also assessed risk of bias due to the following:

5. Incomplete outcome reporting: failure to report study data for all outcomes.

6. Selective outcome reporting: failure to report all study outcomes

For each potential sources of bias, studies were identified as having high, low, or unclear risk. For studies with a randomized control trial (RCT) design, the risk from each potential source of bias was deemed "unclear" if the authors failed to report how it was addressed. For studies without an RCT design, risk of bias from sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors was deemed "low" by default. However, the methods sections of these studies were carefully reviewed in order to ensure that bias was not introduced based on their designs and the nature of their research question. In such cases, the risk of bias was adjusted to "unclear" or "high."

Data Extraction

Data were extracted in Covidence and reviewed for accuracy by the same two authors. Disagreements were resolved by discussion. The following were extracted for all studies: title, author, year, design, setting, location, inclusion criteria, exclusion criteria, sample size, primary and secondary outcomes, interventions delivered, and results.

Effectiveness of Interventions

We gathered empirical evidence of the effectiveness of each intervention. Effectiveness was operationalized as a significant improvement in either therapeutic coverage, adherence rate, number of administered doses, number of missed doses, or

number of nonadherent days. These metrics were all used to quantify adherence in the reviewed studies.

Theoretical Basis of Interventions

For each study, we assessed the theoretical basis of the interventions delivered. We reviewed the methods section to determine whether the authors explicitly provided theoretical evidence (health theories or theoretical constructs) for the design of the interventions.

Taxonomy of BCTs

For each intervention, we determined the BCTs that were delivered and listed them in the taxonomy.

Perceived Utility of BCTs

The taxonomy was used to develop a semi-structured questionnaire in which each BCT was described. Patients and providers were invited to provide experiential evidence and indicate the utility of each BCT in day-to-day management of glaucoma using a 4-point *Not Useful* to *Very Useful* Likert scale. Qualitative responses could also be provided in support of judgements. Patients using ocular hypotensive medication were drawn from an ongoing longitudinal study population (NIH grant EY025756) in which patients were required to have the following at baseline: be above age 18, have a diagnosis of POAG, have visual acuity better than 20/40, mean deviation better than -12dB, spherical and

cylindrical refraction within 5D and 3D, respectively. Patients with a history of secondary glaucoma, diseases affecting the visual field, intraocular surgery, or cognitive impairment were excluded. To ensure the diversity of our sample, patients were randomly selected from each of four previously identified adherence groups.[20] Groups included patients with patterns of near-perfect, good, moderate, declining, and poor adherence. Providers were recruited from the University of Alabama at Birmingham (UAB) School of Medicine, Department of Ophthalmology and Visual Sciences.

Assessing Treatment Compliance and Glaucoma Perspectives

The Glaucoma Treatment Compliance Assessment Tool (GTCAT)[21] was used to assess patient perspectives regarding different aspects of glaucoma treatment. Subscales of the GTCAT map onto constructs of the Health Belief Model (HBM). The HBM aims to predict behavioral intention based on seven key determinants of behavior change described by its constructs, namely perceived disease severity, perceived disease susceptibility, perceived treatment benefits, perceived treatment barriers, self-efficacy, cues to action, and individual factors.[22] The GTCAT uses a 5-point *Strongly Disagree* to *Strongly Agree* Likert scale to measure participants' experiences and perspectives relative to each HBM construct.

Data Collection and Analysis

All questionnaires were administered from September 2021 to October 2021. Patient questionnaires were administered in-person while providers used an anonymous survey link (Qualtrics, Provo, UT). Study approval was obtained from the UAB

Institutional Review Board, and all aspects of this study adhered to HIPAA regulations and the tenets of the Declaration of Helsinki. For each GTCAT subscale, Likert responses were converted to numerical values, with *Strongly Disagree* translating into 1 and *Strongly Agree* translating into 5. Scores were then averaged across the number of questions. Clinical and demographic data were also collected from patients' charts. Spearman's rho was used to assess the relationship between patients' demographic characteristics, GTCAT subscale scores, and perceived utility of each BCT.

RESULTS

Of the 118 studies identified during the literature search, only 13 were included in the review (Figure 1). Reasons for exclusion were failure to meet eligibility criteria (n = 62), duplicate records (n = 29), and insufficient follow-up duration (n = 7). As shown in Table 1, included studies had RCT (n = 8), prospective (n = 4), and mixed-methods designs (n = 1). All studies included patients who were prescribed ocular hypotensive therapy and had a diagnosis of POAG, normal tension glaucoma (NTG),[23, 24] or ocular hypertension (OHT).[6, 24-27] Two studies included patients with secondary glaucoma,[23, 28] and two others included glaucoma suspects.[25, 26] Interventions delivered a single one of the following or a combination: glaucoma education, dosing aides, instillation skill training, eyedrop guides, reminders, combination vs polytherapy, personalized health plans, health coaching, and health counseling, specifically MI counseling—a health counseling technique that employs a gentle and guiding approach to help patients resolve ambivalence and develop plans for achieving treatment goals.[26, 28-30]

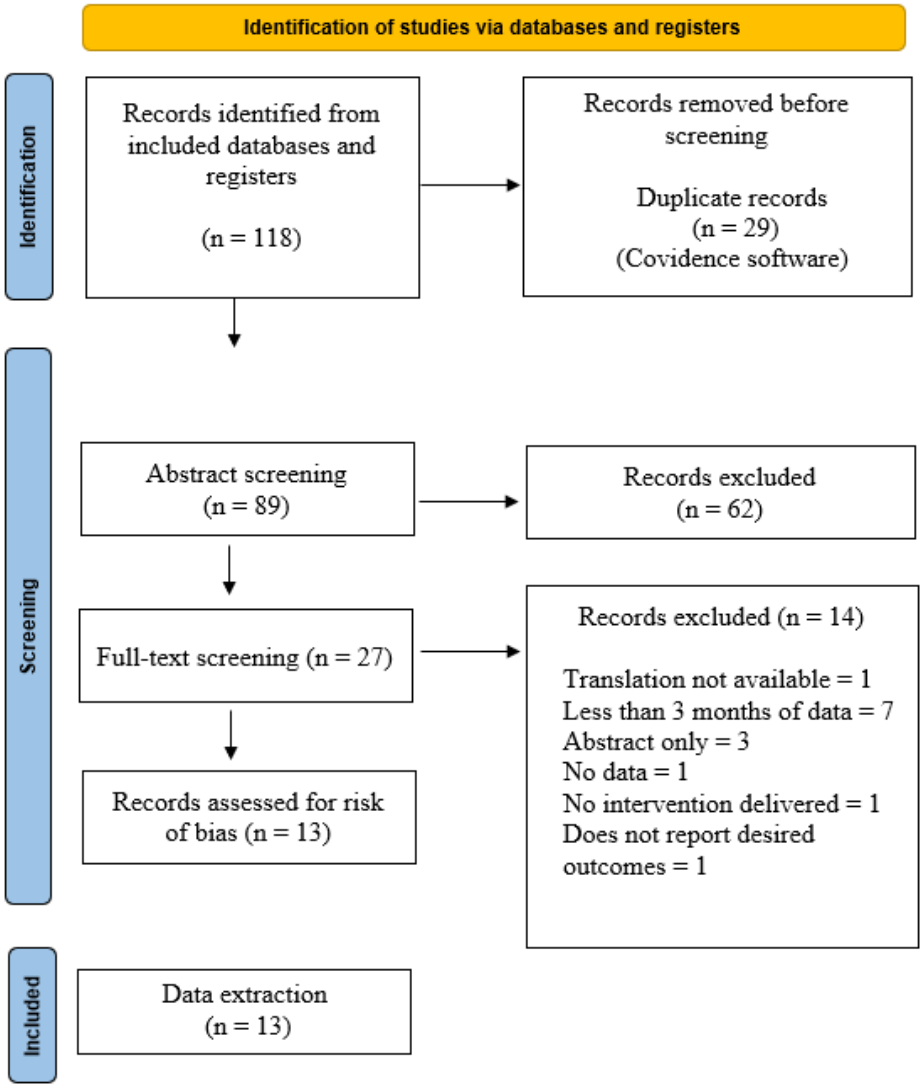

Figure 1. PRISMA diagram showing the number of screened, excluded, and included studies.

Empirical evidence

Five studies reported a significant improvement in adherence.[7, 23, 25, 28, 31] Cook et al. (2010) reported an increase in the percentage of days on which medication was taken as prescribed after an intervention that delivered education and MI (P = 0.032).[28] In a later study, Cook at al. (2017) found that reminder calls led to an increase in adherence

compared to usual care (P = .005).[31] After an intervention delivering glaucoma education and reminders, Rosdahl et al. (2021) reported a significant difference in the proportion of doses taken on schedule (P = 0.0001).[23] Okeke et al. (2009) reported a similar finding after an intervention delivering health coaching, reminders, and alarms (P = .001).[25] In the final study, Boland et al. (2014) found that personalized phone reminders led to an increase in median adherence.[7]

Table 1

Design, Population, Interventions and Outcomes of Included Studies

Author	Design	Population	Sample size	Intervention	Control	Primary Outcome	Results
Barneby, 2017	12-month Randomized, controlled trial	Patients over 18 years old with POAG or OHT	81	Arm 1: Fixed combination (Travoprost 0.004%/Timolol 0.5%) Arm 2: Unfixed (Travoprost 0.004%, Timolol 0.5%)	NA	Change in percentage of participants who are adherent over 12 months	Non-significant differences
Beckers, 2013	6-month Multicenter randomized controlled clinical trial	Patients over 18 years old with POAG or OHT using travoprost 0.004% or the fixed combination timolol 0.5% travoprost 0.004%	805	Arm 1: TravAlert dosing aid Arm 2: TravAlert dosing aid and eyedrop guider Arm 3: TravAlert dosing aid, education Arm 4: TravAlert dosing aid, drop guider, education	NA	Change in adherence rate	Non-significant group differences
Boland, 2014	6-month Prospective study followed by	POAG patients over 18 years old using once-	491 enrolled; 70 randomized	Personalized reminders	Usual care	Change in percent adherence	Significant increase in adherence in intervention

	randomized intervention	daily prostagland in analogs					Group ($P < .05$)
Cate, 2014	8-month Randomize d controlled trial	Patients with a diagnosis of POAG, OHT or were glaucoma suspects	208	Education, MI	Usual care	Change in mean adherence	Non-significant difference (p = 0.47).
Cook, 2010	14-week Randomize d, parallel group design.	Patients with primary or Secondary open-angle glaucoma who were prescribed mono-therapy	12	Education, MI	Usual care	Change in percentage of days on which medication was taken as prescribed	Significant increase (T = 2.25, P = 0.032, β = 2.68)
Cook, 2017	12-week Randomize d Controlled Trial	POAG patients over 18 years old on mono-therapy or combina-tion drop.	201	Arm 1 Reminder calls Arm 2 MI	Usual care	Change in adherence rate	Reminders: Significant increase in adherence compared to usual care (P = .005)
Holló, 2008	6-month Prospective study	Glaucoma patients using once-daily 0.004% Travoprost	34	Travoprost audible alarm	NA	Change in non-adherence rate (ratio of non-adherent days)	Non-significant change (P= 0.059)
Lim, 2013	5-month Randomize d controlled trial	POAG patients over 18 years old with controlled glaucoma and on ocular hypotensive therapy	80	Education, Reminders, Instillation skill	Usual care	1) Change in adherence rate 2) Change in therapeutic coverage.	1) Non-significant group differences (P=0.134) 2) Non-significant group differences (P=0.6138)
Okeke, 2009	3-month Randomize d controlled trial	POAG, OHT, angle-closure glaucoma, or glaucoma suspect patients 18 years or older using topical prostagland in analogs	66	Education, health coaching, Reminders	Usual care	Change in medication adherence (proportion of scheduled doses taken)	Significant change in intervention group (P=.001)

Richardson, 2013	3-month prospective study	Patients over 18 years old with POAG, OHT or NTG receiving once-daily mono-therapy	26	Adult-centered glaucoma education	NA	Change in proportion of days with correct number of doses taken Change in percent adherence	Non-significant difference between pre and post adherence
Rosdahl, 2021	6-month Randomized parallel group study	Patients with POAG, NTG, pigment dispersion glaucoma, pseudo-exfoliation glaucoma, or combined mechanism glaucoma	200	Glaucoma education, Reminders,	Usual care	Change in proportion of prescribed doses taken on schedule.	Significant group differences (P = 0.0001)
Rossi, 2010	6-month prospective cohort study	POAG patients over 18 years old on ocular hypotensive therapy	56	Arm 1: T Travoprost Arm 2: TTFC Travoprost/ timolol fixed combination	NA	Change in percentage of adherent patients (> 90% adherence	Non-significant group differences.
Vin, 2015	6-month, mixed methods pilot study	POAG patients over 18 years, on hypotensive therapy	4	MI, health coaching	NA	Change in percent adherence	Non-significant improvement in adherence (n = 2)

Quality Assessment

Table 2 depicts the results of the quality assessment. Seven studies had low or unclear risk for all potential sources of bias. Four studies had high risk of bias from incomplete outcome reporting due to high study attrition (defined as loss of more than 20% of participants).[6, 7, 24, 28, 31] One study had high risk of bias from insufficient allocation concealment and blinding of participants, personnel, and outcome assessors.[32] This study was not an RCT, however physicians were aware of group allocation, and were required to provide subjective judgements of patients' adherence. The knowledge of group allocation could have biased their judgments. The final study was deemed to have high risk of bias due to selective outcome reporting.[23] However, this study is currently unpublished, and data were only available through a clinical trial register.

Table 2

Risk of Bias for Included Studies

AUTHOR	Sequence Generation	Allocation Concealment	Participant and Personnel Blinding	Blinding of Outcome Assessors	Incomplete Outcome Reporting	Selective Outcome Reporting
Barneby, 2017	Low	Unclear	Unclear	Unclear	Low	Low
Beckers, 2013	Unclear	Unclear	Low	Low	High	Low
Boland, 2014	Low	Unclear	Unclear	Unclear	High	Low
Cate, 2014	Low	Low	Unclear	Low	Low	Low
Cook, 2010	Low	Low	Low	Low	High	Low
Cook, 2017	Low	Low	Low	Low	Low	Low
Hollo, 2008	Low	Low	Low	Low	Low	Low
Lim, 2013	Low	Unclear	Unclear	Unclear	Low	Low
Okeke, 2009	Low	Low	Unclear	Unclear	Low	Low
Richardson, 2013	Low	Low	Low	Low	High	Low
Rosdahl, 2021	Unclear	Unclear	Unclear	Unclear	Low	High
Rossi, 2010	Low	High	High	High	Low	Low
Vin, 2015	Low	Low	Low	Low	Low	Low

Theoretical Evidence

No studies explicitly indicated a reliance on health theory during intervention design.

Taxonomy of BCTs

The following BCTs were included in the taxonomy: 1) education, 2) reminders, 3) health coaching for helping patients gain confidence when speaking with their doctor, discussing their preferences for treatment, and challenging the health system 4) instillation skill training, 5) health counseling for helping patients set treatment goals, as well as recognize and overcome barriers to optimal treatment, and 6) combination therapy vs polytherapy for reducing regimen complexity.

Patient and Provider Characteristics

Table 3 shows the clinical and demographic characteristics of patients and providers who evaluated the taxonomy of BCTs. For patients (n = 13), mean age was 70.8 years ± 8.8 and patients of Black race comprised 69.2% of the sample. Male and female gender were equally represented. Mean number of ocular medications was 1.4 ± 0.7 and median adherence was 74.2% (IQR = 44.3). Providers (n = 5) were predominantly male (80%), White (60%), and had a mean of 12.6 years' clinical experience. GTCAT subscale scores for patients are included in Table 3. Subscale scores have a maximum value of 5 and minimum value of 1. Higher scores indicate a more prominent role for the respective HBM construct in patients' lives.

Table 3

Patient and Provider Characteristics

Patients	**N = 13**
Age (years) , mean ± SD	70.9 ± 9.1
Female gender (%)	54
Race	Percentage (%)
Black	69.2
White	30.8
Highest education level	Percentage (%)
High school	15.4
Some college (Bachelor's degree)	69.2
Graduate or professional degree	15.4
Income level	Percentage (%)
Less than $40, 000	15.4
$40-$80, 000	53.8
$80-$99, 000	15.4
More than $100, 000	7.7
Not reported	15.4
Number of comorbidities	Percentage (%)
0 – 1	38.4
2 – 4	53.8
5 or more	7.7
Percent adherence, median, IQR	74.2, 38.9
Number of ocular medications, mean ± SD	1.4 ± 0.7
GTCAT subscale scores	Median (IQR)
Perceived beliefs	4 (1.0)
Perceived barriers	5 (0.0)
Cues to action	2.5 (1.1)
Self-efficacy	4.2 (0.5)
Perceived glaucoma severity	3 (0.5)
Perceived glaucoma susceptibility	4 (2.0)
Glaucoma knowledge	4.4 (0.85)
Providers	**N = 5**
Male gender (%)	80
Number of years' experience	12.6
Age group	Percentage (%)
25 to 34 years	40
35 to 44 years	20
45 50 54 years	20
55 to 64 years	20
Race	Percentage (%)
Race	60
Asian	20
Not reported	20

Experiential evidence: Perceived Utility of BCTs

Table 4 shows the utility scores for each BCT. For patients, education (median and IQR = 4.0, 0.25), health coaching (3.0, 1.0), and reminders (3.0, 2.0) were the highest-scored BCTs, followed by instillation skill training (3.0, 2.0), MI counseling (3.0, 2.0), and combination versus polytherapy (3.0, 2.0). Among providers, MI counseling (4.0, 0), reminders (3.7, 0.33), and education (3.5, 0.25) were the highest-scored, followed by combination therapy (3.0, 0), instillation skill training (2.5, 0.67), and health coaching (2.5, 0.67). Overall, education, MI counseling, reminders, and health coaching were perceived to have the greatest utility in day-to-day management of glaucoma. All interventions that led to a significant improvement in adherence delivered two or more of these BCTs.

Table 4

Taxonomy Of BCTs

BCT	Empirical evidence	Theoretical evidence	Experiential (Patients)	Experiential (Providers)	Patients' qualitative judgments
Education	Significant improvement of adherence in 3 out of 7 studies	None	Rank = 1 Median = 4.0	Rank = 3 Median = 3.5	"The program would educate me about glaucoma, how does it start, what kicks it off? can it be prevented?" "Make me be more aware earlier in treatment"
Health coaching	Significant improvement of adherence in 1 out of 1 study	None	Rank = 2 Median = 3.0	Rank = 5 Median = 2.7	"Many patients take at face value what a doctor says without question. If they understand something about it prior to the visit, they would be more apt to follow directions"

Reminders	Significant improvement of adherence in 4 out of 5 studies	None	Rank = 3 Median = 3.0	Rank = 2 Median = 3.7	"Sometimes our schedules are so full, we forget to administer the drops" "Either you will, or you won't. Repetition in routine everyday should be enough to take drops"
Instillation skill training	Significant improvement of adherence in 0 out of 2 studies	None	Rank = 4 Median = 3.0	Rank = 5 Median = 2.7	"It's useful because one would be able to know if they use too much medication or less because it was taken incorrectly" "I have no trouble with eye drops"
MI counseling	Significant improvement of adherence in 1 out of 4 studies	None	Rank = 5 Median = 3.0	Rank = 1 Median = 4.0	"I'm old and set in my ways" "Each person has their own method of handling medical issues. Explain the disease management and let the person learn how to cope with it"
Combination therapy versus polytherapy	Significant improvement of adherence in 0 out of 2 studies	None	Rank = 6 Median = 3.0	Rank = 4 Median = 3.0	"Any shortcuts that prove effective would help. "I would definitely be interested in a combination of eye drops. It gets very tedious applying multiple drops sometimes"

Patient Characteristics and Perceived Utility

Correlations between patient characteristics and utility scores are shown in Table 5. Higher glaucoma knowledge was associated with a preference for education (ρ = .603, P = .03), while higher perceived glaucoma severity was associated with a preference for reminders (ρ = .626, P = .02). Black race was associated with a preference for combination versus polytherapy (ρ = -.695, P = .008), as well as MI counseling (ρ = -

.603, P = .03). Higher perceived glaucoma severity (p = .754, P = .003) and lower education level (p = -.592, P = .03) were associated with a preference for instillation skill training. Higher perceived glaucoma severity (p = .754, P = .003) and lower education level (p = -.694, p = .03) were also associated with a preference for MI counseling.

Table 5

Correlation Values Between Patient Characteristics and Perceived Utility

	Education	Health coaching	Reminders	Instillation skill training	Combination therapy	MI Counseling
Perceived barriers	-.189	.170	-.395	-.060	.345	-.155
Perceived benefits	-.189	-.323	-.368	-.288	.161	-.321
Cues to action	-.263	-.172	-.395	-.204	.169	-.172
Glaucoma knowledge	.603*	.001	-.036	-.036	.160	-.017
Self-efficacy	.237	-.091	-1.00	-1.00	-.199	-.032
Perceived severity	.274	.348	.626*	.754**	.524	.754**
Perceived susceptibility	.241	.151	.258	.062	.036	.208
Age	.089	-.068	.157	.125	-.346	.000
Sex	.202	-.215	.000	-.110	-.086	-.215
Race	.000	-.237	-.486	-.545	-.695**	-.603*
Education Level	-.363	-.504	-.530	-.592*	-.193	-.694**
Income level	-.049	-.090	-.461	-.284	-.406	-.320
Adherence rate	-.185	-.241	-.419	-.404	.177	-.532

Significant correlation at .05 level* (two-tailed)
Significant correlation at .01 level** (two-tailed)

DISCUSSION

We aimed to develop an evidence-based taxonomy of BCTs for improving medication adherence in glaucoma, and identified education, reminders, health coaching, and MI counseling as being associated with an improvement in adherence.[7, 23, 25, 28, 31] These were also the most highly ranked BCTs by patients and providers. We found that patients with higher glaucoma knowledge preferred education, while reminders were preferred by patients with higher perceived glaucoma severity. Patients of black race preferred combination vs polytherapy and MI counseling, and patients with higher perceived glaucoma severity and lower income level preferred instillation skill training and MI counseling.

Seven studies delivered interventions that included education.[25, 6, 9, 23, 24, 26, 28] Education has demonstrated success in improving both medication adherence and medication persistence in glaucoma.[5, 33, 34] After delivering an adult-centered glaucoma education program, Richardson et al. (2013)[24] did not find an increase in adherence, but reported a significant increase in glaucoma knowledge. Both education level and disease knowledge play important roles in treatment as informed decision-making requires patients to be able to interpret technical clinical information. Research has identified two specific domains as pivotal to the success of educational interventions: knowledge of potential future vision loss [35] and knowledge about treatment efficacy.[36] In this analysis,

we found that patients with higher levels of glaucoma knowledge also had greater appreciation for glaucoma education as a BCT.

Six studies used reminders to improve medication adherence.[7, 9, 31, 37, 38, 39] Alarms and reminders have been lauded for their utility in helping patients to remember to use eyedrops,[40] particularly those with increased likelihood of non-adherence due to busy schedules or complex regimens. Interventions that delivered reminders were preferred by patients with higher perceived glaucoma severity. As the perceived threat posed by glaucoma increases, patients may be more willing to use memory aides to ensure that they maintain optimal adherence. Patients with higher perceived glaucoma severity also preferred instillation skill training, although it was not among the highest-scored BCTs. Devices such as the TravAlert dosing aide [6] have been used in research, albeit to varying degrees of success. Developing devices that successfully overcome the obstacles posed by dexterity and frailty in the elderly has been a challenge, and the devices themselves may be difficult to use. As a result, dosing aides are believed to play a minimal role in improving adherence for many patients.[41]

MI counseling was associated with improved medication adherence in one of four studies.[26, 28, 31, 42] Cook et al. (2010) found that MI counseling led to improved adherence as well as increased patient satisfaction and engagement—important determinants of adherence behavior.[31] Based on health models such as the Information-Motivation-Behavior skills model (IMB), MI counseling is believed to effect behavior change by improving motivation and self-perception while reducing perceived barriers.[43] Overall, MI counseling was prioritized by patients of black race, as well as those with higher perceived glaucoma severity and lower education level. As many patients of black race

and patients of lower income levels often experience systemic barriers to care, their interest in recognizing and overcoming habits that interfere with treatment is intuitive.

Evidence-based research and practice rely on patient experience and clinical expertise, as well as empirical and theoretical evidence.[15] While few studies in this review explicitly stated a reliance on health theory during intervention design, several BCTs addressed one or more constructs in health behavior theory. For instance, education likely influenced *perceived treatment benefits* and emphasized the consequences of poor adherence (HBM).[22] Reminders likely aided in the *reinforcement* of previously learned behaviors such as eyedrop instillation (Social Cognitive Theory, SCT).[44] By comparison, health coaching and MI counseling potentially delivered *processes of change* that helped patients to increase their motivation and improve adherence (Transtheoretical Model, TTM).[45] Health theories allow researchers to conceptualize complex behavioral phenomena by providing frameworks in which to interpret health behavior. Additionally, incorporating health theory into intervention design helps researchers to identify both gaps and merits of intervention design and delivery.[46]

It is surprising that no studies explicitly stated that researchers utilized health theory during intervention design. While most BCTs addressed at least one health theory or construct, being more intentional about incorporating health theories and models is likely to strengthen the interventions as they provide a scaffold for the design of complex interventions, and guide the allocation of research and clinic resources.[47] Outside of this review, several interventions in glaucoma have used health theories in their design. Newman-Casey et al. (2020) applied Self-Determination Theory (SDT) in the development of a personalized intervention for improving medication adherence,[48] and

SCT was used to develop interventions for improving healthcare engagement and medication adherence.[49, 50] The Theory of Planned Behavior (TPB) has also been used to identify principal determinants of medication adherence in glaucoma.[51]

Developing theory-informed taxonomies of BCTs can promote the faithful implementation and accurate replication of interventions, potentially improving their effectiveness.[52] While several taxonomies of BCTs exist across health conditions,[13, 52, 53] none are specific to glaucoma. Medication adherence in glaucoma is a complex behavior. As such, it is important to develop a keen understanding of the factors that influence it, as well as standardized accounts of effective BCTs for addressing these deterministic factors. However, mere understanding is not enough as patients with different demographic and clinical profiles may have different treatment needs and priorities. Addressing these differences through BCT selection may allow investigators to deliver tailored interventions that are more relevant to the patients in greatest need of them.

We aimed to compile the highest level of research evidence and therefore focused on studies that used electronic monitoring. As a result, studies delivering effective BCTs that used other assessment methods were excluded. We did not include self-report, as patients are known to overestimate adherence through this method.[17] However, claims data do not have this drawback, and are less limited by sampling bias than electronic monitoring due to the unobtrusive collection of adherence data.[54] Bilger et al. (2019) reported that issuing prescription rebates led to a significant increase in adherence, expressed in MPR.[55] Such incentives may be especially attractive to patients of lower socioeconomic backgrounds, who are also more likely to be non-adherent.[33] Real-time feedback through use of health apps and trackers may also help patients to identify and

correct patterns of poor adherence such as drug holidays.[56] Personal monitors with built-in reminders and displays may also be a promising commercial option in the future.

We incorporated patient and provider perspectives in the creation of a taxonomy of BCTs for improving adherence in glaucoma—one of several strengths of this study. Other strengths include the reduction of reactivity bias which was achieved by limiting our review to studies with three or more months of follow-up, and use of the most valid and reliable data possible, which was achieved by only including studies that used objective monitoring. This study is not without limitations, however. We did not perform a secondary search to identify studies that were published after our initial search, and therefore could have missed eligible studies. Additionally, because most of the studies delivered complex interventions, it was not possible to evaluate the effectiveness of individual BCTs. Thus, participants using the semi-structured instruments to provide assessments of utility were evaluating BCTs outside of the context in which they were delivered. Lastly, our sample size was small and demographically unrepresentative of the wider population. This was likely due to the non-uniform racial distribution of patients across the four adherence groups from which they were randomly selected. Our primary aim in collecting these data was not to perform inferential statistical analysis, but to assess preferences and perspectives regarding interventions for improving adherence from the populations who typically deliver or receive them—patients and providers.

In this study, we identified education, reminders, MI counseling, and health coaching to be most effective and useful in day-to-day management of glaucoma. Researchers should aim to develop interventions that are grounded in both empirical and theoretical evidence, and should also aim to deliver a combination of BCTs. Tailoring is

often necessary as BCTs that are effective or preferred in one population may not be equally so in another. By being more intentional about use of health theory, researchers can improve the precision with which clinical priorities and major determinants of behavior change are targeted during intervention delivery.

REFERENCES

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121(11):2081-90.
2. Newman-Casey PA, Woodward MA, Niziol LM, et al. Brand Medications and Medicare Part D: How Eye Care Providers' Prescribing Patterns Influence Costs. Ophthalmology 2018;125(3):332–9.
3. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology 2011;118(12):2398-402.
4. Rossi GCM, Pasinetti GM, Scudeller L, et al. Do Adherence Rates and Glaucomatous Visual Field Progression Correlate? Eur J Ophthalmol 2011;21(4):410-4.
5. Norell SE. Improving medication compliance: a randomised clinical trial. Br Med J 1979;2(6197):1031-3.
6. Beckers HJ, Webers CA, Busch MJ, et al. Adherence improvement in Dutch glaucoma patients: a randomized controlled trial. Acta Ophthalmol 2013;91(7):610-8.
7. Boland MV, Chang DS, Frazier T, et al. Automated telecommunication-based reminders and adherence with once-daily glaucoma medication dosing: the automated dosing reminder study. JAMA Ophthalmol 2014;132(7):845-50.
8. Dreer LE, Owsley C, Campbell L, et al. Feasibility, Patient Acceptability, and Preliminary Efficacy of a Culturally Informed, Health Promotion Program to Improve Glaucoma Medication Adherence Among African Americans: "Glaucoma Management Optimism for African Americans Living with Glaucoma" (GOAL). Curr Eye Res 2016;41(1):50-8.
9. Lim MC, Watnik MR, Imson KR, et al. Adherence to glaucoma medication: the effect of interventions and association with personality type. J Glaucoma 2013;22(6):439-46.
10. Zullig LL, Blalock DV, Dougherty S, et al. The new landscape of medication adherence improvement: where population health science meets precision medicine. Patient Prefer Adherence 2018;12:1225-30.
11. Pizzi LT, Tran J, Shafa A, et al. Effectiveness and Cost of a Personalized Reminder Intervention to Improve Adherence to Glaucoma Care. Appl Health Econ Health Policy 2016;14(2):229-40.
12. Gray TA, Fenerty C, Harper R, et al. Preliminary survey of educational support for patients prescribed ocular hypotensive therapy. Eye (Lond) 2010;24(12):1777-86.
13. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol 2008;27(3):379-87.

14. Bartholomew LK, Parcel GS, Kok G, Gottlieb N. Planning Health Promotion Programs: An Intervention Mapping Approach 2nd ed ed. San Francisco: Jossey-Bass, 2006.
15. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. BMJ 1996;312(7023):71-2.
16. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;73(5):691-705.
17. Litcher-Kelly L, Kellerman Q, Hanauer SB, Stone AA. Feasibility and utility of an electronic diary to assess self-report symptoms in patients with inflammatory bowel disease. Ann Behav Med 2007;33(2):207-12.
18. Cook P, Schmiege S, McClean M, et al. Practical and analytic issues in the electronic assessment of adherence. West J Nurs Res 2012;34(5):598-620.
19. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed) 2011;343:d5928-d.
20. Poleon S, Abu S, Thomas T, Racette L. Group-based trajectory modeling in electronically monitored adherence data in patients with glaucoma. Invest Ophthalmol Vis Sci 2021;62(8):1586-.
21. Mansberger SL, Sheppler CR, McClure TM, et al. Psychometrics of a new questionnaire to assess glaucoma adherence: the Glaucoma Treatment Compliance Assessment Tool (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2013;111:1-16.
22. Rosenstock IM. Historical Origins of the Health Belief Model. Health Educ Monogr 1974;2(4):328-35.
23. Rosdahl JA, Hein AM, Bosworth HB, et al. Randomized controlled trial of an education-based intervention to improve medication adherence: Design considerations in the medication adherence in glaucoma to improve care study. Clinical Trials 2021;18(3):343-50.
24. Richardson C, Brunton L, Olleveant N, et al. A study to assess the feasibility of undertaking a randomized controlled trial of adherence with eye drops in glaucoma patients. Patient Preference and Adherence 2013;7:1025-39.
25. Okeke CO, Quigley HA, Jampel HD, et al. Interventions improve poor adherence with once daily glaucoma medications in electronically monitored patients. Ophthalmology 2009;116(12):2286-93.
26. Cate H, Bhattacharya D, Clark A, et al. Improving adherence to glaucoma medication: a randomised controlled trial of a patient-centred intervention (The Norwich Adherence Glaucoma Study). BMC Ophthalmol 2014;14:32.
27. 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;176:61-9.
28. Cook PF, Bremer RW, Ayala AJ, Kahook MY. Feasibility of motivational interviewing delivered by a glaucoma educator to improve medication adherence. Clin Ophthalmol 2010;4:1091-101.
29. Abdull MM, Gilbert C, McCambridge J, Evans J. Adapted motivational interviewing to improve the uptake of treatment for glaucoma in Nigeria: study protocol for a randomized controlled trial. Trials 2014;15:149.

30. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners 2005;55(513):305-12.
31. Cook PF, Schmiege SJ, Mansberger SL, et al. Motivational interviewing or reminders for glaucoma medication adherence: Results of a multi-site randomised controlled trial. Psychol Health 2017;32(2):145-65.
32. Rossi GC, Pasinetti GM, Scudeller L, et al. Monitoring adherence rates in glaucoma patients using the Travatan Dosing Aid. A 6-month study comparing patients on travoprost 0.004% and patients on travoprost 0.004%/timolol 0.5% fixed combination. Expert Opin Pharmacother 2010;11(4):499-504.
33. Dreer LE, Girkin C, Mansberger SL. Determinants of medication adherence to topical glaucoma therapy. J Glaucoma 2012;21(4):234-40.
34. Djafari F, Lesk MR, Giguere CE, et al. Impact of a Brief Educational Intervention on Glaucoma Persistence: A Randomized Controlled Clinical Trial. Ophthalmic Epidemiol 2015;22(6):380-6.
35. Friedman DS, Hahn SR, Gelb L, et al. Doctor-patient communication, health-related beliefs, and adherence in glaucoma results from the Glaucoma Adherence and Persistency Study. Ophthalmology 2008;115(8):1320-7, 7.e1-3.
36. Lacey J, Cate H, Broadway DC. Eye (Lond) 2009;23(null):924.
37. Okeke CO, Quigley HA, Jampel HD, et al. Adherence with Topical Glaucoma Medication Monitored Electronically: The Travatan Dosing Aid Study. Ophthalmology 2009;116(2):191-9.
38. Boland MV, Chang DS, Frazier T, et al. Electronic monitoring to assess adherence with once-daily glaucoma medications and risk factors for nonadherence: The automated dosing reminder study. JAMA Ophthalmology 2014;132(7):838-44.
39. Holló G, Kóthy P. Can Adherence to Topical Glaucoma Medication be Improved by Using an Audible Alarm? Pharmaceut Med 2008;22(3):175-9.
40. Tsai JC. Barriers to Adherence With Glaucoma Therapy: Potential Relationships to Disease Progression. Adv Stud Ophthalmol 2007;4(3):72-5.
41. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int 2015;2015:217047.
42. Vin A, Schneider S, Muir KW, Rosdahl JA. Health coaching for glaucoma care: a pilot study using mixed methods. Clin Ophthalmol 2015;9:1931-43.
43. McGonagle AK, Beatty JE, Joffe R. Coaching for workers with chronic illness: evaluating an intervention. J Occup Health Psychol 2014;19(3):385-98.
44. Deci E, Ryan R. Intrinsic Motivation and Self-Determination in Human Behavior. Perspectives in Social Psychology1985.
45. Prochaska JO DC. The Transtheoretical Approach: Towards a Systematic Eclectic Framework Homewood, IL: Dow Jones Irwin, 1984.
46. Heath G, Cooke R, Cameron E. A Theory-Based Approach for Developing Interventions to Change Patient Behaviours: A Medication Adherence Example from Paediatric Secondary Care. Healthcare 2015;3(4):1228-42.
47. Amico KR, Mugavero M, Krousel-Wood MA, et al. Advantages to Using Social-Behavioral Models of Medication Adherence in Research and Practice. Journal of general internal medicine 2018;33(2):207-15.

48. 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;3(4):228-37.
49. Glanz K BA, Bundy L, Primo S, Lynn MJ, Cleveland J, Wold JA, Echt KV. Impact of a health communication intervention to improve glaucoma treatment adherence. Results of the interactive study to increase glaucoma adherence to treatment trial. . Arch Ophthalmol 2012;130:1252-8.
50. Sleath B, Davis SA, Carpenter DM, et al. Increasing Engagement of African American Patients with Glaucoma during Medical Encounters: Creation of a Pre-visit Video. Optom Vis Sci 2020;97(7):503-8.
51. Cook PF, Schmiege SJ, Mansberger SL, et al. Predictors of Adherence to Glaucoma Treatment in a Multisite Study. Ann Behav Med 2015;49(1):29-39.
52. Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013;46(1):81-95.
53. Susan Michie MMvS, Robert West. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implementation Science 2011(6):42.
54. Cate H, Bhattacharya D, Clark A, et al. A comparison of measures used to describe adherence to glaucoma medication in a randomised controlled trial. Clin Trials 2015;12(6):608-17.
55. Bilger M, Wong TT, Lee JY, et al. Using Adherence-Contingent Rebates on Chronic Disease Treatment Costs to Promote Medication Adherence: Results from a Randomized Controlled Trial. Appl Health Econ Health Policy 2019;17(6):841-55.
56. Hermann MM, Bron AM, Creuzot-Garcher CP, Diestelhorst M. Measurement of adherence to brimonidine therapy for glaucoma using electronic monitoring. J Glaucoma 2011;20(8):502-8.

CONCLUSION

Adherence behavior is determined by a myriad of personal, clinical, cultural, socioeconomic, and biological factors, making it a complex endeavor, particularly in chronic conditions such as glaucoma where medication must be taken for the duration of one's life. Perhaps as a reflection of this complexity, medication adherence in glaucoma is often suboptimal. For many patients, the ultimate cost of poor adherence is high—irreversible loss of vision, loss of independence, and psychological stress. For newly diagnosed and established patients without significant visual impairment, it is not too late to prevent such adverse outcomes. A thorough understanding of the factors that contribute to poor adherence can help researchers develop effective and well-designed interventions that appropriately target these deterministic factors.

Simply identifying the factors that negatively affect medication adherence is not sufficient because of the highly variable nature of treatment needs and barriers across the demographic, cultural, ethnic, and socioeconomic strata that comprise the patient population. Patient perspectives may differ considerably from those of the other major stakeholder in glaucoma treatment—providers. Without concordance between patients and providers, it can be difficult to achieve optimal management of glaucoma.

In the first of three research aims, I sought to identify both shared and unique values related to glaucoma treatment among patients and providers. The analysis revealed

concordance between patients and providers regarding several factors, namely the importance of perceived treatment efficacy, glaucoma knowledge, and good patient-provider relationship in day-to-day management of glaucoma. Barriers to optimal adherence were also identified, and included forgetfulness, psychological stress, and poor instillation skill. These shared values can serve as a launchpad for increased partnership and synergy between patients and providers, which may help to improve not only medication adherence but also healthcare engagement.

It is important to note that while both patients and providers identified socioeconomic and sociobehavioral factors, providers tended to recognize socioeconomic barriers to care such as treatment cost and transportation. By contrast, patients tended to recognize sociobehavioral facilitators of care such as social support and wanting good QoL. There is value in discordance, as juxtaposition of patient and provider perspectives could spotlight other underexplored areas and guide the development of effective and relevant interventions for improving medication adherence.

Even after shared clinical priorities between patients and providers are identified, translating them into interventions that are beneficial to all patients can be difficult as strategies that are effective for one patient population by ineffective or even irrelevant in another. Therefore, tailoring of interventions so that they adequately meet the needs of patient subgroups who are clinically, culturally, or economically distinct from each other is critical. In my second aim, I sought to highlight this diversity by using statistical modeling to identify distinct patterns of medication adherence in glaucoma patients. The data revealed four patterns: Near-perfect adherence, Good adherence, Declining adherence, and Poor adherence. Identifying these patterns is important because compared

to summary metrics of adherence, patterns can provide more meaningful insight into the dynamic nature of adherence and the factors that influence it.

Clinic visits and research studies only sample a small slice of patients' day to day lives. The collected data are static—a single number value standing in place of the complex function that is day-to-day adherence. For all their limitations, claims databases provide invaluable long-term data that are free from reactivity bias due to being unobtrusively collected, and allow a tiny glimpse into the reality of adherence behavior. Once patterns are identified, characterization of patients who follow similar patterns is needed because it may reveal shared needs and barriers related to care. These attributes may then be leveraged to develop interventions specific to these patient subgroups. For patients with declining adherence, barriers may be related to medication cost, denial of diagnosis, or insufficient understanding of the progressive nature of glaucoma. Rather than delivering broad interventions to patients with diverse needs, researchers can use their knowledge about shared attributes to successfully tailor interventions so that they better meet the needs of the target population.

While such interventions may be well-designed and well-meaning, if they do not appropriately identify the principal determinants of behavior change, they may be ineffective. This is most regrettable, given the investment of financial and personnel resources during intervention design and delivery. Health theories can help to identify antecedents of behavior, as well as inform the proper allocation of clinic and research resources. By incorporating health theory, interventions that are tailored to meet the needs of distinct patient subgroups can be more rigorous, focused, and effective.

Therefore, in my third and final aim, I sought to gather three levels of support which would help to identify the most effective strategies for improving medication adherence in glaucoma: evidential support gathered through empirical scientific research, theoretical support gained through reliance on health theory, and experiential support gathered through inclusion of patent and provider perspectives. Through literature review, I identified four strategies that led to a significant improvement in adherence: education, reminders, health coaching, and motivational interviewing. Incidentally, patients and providers considered these strategies to have the greatest utility in day-to-day management of glaucoma. Unfortunately, no studies clearly indicated a reliance on health theory during intervention design.

Making meaningful contributions in adherence research, as well as in the lives patients who live with glaucoma requires a multipronged approach. Through my research aims, I sought to answer three questions that address each of the major stakeholders in glaucoma care: 1. How do providers differ from patients in terms of their treatment values and clinical priorities? 2. How do patients themselves differ from each other, and what can we learn from these differences? and 3. How can the healthcare system (and research institutions) leverage these differences—and similarities—between stakeholders to successfully improve medication adherence in glaucoma patients? Answering these questions helped to develop foundational knowledge that can be leveraged to improve the design and delivery of interventions in the future.

GENERAL LIST OF REFERENCES

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121(11):2081-90.
2. Rossi GC, Pasinetti GM, Scudeller L, et al. Monitoring adherence rates in glaucoma patients using the Travatan Dosing Aid. A 6-month study comparing patients on travoprost 0.004% and patients on travoprost 0.004%/timolol 0.5% fixed combination. Expert Opin Pharmacother 2010;11(4):499-504.
3. Olthoff C, Schouten J, Borne B, Webers C. Noncompliance with Ocular Hypotensive Treatment in Patients with Glaucoma or Ocular HypertensionAn Evidence-Based Review. Ophthalmology 2005;112:953-61.
4. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). Invest Ophthalmol Vis Sci 2007;48(11):5052-7.
5. Murakami Y, Lee BW, Duncan M, et al. Racial and Ethnic Disparities in Adherence to Glaucoma Follow-up Visits in a County Hospital Population. Archives of Ophthalmology 2011;129(7):872-8.
6. Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol 2011;152(4):515-22.
7. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90(3):262-7.
8. Friedman DS, Wolfs RCW, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. Archives of ophthalmology (Chicago, Ill : 1960) 2004;122(4):532-8.
9. Sommer A, Tielsch JM, Katz J, et al. Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans: The Baltimore Eye Survey. Archives of Ophthalmology 1991;109(8):1090-5.
10. Wolfs RC, Borger PH, Ramrattan RS, et al. Changing views on open-angle glaucoma: definitions and prevalences--The Rotterdam Study. Investigative ophthalmology & visual science 2000;41(11):3309-21.
11. Leske MC, Connell AMS, Schachat AP, Hyman L. The Barbados Eye Study: Prevalence of Open Angle Glaucoma. Archives of Ophthalmology 1994;112(6):821-9.
12. Varma R, Ying-Lai M, Francis BA, et al. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology 2004;111(8):1439-48.
13. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA 2014;311(18):1901-11.

14. Memarzadeh F, Ying-Lai M, Chung J, et al. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study. Invest Ophthalmol Vis Sci 2010;51(6):2872-7.
15. Shetgar AC, Mulimani MB. The central corneal thickness in normal tension glaucoma, primary open angle glaucoma and ocular hypertension. Journal of clinical and diagnostic research : JCDR 2013;7(6):1063-7.
16. 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. Archives of Ophthalmology 2002;120(6):701-13.
17. Moore D, Harris A, WuDunn D, et al. Dysfunctional regulation of ocular blood flow: A risk factor for glaucoma? Clinical ophthalmology (Auckland, NZ) 2008;2(4):849.
18. Leske MC. Open-angle glaucoma—an epidemiologic overview. Ophthalmic Epidemiol 2007;14(4):166-72.
19. Bonovas S, Peponis V, Filioussi K. Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis. Diabet Med 2004;21(6):609-14.
20. Tielsch JM, Katz J, Singh K, et al. A Population-based Evaluation of Glaucoma Screening: The Baltimore Eye Survey. Am J Epidemiol 1991;134(10):1102-10.
21. Boden C, Blumenthal EZ, Pascual J, et al. Patterns of glaucomatous visual field progression identified by three progression criteria. Am J Ophthalmol 2004;138(6):1029-36.
22. Zhang X, Olson DJ, Le P, et al. The Association Between Glaucoma, Anxiety, and Depression in a Large Population. American Journal of Ophthalmology 2017;183:37-41.
23. Shin DY, Jung KI, Park HYL, Park CK. The effect of anxiety and depression on progression of glaucoma. Sci Rep 2021;11(1):1769.
24. Newman-Casey PA, Woodward MA, Niziol LM, et al. Brand Medications and Medicare Part D: How Eye Care Providers' Prescribing Patterns Influence Costs. Ophthalmology 2018;125(3):332–9.
25. Traverso CE, Walt JG, Kelly SP, et al. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. Br J Ophthalmol 2005;89(10):1245-9.
26. Meier-Gibbons F, Töteberg-Harms M. Influence of Cost of Care and Adherence in Glaucoma Management: An Update. Journal of Ophthalmology 2020;2020:5901537.
27. Quaranta L, Riva I, Gerardi C, et al. Quality of Life in Glaucoma: A Review of the Literature. Adv Ther 2016;33(6):959-81.
28. Haymes SA, Leblanc RP, Nicolela MT, et al. Risk of falls and motor vehicle collisions in glaucoma. Invest Ophthalmol Vis Sci 2007;48(3):1149-55.
29. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. Surv Ophthalmol 1994;39(1):23-42.
30. AmarilloICare. 2020. Glaucoma. Retrieved from http://amarilloicare.com/component/content/article/82-patient-education/96-glaucoma
31. Burgoyne CF, Crawford Downs J, Bellezza AJ, et al. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res 2005;24(1):39-73.

32. Leske MC. Ocular perfusion pressure and glaucoma: clinical trial and epidemiologic findings. Curr Opin Ophthalmol 2009;20(2):73-8.
33. Evans DW, Harris A, Garrett M, et al. Glaucoma patients demonstrate faulty autoregulation of ocular blood flow during posture change. British Journal of Ophthalmology 1999;83(7):809.
34. Harris A, Ciulla TA, Chung HS, Martin B. Regulation of retinal and optic nerve blood flow. Arch Ophthalmol 1998;116(11):1491-5.
35. Berdahl JP, Yu DY, Morgan WH. The translaminar pressure gradient in sustained zero gravity, idiopathic intracranial hypertension, and glaucoma. Med Hypotheses 2012;79(6):719-24.
36. Matuoka ML, Santos KS, Cruz NF, Kasahara N. Correlation between ocular perfusion pressure and translaminar pressure difference in glaucoma: Evidence for a three-pressure disease? Eur J Ophthalmol 2020:1120672120960584.
37. Willemse RB, Mager JJ, Westermann CJJ, et al. Bleeding risk of cerebral vascular malformations in hereditary hemorrhagic telangiectasia. J Neurosurg 2000;92(5):779-84.
38. Lee D, Shim MS, Kim KY, et al. Coenzyme Q10 inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in a mouse model of glaucoma. Invest Ophthalmol Vis Sci 2014;55(2):993-1005.
39. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. Ophthalmology 1999;106(4):653-62.
40. 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 (London, England) 2019;393(10180):1505-16.
41. Bhowmik D. The Pharma Innovation. Glaucoma -A Eye Disorder Its Causes, Risk Factor, Prevention and Medication. 2012.
42. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clinic proceedings 2011;86(4):304-14.
43. Sabate E, ed. Adherence to Long Term Therapies: Evidence for Action. World Health Organization. Switzerland2003.
44. Iuga AO, McGuire MJ. Adherence and health care costs. Risk management and healthcare policy 2014;7:35-44.
45. Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. Preventive medicine reports 2018;12:284-93.
46. Tapply I, Broadway DC. Improving Adherence to Topical Medication in Patients with Glaucoma. Patient preference and adherence 2021;15:1477-89.
47. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;73(5):691-705.
48. Zullig LL, Blalock DV, Dougherty S, et al. The new landscape of medication adherence improvement: where population health science meets precision medicine. Patient Prefer Adherence 2018;12:1225-30.
49. Howe LC, Leibowitz KA, Crum AJ. When Your Doctor “Gets It” and “Gets You”: The Critical Role of Competence and Warmth in the Patient–Provider Interaction. Frontiers in Psychiatry 2019;10(475).

50. Sanchez FG, Mansberger SL, Newman-Casey PA. Predicting Adherence With the Glaucoma Treatment Compliance Assessment Tool. J Glaucoma 2020;29(11):1017-24.
51. Vitolins MZ, Rand CS, Rapp SR, et al. Measuring adherence to behavioral and medical interventions. Control Clin Trials 2000;21(5 Suppl):188s-94s.
52. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int 2015;2015:217047.
53. Kass MA, Meltzer DW, Gordon M, et al. Compliance with Topical Pilocarpine Treatment. American Journal of Ophthalmology 1986;101(5):515-23.
54. Gray TA, Orton LC, Henson D, et al. Interventions for improving adherence to ocular hypotensive therapy. Cochrane Database Syst Rev 2009(2):Cd006132.
55. Tan X, Patel I, Chang J. Review of the four item Morisky Medication Adherence Scale (MMAS-4) and eight item Morisky Medication Adherence Scale (MMAS-8). Inov Pharm 2014;5:5.
56. Mansberger SL, Sheppler CR, McClure TM, et al. Psychometrics of a new questionnaire to assess glaucoma adherence: the Glaucoma Treatment Compliance Assessment Tool (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2013;111:1-16.
57. Sleath B, Blalock SJ, Stone JL, et al. Validation of a short version of the glaucoma medication self-efficacy questionnaire. Br J Ophthalmol 2012;96(2):258-62.
58. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. Surv Ophthalmol 2008;53 Suppl1:S57-68.
59. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. Ann Pharmacother 2004;38(2):303-12.
60. Cate H, Bhattacharya D, Clark A, et al. Patterns of adherence behaviour for patients with glaucoma. Eye (Lond) 2013;27(4):545-53.
61. Muir KW, Santiago-Turla C, Stinnett SS, et al. Glaucoma patients' trust in the physician. Journal of ophthalmology 2009;2009:476726-.
62. Gatwood JD, Johnson J, Jerkins B. Comparisons of Self-reported Glaucoma Medication Adherence With a New Wireless Device: A Pilot Study. J Glaucoma 2017;26(11):1056-61.
63. Mauro J, Mathews KB, Sredzinski ES. Effect of a Smart Pill Bottle and Pharmacist Intervention on Medication Adherence in Patients with Multiple Myeloma New to Lenalidomide Therapy. J Manag Care Spec Pharm 2019;25(11):1244-54.
64. WestRockCompany. 2020. MEMS® Cap Medication Event Monitoring System. Retrieved from https://www.westrock.com/products/folding-cartons/memscap
65. KaliCare. 2020. Kali Care supports the world's first known study into adherence to steroid eyedrops after Glaucoma surgery. Retrieved from https://www.kali.care/johns-hopkins-post-glaucoma-surgery-study
66. Cate H, Bhattacharya D, Clark A, et al. Protocol for a randomised controlled trial to estimate the effects and costs of a patient centred educational intervention in glaucoma management. BMC Ophthalmol 2012;12:57.
67. Friedman DS, Jampel HD, Congdon NG, et al. The TRAVATAN Dosing Aid Accurately Records When Drops Are Taken. American Journal of Ophthalmology 2007;143(4):699-701.

68. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999;21(6):1074-90; discussion 3.
69. Muir KW, Lee PP. Glaucoma medication adherence: room for improvement in both performance and measurement. Archives of ophthalmology (Chicago, Ill : 1960) 2011;129(2):243-5.
70. Cook P, Schmiege S, McClean M, et al. Practical and analytic issues in the electronic assessment of adherence. West J Nurs Res 2012;34(5):598-620.
71. Lampert A, Bruckner T, Haefeli W, Seidling H. Improving eye-drop administration skills of patients – A multicenter parallel-group cluster-randomized controlled trial. PLoS One 2019;14(2).
72. Okeke CO, Quigley HA, Jampel HD, et al. Interventions improve poor adherence with once daily glaucoma medications in electronically monitored patients. Ophthalmology 2009;116(12):2286-93.
73. Okeke CO, Quigley HA, Jampel HD, et al. Adherence with Topical Glaucoma Medication Monitored Electronically: The Travatan Dosing Aid Study. Ophthalmology 2009;116(2):191-9.
74. Dreer LE, Girkin C, Mansberger SL. Determinants of medication adherence to topical glaucoma therapy. J Glaucoma 2012;21(4):234-40.
75. Santschi V, Wuerzner G, Schneider M-P, et al. Clinical evaluation of IDAS II, a new electronic device enabling drug adherence monitoring. Eur J Clin Pharmacol 2007;63(12):1179-84.
76. Ajit RR, Fenerty CH, Henson DB. Patterns and rate of adherence to glaucoma therapy using an electronic dosing aid. Eye (Lond) 2010;24(8):1338-43.
77. Norell SE. Improving medication compliance: a randomised clinical trial. Br Med J 1979;2(6197):1031-3.
78. Holló G, Kóthy P. Can Adherence to Topical Glaucoma Medication be Improved by Using an Audible Alarm? Pharmaceut Med 2008;22(3):175-9.
79. Ho LY, Camejo L, Kahook MY, Noecker R. Effect of audible and visual reminders on adherence in glaucoma patients using a commercially available dosing aid. Clin Ophthalmol 2008;2(4):769-72.
80. Beckers HJ, Webers CA, Busch MJ, et al. Adherence improvement in Dutch glaucoma patients: a randomized controlled trial. Acta Ophthalmol 2013;91(7):610-8.
81. Newman-Casey PA, Blachley T, Lee PP, et al. Patterns of Glaucoma Medication Adherence over Four Years of Follow-Up. Ophthalmology 2015;122(10):2010-21.
82. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol 2010;6:109-38.
83. Nagin DS. Group-based trajectory modeling: an overview. Ann Nutr Metab 2014;65(2-3):205-10.
84. Jones BL, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. Sociological Methods & Research 2001;29(3):374-93.
85. Shi Q, Mendoza TR, Gunn GB, et al. Using group-based trajectory modeling to examine heterogeneity of symptom burden in patients with head and neck cancer undergoing aggressive non-surgical therapy. Qual Life Res 2013;22(9):2331-9.

86. Paranjpe R, Johnson ML, Essien EJ, et al. Group-Based Trajectory Modeling to Identify Patterns of Adherence and Its Predictors Among Older Adults on Angiotensin-Converting Enzyme Inhibitors (ACEIs)/Angiotensin Receptor Blockers (ARBs). Patient Prefer Adherence 2020;14:1935-47.
87. Elmer J, Gianakas JJ, Rittenberger JC, et al. Group-Based Trajectory Modeling of Suppression Ratio After Cardiac Arrest. Neurocrit Care 2016;25(3):415-23.
88. Cate H, Bhattacharya D, Clark A, et al. A comparison of measures used to describe adherence to glaucoma medication in a randomised controlled trial. Clin Trials 2015;12(6):608-17.
89. Burkhart PV, Sabaté E. Adherence to long-term therapies: evidence for action. J Nurs Scholarsh 2003;35(3):207.
90. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. Am J Health Syst Pharm 2003;60(7):657-65.
91. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology 2011;118(12):2398-402.
92. Rossi GCM, Pasinetti GM, Scudeller L, et al. Do Adherence Rates and Glaucomatous Visual Field Progression Correlate? Eur J Ophthalmol 2011;21(4):410-4.
93. Stewart WC, Chorak RP, Hunt HH, Sethuraman G. Factors associated with visual loss in patients with advanced glaucomatous changes in the optic nerve head. Am J Ophthalmol 1993;116(2):176-81.
94. Curtis RJ, Juan Xi, Andrew O. Westfall, Hong Cheng, Kenneth Lyles, Kenneth G. Saag, MD, Elizabeth Delzell. Improving the Prediction of Medication Compliance. Med Care 2009;47(3).
95. Kumar JB, Bosworth HB, Sleath B, et al. Quantifying Glaucoma Medication Adherence: The Relationship Between Self-Report, Electronic Monitoring, and Pharmacy Refill. J Ocul Pharmacol Ther 2016;32(6):346-54.
96. Robin AL, Novack GD, Covert DW, et al. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. Am J Ophthalmol 2007;144(4):533-40.
97. Deokule S, Sadiq S, Shah S. Chronic open angle glaucoma: patient awareness of the nature of the disease, topical medication, compliance and the prevalence of systemic symptoms. Ophthalmic Physiol Opt 2004;24(1):9-15.
98. Boland MV, Chang DS, Frazier T, et al. Automated telecommunication-based reminders and adherence with once-daily glaucoma medication dosing: the automated dosing reminder study. JAMA Ophthalmol 2014;132(7):845-50.
99. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev 2002(2):Cd000011.
100. Tsai JC, McClure CA, Ramos SE, et al. Compliance Barriers in Glaucoma: A Systematic Classification. J Glaucoma 2003;12(5):393-8.
101. Addario BJ, Fadich A, Fox J, et al. Patient value: Perspectives from the advocacy community. Health Expect 2017;21:57-63.
102. Butow PN, Maclean M, Dunn SM, et al. The dynamics of change: cancer patients' preferences for information, involvement and support. Ann Oncol 1997;8(9):857-63.

103. Elkin EB, Kim SH, Casper ES, et al. Desire for information and involvement in treatment decisions: elderly cancer patients' preferences and their physicians' perceptions. J Clin Oncol 2007;25(33):5275-80.
104. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. ACP J Club 2002;136(2):A11-4.
105. Park MH, Kang KD, Moon J. Noncompliance with glaucoma medication in Korean patients: a multicenter qualitative study. Jpn J Ophthalmol 2013;57(1):47-56.
106. Apter AJ, Wan F, Reisine S, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. J Allergy Clin Immunol 2013;132(2):321-7.
107. Davis SA, Carpenter DM, Blalock SJ, et al. Glaucoma Patient Preferences for Video Education on Eye Drop Technique. Optom Vis Sci 2019;96(5).
108. Newman-Casey PA, Weizer JS, Heisler M, et al. Systematic review of educational interventions to improve glaucoma medication adherence. Semin Ophthalmol 2013;28(3):191-201.
109. Racette L, Abu SL, Poleon S, et al. The impact of the COVID-19 pandemic on adherence to ocular hypotensive medication in patients with primary open-angle glaucoma. Ophthalmology 2021.
110. Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. JAMA 2019;322(2):113-4.
111. Spencer SKR, Shulruf B, McPherson ZE, et al. Factors Affecting Adherence to Topical Glaucoma Therapy: A Quantitative and Qualitative Pilot Study Analysis in Sydney, Australia. Ophthalmol Glaucoma 2019;2(2):86-93.
112. Sleath B, Blalock SJ, Carpenter DM, et al. Ophthalmologist-patient communication, self-efficacy, and glaucoma medication adherence. Ophthalmology 2015;122(4):748-54.
113. Mohammed M Abdull CG, Jim McCambridge, Jennifer Evans. Adapted motivational interviewing to improve the uptake of treatment for glaucoma in Nigeria: study protocol for a randomized controlled trial. Trials 2014(15):149.
114. Dreer LE, Owsley C, Campbell L, et al. Feasibility, Patient Acceptability, and Preliminary Efficacy of a Culturally Informed, Health Promotion Program to Improve Glaucoma Medication Adherence Among African Americans: "Glaucoma Management Optimism for African Americans Living with Glaucoma" (GOAL). Curr Eye Res 2016;41(1):50-8.
115. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners 2005;55(513):305-12.
116. Sayner R, Carpenter DM, Robin AL, et al. How glaucoma patient characteristics, self-efficacy and patient-provider communication are associated with eye drop technique. The International journal of pharmacy practice 2016;24(2):78-85.
117. Carpenter DM, Blalock SJ, Sayner R, et al. Communication Predicts Medication Self-Efficacy in Glaucoma Patients. Optom Vis Sci 2016;93(7):731-7.
118. Bandura A. Self-efficacy: The exercise of control. New York, NY, US: W H Freeman/Times Books/ Henry Holt & Co, 1997; ix, 604-ix, .

119. Wang Y, Zhao Y, Xie S, et al. Resilience Mediates the Relationship Between Social Support and Quality of Life in Patients With Primary Glaucoma. Frontiers in psychiatry 2019;10:22-.
120. Gamiochipi-Arjona JE, Azses-Halabe Y, Tolosa-Tort P, et al. Depression and Medical Treatment Adherence in Mexican Patients With Glaucoma. J Glaucoma 2021;30(3):251-6.
121. Freeman EE, Lesk MR, Harasymowycz P, et al. Maladaptive coping strategies and glaucoma progression. Medicine (Baltimore) 2016;95(35):e4761.
122. Hermann MM, Bron AM, Creuzot-Garcher CP. J Glaucoma 2011;20(null):502.
123. Stone JL, Robin AL, Novack GD, et al. An objective evaluation of eyedrop instillation in patients with glaucoma. Arch Ophthalmol 2009;127(6):732-6.
124. Atey TM, Shibeshi W, A TG, Asgedom SW. The Impact of Adherence and Instillation Proficiency of Topical Glaucoma Medications on Intraocular Pressure. J Ophthalmol 2017;2017:1683430.
125. Boso A, Gasperi E, Fernandes L, et al. Impact of Ocular Surface Disease Treatment in Patients with Glaucoma. Clin Ophthalmol 2020;14:103-11.
126. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and Adherence With Topical Glaucoma Therapy. American Journal of Ophthalmology 2005;140(4):598.e1-.e11.
127. Buller AJ, Connell B, Spencer AF. Compliance: clear communication's critical. British journal of ophthalmology 2005;89(10):1370.
128. Rees G, Chong XL, Cheung CY, et al. Beliefs and adherence to glaucoma treatment: a comparison of patients from diverse cultures. J Glaucoma 2014;23(5):293-8.
129. Scharff DP, Mathews KJ, Jackson P, et al. More than Tuskegee: understanding mistrust about research participation. J Health Care Poor Underserved 2010;21(3):879-97.
130. Doescher MP, Saver BG, Franks P, Fiscella K. Racial and ethnic disparities in perceptions of physician style and trust. Arch Fam Med 2000;9(10):1156-63.
131. Thom DH, Ribisl KM, Stewart AL, Luke DA. Further validation and reliability testing of the Trust in Physician Scale. The Stanford Trust Study Physicians. Med Care 1999;37(5):510-7.
132. Ikegami N. Fee-for-service payment - an evil practice that must be stamped out? International journal of health policy and management 2015;4(2):57-9.
133. Tariman J, Doorenbos A, Schepp K, et al. Patient, Physician and Contextual Factors Are Influential in the Treatment Decision Making of Older Adults Newly Diagnosed with Symptomatic Myeloma. Cancer Treatment Communications 2014;2.
134. Schwartz GF, Quigley HA. Surv Ophthalmol 2008;53(null):S57.
135. Subathra GN, Rajendrababu SR, Senthilkumar VA, et al. Impact of COVID-19 on follow-up and medication adherence in patients with glaucoma in a tertiary eye care centre in south India. Indian J Ophthalmol 2021;69(5):1264-70.
136. Djafari F, Lesk MR, Giguere CE, et al. Impact of a Brief Educational Intervention on Glaucoma Persistence: A Randomized Controlled Clinical Trial. Ophthalmic Epidemiol 2015;22(6):380-6.
137. Friedman DS, Hahn SR, Gelb L, et al. Doctor-patient communication, health-related beliefs, and adherence in glaucoma results from the Glaucoma Adherence and Persistency Study. Ophthalmology 2008;115(8):1320-7, 7.e1-3.

138. Lacey J, Cate H, Broadway DC. Eye (Lond) 2009;23(null):924.
139. Muir KW, Ventura A, Stinnett SS, et al. The influence of health literacy level on an educational intervention to improve glaucoma medication adherence. Patient Educ Couns 2012;87(2):160-4.
140. Cate H, Bhattacharya D, Clark A, et al. Improving adherence to glaucoma medication: a randomised controlled trial of a patient-centred intervention (The Norwich Adherence Glaucoma Study). BMC Ophthalmol 2014;14:32.
141. Abdull MM, Gilbert C, McCambridge J, Evans J. Adapted motivational interviewing to improve the uptake of treatment for glaucoma in Nigeria: study protocol for a randomized controlled trial. Trials 2014;15:149.
142. Cook PF, Bremer RW, Ayala AJ, Kahook MY. Feasibility of motivational interviewing delivered by a glaucoma educator to improve medication adherence. Clin Ophthalmol 2010;4:1091-101.
143. Willard-Grace R, Chen EH, Hessler D, et al. Health coaching by medical assistants to improve control of diabetes, hypertension, and hyperlipidemia in low-income patients: a randomized controlled trial. Ann Fam Med 2015;13(2):130-8.
144. McGonagle AK, Beatty JE, Joffe R. Coaching for workers with chronic illness: evaluating an intervention. J Occup Health Psychol 2014;19(3):385-98.
145. Cook PF, Schmiege SJ, Mansberger SL, et al. Motivational interviewing or reminders for glaucoma medication adherence: Results of a multi-site randomised controlled trial. Psychol Health 2017;32(2):145-65.
146. Boland MV, Chang DS, Frazier T, et al. Electronic monitoring to assess adherence with once-daily glaucoma medications and risk factors for nonadherence: The automated dosing reminder study. JAMA Ophthalmology 2014;132(7):838-44.
147. Tsai JC. Barriers to Adherence With Glaucoma Therapy: Potential Relationships to Disease Progression. Adv Stud Ophthalmol 2007;4(3):72-5.
148. Odegard PS, Carpinito G, Christensen DB. Medication adherence program: Adherence challenges and interventions in type 2 diabetes. J Am Pharm Assoc (2003) 2013;53(3):267-72.
149. Lim MC, Watnik MR, Imson KR, et al. Adherence to glaucoma medication: the effect of interventions and association with personality type. J Glaucoma 2013;22(6):439-46.
150. Junqueira DM, Lopes FS, de Souza FC, et al. Evaluation of the efficacy and safety of a new device for eye drops instillation in patients with glaucoma. Clin Ophthalmol 2015;9:367-71.
151. Bagnis A, Papadia M, Scotto R, Traverso CE. Current and emerging medical therapies in the treatment of glaucoma. Expert Opin Emerg Drugs 2011;16(2):293-307.
152. Pillunat LE, Eschstruth P, Häsemeyer S, et al. Preservative-free bimatoprost 0.03% in patients with primary open-angle glaucoma or ocular hypertension in clinical practice. Clin Ophthalmol 2016;10:1759-65.
153. Hommer A, Mohammed Ramez O, Burchert M, Kimmich F. IOP-lowering efficacy and tolerability of preservative-free tafluprost 0.0015% among patients with ocular hypertension or glaucoma. Curr Med Res Opin 2010;26(8):1905-13.
154. 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;176:61-9.

155. Parkkari M, Latvala T, Ropo A. Handling test of eye drop dispenser--comparison of unit-dose pipettes with conventional eye drop bottles. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 2010;26(3):273-6.
156. Tian C, Zeng L, Tang L, et al. Sustained Delivery of Timolol Using Nanostructured Lipid Carriers-Laden Soft Contact Lenses. AAPS PharmSciTech 2021;22(6):212.
157. Desai AR, Maulvi FA, Pandya MM, et al. Co-delivery of timolol and hyaluronic acid from semi-circular ring-implanted contact lenses for the treatment of glaucoma: in vitro and in vivo evaluation. Biomater Sci 2018;6(6):1580-91.
158. 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;112:110885.
159. Poleon S, Racette L, Fifolt M, et al. Patient and Provider Perspectives on Glaucoma Treatment Adherence: A Delphi Study in Urban Alabama. Optometry and vision science : official publication of the American Academy of Optometry 2021.
160. Blackhall LJ, Murphy ST, Frank G, et al. Ethnicity and attitudes toward patient autonomy. JAMA 1995;274(10):820-5.
161. Safran DG, Taira DA, Rogers WH, et al. Linking primary care performance to outcomes of care. J Fam Pract 1998;47(3):213-20.
162. Bilger M, Wong TT, Lee JY, et al. Using Adherence-Contingent Rebates on Chronic Disease Treatment Costs to Promote Medication Adherence: Results from a Randomized Controlled Trial. Appl Health Econ Health Policy 2019;17(6):841-55.
163. mHealthWellness. easyGlaucoma. [Multimedia Application]. Retrieved from https://apps.apple.com/us/app/easyglaucoma/id1516173647?ls=1
164. Gazzard G. Glaucoma Simulation. [Multimedia Application]. Retrieved from https://www.gusgazzard.com/glaucoma-simulation/
165. ResponsumHealth. The Glaucoma Community. [Multimedia Application]. Retrieved from https://responsumhealth.com/glaucoma/
166. AmazonPharmacy. Pill Pack. [Multimedia Application]. Retrieved from https://www.pillpack.com/
167. CapsuleCorporation. Capsule. [Multimedia Application]. Retrieved from https://capsule.com/
168. NowRx. NowRx. [Multimedia Application]. Retrieved from https://play.google.com/store/apps/details?id=com.nowrx.client
169. Gan K, Liu Y, Stagg B, et al. Telemedicine for Glaucoma: Guidelines and Recommendations. Telemedicine journal and e-health : the official journal of the American Telemedicine Association 2020;26(4):551-5.
170. Thomas S, Hodge W, Malvankar-Mehta M. The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS One 2015;10(9):e0137913.
171. Court JH, Austin MW. Virtual glaucoma clinics: patient acceptance and quality of patient education compared to standard clinics. Clin Ophthalmol2015; v. 9.
172. Amico KR, Mugavero M, Krousel-Wood MA, et al. Advantages to Using Social-Behavioral Models of Medication Adherence in Research and Practice. Journal of general internal medicine 2018;33(2):207-15.

173. Rosenstock IM. Historical Origins of the Health Belief Model. Health Educ Monogr 1974;2(4):328-35.
174. Goulia O, Zlatanos D, Gkika M, Tsekoyra A. Development of a health believe model (HBM) scale for glaucoma. Acta Ophthalmol (Copenh) 2010;88(s246):0-.
175. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991;50(2):179-211.
176. Ajzen I, Fishbein M. Questions raised by a reasoned action approach: comment on Ogden (2003). 2004.
177. Cook PF, Schmiege SJ, Mansberger SL, et al. Predictors of Adherence to Glaucoma Treatment in a Multisite Study. Ann Behav Med 2015;49(1):29-39.
178. Prior M, Burr JM, Ramsay CR, et al. Evidence base for an intervention to maximise uptake of glaucoma testing: a theory-based cross-sectional survey. BMJ Open 2012;2(2):e000710.
179. Bandura A. Self-efficacy mechanism in human agency. Am Psychol 1982;37(2):122-47.
180. Sleath B, Blalock S, Robin A, et al. Development of an instrument to measure glaucoma medication self-efficacy and outcome expectations. Eye (Lond) 2009;24:624-31.
181. Sleath B, Davis SA, Carpenter DM, et al. Increasing Engagement of African American Patients with Glaucoma during Medical Encounters: Creation of a Pre-visit Video. Optom Vis Sci 2020;97(7):503-8.
182. Glanz K, Beck A, Bundy L, et al. Impact of a health communication intervention to improve glaucoma treatment adherence. Results of the interactive study to increase glaucoma adherence to treatment trial. . Arch Ophthalmol 2012;130:1252-8.
183. Deci E, Ryan R. Intrinsic Motivation and Self-Determination in Human Behavior. Perspectives in Social Psychology1985.
184. 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;3(4):228-37.
185. Miller WR, Rollnick S. Meeting in the middle: motivational interviewing and self-determination theory. Int J Behav Nutr Phys Act 2012;9:25.
186. Prochaska JO, DiClemente C. The Transtheoretical Approach: Towards a Systematic Eclectic Framework Homewood, IL: Dow Jones Irwin, 1984.
187. Prochaska JO, Velicer WF. The transtheoretical Model of Health Behavior Change. Am J Health Promot 1997;12(1):38-48.
188. Rimer B, Glanz K. Theory at a glance: a guide for health promotion practice 2ed: U.S. Dept. of Health and Human Services, 2005.
189. Schwartz G, Plake K, Mychaskiw M. An assessment of readiness for behaviour change in patients prescribed ocular hypotensive therapy. Eye (Lond) 2008;23:1668-74.
190. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol 2008;27(3):379-87.
191. Hahn SR. Patient-centered communication to assess and enhance patient adherence to glaucoma medication. Ophthalmology 2009;116(11 Suppl):S37-42.
192. Davidson KW, Goldstein M, Kaplan RM, et al. Evidence-based behavioral medicine: what is it and how do we achieve it? Ann Behav Med 2003;26(3):161-71.

193. Davis R, Campbell R, Hildon Z, et al. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev 2015;9(3):323-44.

APPENDIX A

MEDIAN LIKERT SCORES AND MAJORITY RESPONSE TYPES FOR STATEMENTS IN ROUND 1

Median Likert Scores and Majority Response Types for Statements in Round 1

STATEMENTS INCLUDED IN ROUND 1 QUESTIONNAIRE	MEDIAN LIKERT SCORE			RESPONSE TYPE AND LEVEL (%)		
Treatment beliefs (N=8)	Overall	Patient	Provider	Overall	Patient	Provider
The glaucoma medication prescribed by my doctor is working	4	4	4	94	90	100
I can take my eye drops as prescribed for as long as I have glaucoma	4.5	5	3	72	100	-38
I can manage my glaucoma without any help from others	3	5	2	44	70	-63
I can openly discuss problems with my doctor	5	5	5	89	100	75
I need support from loved ones to help manage glaucoma	3	2	4	47	-60	50
I have a good understanding of how glaucoma affects my vision	4	4	4	83	100	63
Not taking medication as prescribed has negative effect on my vision	5	5	4	94	100	63
It is hard for me to tell if my glaucoma is stable	3	2	3	44	-60	38
Treatment barriers (N=14)	Overall	Patient	Provider	Overall	Patient	Provider
Eye drops are very expensive for me	4	2	5	61	-60	88
I have trouble keeping up with my medications (complex regimen)	3	1.5	4	44	-80	88
I do not have reliable transportation to go to the clinic or pharmacy	1	1	3	67	-100	38
I dislike the side effects of eye drops	2	1.5	2	67	-70	-63
I am not as disciplined as I could be	3	3	3	44	-50	38
It is difficult for me to open the medication bottle	2	1	2	83	-90	-75
I have difficulty getting eye drops into my eye	2	2	4	56	-90	63
I am sometimes forgetful	4	4	5	72	60	75
I have a busy daily schedule	3	4	3	44	60	-38
I have little or no motivation	1.5	1	3	72	-100	38
I do not believe that the doctor is being honest about my condition	1	1	1	89	-100	-75
I am not able to freely discuss needs and challenges with my doctor	1	1	3	72	-100	-38
It is hard to keep up with drops during special life events	2.5	1.5	4	50	-70	63
Medication instructions are not easy for me to understand	2	1	2	78	-90	-63
Treatment facilitators (N=9)	Overall	Patient	Provider	Overall	Patient	Provider
Making schedules to keep track of medications	4	2.5	5	67	-50	100
Remembering upcoming clinic visits	4	4	4	72	70	75
Not wanting to disappoint my doctor	3	4	3	44	60	-25

Thinking of the negative effect of not using drops on me and others	4	5	3	56	90	-25
Help from friends, family members, loved ones or caregivers	4	4	4	67	60	75
Talking to someone who understands the challenges of glaucoma	4	4	2	56	80	-63
Information about glaucoma on television, online, newspapers etc.	2	4	2	56	60	-75
Using affirmations to encourage you me take medication	4	4.5	3	61	80	38
Making promises to self and others	2	4	2	56	70	-88
Treatment motivators (N=8)	Overall	Patient	Provider	Overall	Patient	Provider
Being able to read in fine detail	5	5	4	78	90	63
Being able to navigate freely	5	5	5	89	100	75
Being able to reduce darkness or glare	3	4	3	67	60	25
Being able to drive	5	5	5	83	80	88
Remaining independent	5	5	5	100	100	100
Reducing worry about going blind	5	5	5	89	90	100
Not becoming a burden	4.5	5	3	72	100	38
Being included in social events	4	4.5	2	56	80	-63
Treatment needs (N=7)	Overall	Patient	Provider	Overall	Patient	Provider
Additional information about glaucoma	4	4	5	67	70	63
Guides for applying drops	4.5	4	5	83	80	88
Tips and aides for remembering drops	4	4	5	82	60	100
Resources for managing a worry and anxiety	3	2	4	39	-60	-63
Resources for affording medications	4	3	4	67	-50	88
Help with transportation	3	2	3	44	-70	38
Additional care and support from provider	3	3	3	39	50	25

Appendix B**.** Appendix B depicts the median Likert score and majority response type for questionnaire statements in Round 1. For each statement, median scores are reported for the entire panel (overall), as well as for patient and provider groups. Neutral scores (3) were removed, and responses were dichotomized as agreement (positive values) or disagreement (negative values). Response levels indicate the proportion of panelists who agreed or disagreed. Statement phrasing is consistent with patient questionnaires.

Note: From “Patient and Provider Perspectives on Glaucoma Treatment Adherence: A Delphi Study in Urban Alabama” by Poleon S, Racette L, Fifolt M, Schoenberger-Godwin YM, Abu SL, and Twa MD. 2021. Optometry and Vision Science 98(9), 1085-1093.

APPENDIX B

IRB APPROVAL LETTER (082519)

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Poleon, Shervonne

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 25-Aug-2019

RE: IRB-300003445
Adherence Patterns in Glaucoma

The IRB reviewed and approved the Revision/Amendment submitted on 14-Aug-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	5, 6, 7
Determination:	Approved
Approval Date:	25-Aug-2019
Expiration Date:	24-Aug-2022

Although annual continuing review is not required for this project, the principal investigator is still responsible for (1) obtaining IRB approval for any modifications before implementing those changes except when necessary to eliminate apparent immediate hazards to the subject, and (2) submitting reportable problems to the IRB. Please see the IRB Guidebook for more information on these topics.

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA
- Waiver of 24 Hour Waiting Period

Documents Included in Review:

- recruitmentcomms(Aim1Providers).tracked.190813
- phonescript(Aim1Patients).tracked.190813
- Consent(Aim1providers).tracked.190813
- surveyquest(Aim2).clean.190813

- praf.190813
- phonescript(Aim1Providers).tracked.190813
- recruitmentcomms(Aim1Patients).clean.190813
- recruitmentcomms(Aim1Patients).tracked.190813
- phonescript(Aim1Patients).clean.190813
- surveyquest(Aim2).tracked.190813
- phonescript(Aim1Providers).clean.190813
- Consent(Aim1Patients).clean.190813
- recruitmentcomms(Aim1Providers).clean.190813
- hsp.tracked.190813
- hsp.clean.190813
- Consent(Aim1Providers).clean.190813
- Consent(Aim1Patients).tracked.190813

APPENDIX C

IRB APPROVAL LETTER (073121)

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Poleon, Shervonne

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 31-Jul-2021

RE: IRB-300003445
IRB-300003445-016
Adherence Patterns in Glaucoma

The IRB reviewed and approved the Revision/Amendment submitted on 29-Jul-2021 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	5, 6, 7,
Determination:	Approved
Approval Date:	31-Jul-2021
Expiration Date:	30-Jul-2024

Although annual continuing review is not required for this project, the principal investigator is still responsible for (1) obtaining IRB approval for any modifications before implementing those changes except when necessary to eliminate apparent immediate hazards to the subject, and (2) submitting reportable problems to the IRB. Please see the IRB Guidebook for more information on these topics.

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA
- Waiver of Consent Documentation
- Waiver (Partial) of HIPAA
- Waiver of 24 Hour Waiting Period

Documents Included in Review:

- REVISION/AMENDMENT EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be “Approved.”
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document (CF, AF, Info Sheet, Phone Script, etc.)