Current Ophthalmology Reports (2021) 9:184–189
https://doi.org/10.1007/s40135-021-00273-1

DIAGNOSIS AND MONITORING OF GLAUCOMA (J KAMMER, SECTION EDITOR)

Adherence With Glaucoma Medications: Barriers to Success and Prospects for Improvement

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Accepted: 8 July 2021 / Published online: 1 October 2021

Abstract

Purpose of Review Patient adherence to prescribed medications is critical to prevent progression of glaucoma. This review summarizes recent literature about glaucoma treatment adherence including current strategies to aid in medication administration and opportunities for improvement.

Recent Findings Multiple studies have identified poor medication adherence as a major contributor to disease progression in glaucoma. There have been a variety of proposed and investigated techniques to improve adherence including eye drop monitors and reminders, patient education programs, eye drop delivery aids, and alternative medication delivery systems.

Summary Many approaches have shown promise in helping to improve medication adherence. A multifaceted and individualized patient treatment strategy is required to face this complex problem.

Keywords Glaucoma · Adherence · Eye drops · Medication aids

Introduction

Consistent use of prescribed medication is crucial to prevent worsening of disease across all areas of medicine, and glaucoma is no exception. Topical hypotensive medications can prevent or slow the progression of vision loss in patients with glaucoma [1–5], and studies clearly show that poor adherence to these medications can lead to glaucomatous visual field progression [6, 7, 8•]. Poor adherence also adds costs to the healthcare system and society [9, 10].

Given the importance of consistent medication usage, research on this topic has rapidly increased since the 1970s [11]. Researchers traditionally used the term "compliance" to describe a patient's ability to maintain a prescription drug regimen, but in recent years, this term has been replaced by "adherence" and "persistence." The original language portrayed a power dynamic wherein the doctor orders the patient to follow a treatment plan. The updated language involves a successful patient-physician relationship, with shared decision-making and active patient participation. Adherence is used to describe the percentage of times a patient takes their medication as prescribed. If a patient takes a medication that is prescribed three times daily only once daily, their adherence is calculated as 33%. Persistence defines the length of time that a patient takes their medication, regardless of adherence, before it is completely discontinued. Both metrics are useful in analyzing and contextualizing patient response to prescribed therapies.

An early study by Kass et al. in 1986 investigated patient adherence through electronic monitors on eye drop bottles and found that there was a significant discrepancy between self-reported adherence and true adherence [12]. Adherence rates have not improved over the years, with multiple studies demonstrating adherence to be 25–69% below the patient-reported rates [13–21]. Additionally, elderly patients and those with asymptomatic chronic conditions are at higher risk for poor medication adherence [13, 22], which are both factors relevant to glaucoma patients. Although many physicians believe they can identify which patients have poor adherence, studies have shown that doctors are unable to accurately distinguish

This article is part of the Topical Collection on *Diagnosis and Monitoring of Glaucoma*

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adherent from non-adherent patients [23, 24]. Additionally, patients often overestimate their adherence rates [25, 26], which creates a situation where both individuals in the patient-physician relationship believe that medications are being used more frequently than they actually are. While adherence is necessary for optimal outcomes, persistence is also a critical determinant of successful long-term glaucoma treatment. Unfortunately, persistence is overall very poor for glaucoma medications, with rates reported in the 33–39% range at only 1 year from initiation of therapy [21, 27–30].

With the above framework in mind, how can the patient-physician partnership be optimized to increase adherence and persistence, with the ultimate goal of improving outcomes? There are a multitude of reasons why patients develop low adherence and persistence, including but not limited to medication cost and side effects, difficulty administering drops, work and travel schedules, misunderstanding or denial of the disease, and forgetfulness [31•, 32]. The purpose of this review article is to summarize the most recent advances in glaucoma medication adherence and persistence tools, while also exploring areas for potential growth in glaucoma medication utilization and management.

Improving Adherence and Persistence

Eye Drop Monitors

Reliable and standardized systems that accurately assess medication usage are needed to improve adherence rates. Most prior studies that estimated adherence rates used patient self-reporting or pharmacy claims data. Self-reporting is fraught with pitfalls and tends to significantly overestimate adherence rates [12–21]. Pharmacy claims are also often inaccurate. Just because patients fill a prescription does not guarantee that they will use the drop in a consistent manner, and tracking prescription changes can be challenging [33]. Electronic monitoring offers the most promise in terms of accurate and real-time medication adherence reporting. However, these devices have historically been very cumbersome to use and prohibitively expensive outside of a research setting.

Recently, there have been some promising advances in the field of electronic medication monitoring including the Kali Drop (Kali Care, Santa Clara, CA) and the Devers Drops Device (D3, Universal Adherence, Portland, OR, Fig. 1). The Kali Drop uses 3G to transmit medication use data in real time [34]. The device is relatively small, light-weight and fits most standard-size eye drop bottles inside. Pressure sensors on the sides of the device determine if enough force

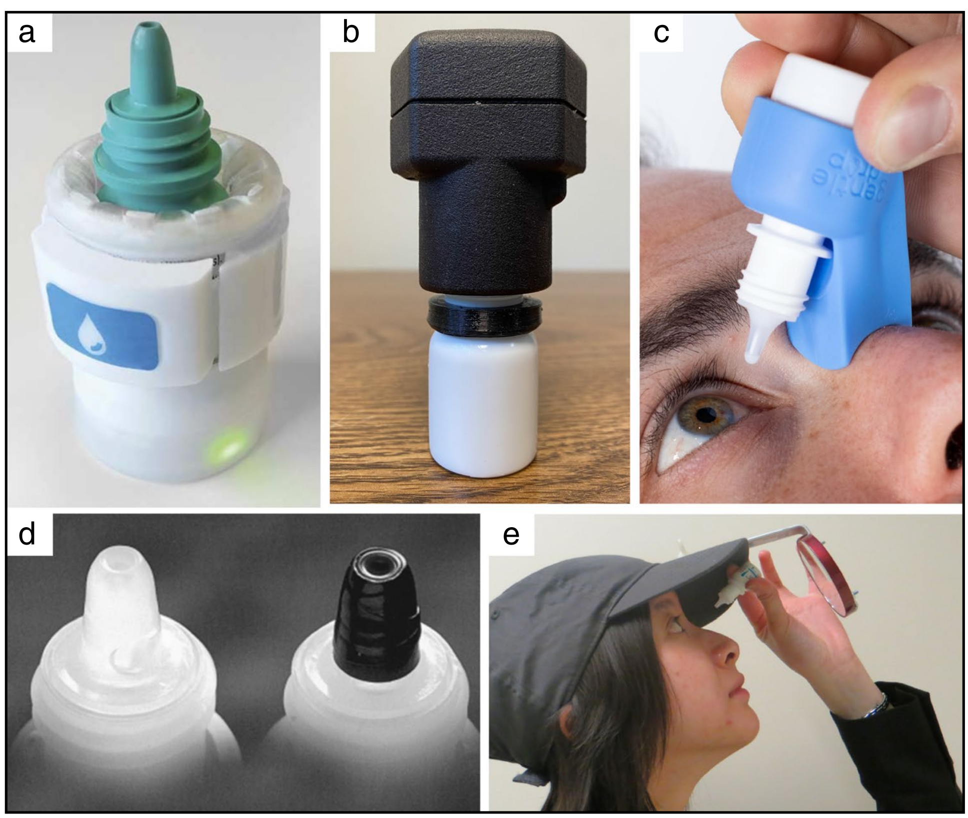

Fig. 1 Examples of eye drop monitors and delivery aids to improve adherence including Kali Drop (Kali Care, Santa Clara, CA) (**a**); Devers Drops Device (D3, Universal Adherence, Portland, OR) (**b**); GentleDrop eye drop aid (Bedo Solutions, Portland, OR) (**c**); Black eye drop bottle tip (**d**); and mirror-hat device (**e**)

was applied to dispense a drop, and a positional sensor on the base confirms that the bottle was inverted during drop administration. Adherence data is automatically transferred to a housing base. The device comes with a charger, and a single charge can last up to 2 weeks. A recent study found the device to be highly effective and reliable in both monitoring and recording patient drop administration data without significant inconvenience to the patient.

The Devers Drops Device tracks eye drop usage by registering when the eye drop bottle cap is removed and replaced. The D3 monitor securely attaches to a wide range of eye drop bottle caps. After a small piece of magnetic tape is applied to the bottle, the monitor uses a magnetic sensor to detect bottle cap movement. When a bottle empties, the monitor can be easily transferred to a new eye drop bottle. Because all electronics are contained within the monitor on top of the bottle cap, the D3 does not interfere with normal eye drop administration in any way. Adherence information is automatically transferred to a central server and can then be shared with patients, family members, or other contacts. In an ongoing pilot study, the D3 has been capable of remaining attached to the eye drop bottle cap and measuring adherence in 49 of 50 (98%, one device failure) patients.

Widespread use of such monitors would help detect poor adherence and allow for earlier implementation of personalized treatment plans.

Eye Drop Delivery Aids

While accurately monitoring eye drop administration is important, drop monitors cannot guarantee that dispensed drops reach the patient's eyes. Successful drop instillation requires expelling an appropriate volume while maintaining the bottle at the proper location above the ocular surface. For many patients, this is no small feat. In one study, over 90% of patients placed eye drops incorrectly, either by missing the eye, touching the eye with the bottle tip, or placing more than one drop. Bottle tip contact against the ocular surface can contaminate the medication and cause trauma to the eye [35, 36]. Administering more than one drop increases the medication cost and risk for local and systemic side effects [37, 38]. Furthermore, a prematurely empty bottle may worsen adherence.

Multiple devices have been created to help combat these issues and help patients effectively administer eye drops (Fig. 1) [39, 40••]. One study enhanced patient visualization by making the tip of the bottle black, which 87.5% of patients said made drop instillation easier compared to a conventional white bottle [41]. Other instillation aids include devices that rest on the bridge of the nose, orbit, or eyelids to assist in drop delivery [40••, 42–45]. The GentleDrop is a nose-pivoted aid that balances on the bridge of the nose to keep the device out of the visual axis and avoid contact with periocular surfaces while placing eye drops. The aid was recently found to improve eye drop delivery success from 54 to 86%, and 47 of 50 (94%) patients preferred the device over traditional delivery [40••]. The "mirror-hat device" uses of a hat with a mirror attached to the brim in order to help patients guide the bottle into the appropriate position; this device was also reviewed favorably by patients and led to a statistically significant improvement in drop administration [46]. Although two devices were found to be more challenging than traditional delivery [43, 44], most aids have been found to be helpful compared to the traditional handheld bottle technique [40••, 42, 45].

The majority of instillation aids help patients administer drops more safely and effectively than traditional methods. These aids may help improve adherence if the patient if more confident in their ability to successfully administer their own eye drop. However, these devices are severely underutilized outside of a research setting perhaps because patients are often unaware of assistive devices for eye drop administration. Future research should evaluate whether patients continue to use such drop delivery devices over time outside of the research setting.

Alternatives to Eye Drops

While topical ocular hypotensive medications are currently the most commonly used treatment for glaucoma, there is significant promise in other non-surgical management strategies, especially when adherence remains low or patients are unable to administer eye drops.

Sustained-Release Therapies

Punctal plugs have long been used to improve ocular surface disease by reducing the drainage of natural tears through the canalicular system. This established technology serves as the platform for a recently developed punctal plug-based medication delivery system, the Evolute from Mati Therapeutics, Inc. (Austin, TX). An L-shaped canalicular insert uses a latanoprost-polymer matrix surrounded by silicone to deliver medication to the tear film at a constant rate. A phase II clinical trial of this device demonstrated good patient comfort with a greater than 90% retention rate and a 20% decrease in IOP from baseline [47]. A device from Ocular Therapeutix, Inc. (Bedford, MA) is similar in that it delivers a prostaglandin medication to the ocular surface using a dissolvable intracanalicular drug depot that resorbs over a 3-month period, and in a recent study, it demonstrated an IOP reduction of 5.4–7.5 mmHg [48].

Additional drug devices are under investigation including subconjunctival, suprachoroidal, intracameral, and intravitreal sustained-release medication depots. A recently developed biodegradable bimatoprost sustained-release implant

(Allergan, Dublin, IE) can be injected into the anterior chamber. A phase I/II paired-eye controlled clinical trial showed favorable efficacy and safety profiles up to 24 months after implantation, with comparable IOP-lowering effects compared to the topical bimatoprost fellow eye [49]. A phase III trial demonstrated non-inferiority to the timolol control arm, but had a statistically significant decrease in corneal endothelial cell counts [50]. While sustained release drug delivery systems are promising, they are generally less efficacious when compared directly to their topical medication equivalent, which may be related to intermittent dosing having higher efficacy when compared to continued dosing of ocular medications.

Laser Trabeculoplasty

Another alternative to eye drops is laser trabeculoplasty using argon laser trabeculoplasty (ALT) or selective laser trabeculoplasty (SLT). The LiGHT trial was an observer-masked, randomized controlled trial of treatment-naïve patients with ocular hypertension or open angle glaucoma. Study patients were randomized to SLT or topical medical therapy and were found to have no statistically significant difference between quality of life metrics, intraocular pressure reduction, or need for surgical intervention [51]. Additionally, SLT was found to be overall more cost-effective when compared to eye drops, making it a viable first-line treatment option for early-stage glaucoma. Similar to sustained-release medications, this glaucoma treatment modality has the distinct advantage of circumventing adherence issues that are common with topical therapies.

Patient Education and Instruction

While there are many promising glaucoma therapeutic options in development that aim to improve adherence and persistence, topical medications will likely remain the mainstay of treatment in the near future. Given this reality, the optimization of medication usage via improved patient education is a potentially highly effective strategy.

Not every patient requires additional attention when it comes to medication instructions. In-depth, in-person patient education is a time-consuming process and ideally would only be utilized for appropriate patients. However, identification of patients that are at higher risk for poor adherence remains a challenging task [23, 24]. A recent study used patient-specific factors to develop the Glaucoma Treatment Compliance Assessment Tool (GTCAT), which identifies health behavior factors linked to increased risk for poor adherence [52]. It includes measures of depression, dexterity of eye drops, severity, susceptibility, cues-to-action, benefits, and barriers to using eye drops. This type of tool could be utilized to screen for barriers to adherence such as cost of eye drops, and difficulty administering eye drops. It can determine whether the patient has a reminder system for drops, or whether they trust their doctor. While it is currently used only in research, further iterations could include automated education and focused discussion based on the results of such a survey.

One of these potential interventions is the Support, Educate, and Empower (SEE) glaucoma coaching program which was recently created and studied by Newman-Casey et al. [53]. The investigators enrolled patients using at least 1 glaucoma drop and who self-reported poor adherence. The program included automated medication reminders, motivational interviewing counseling sessions, and phone calls with a trained coach for personalized support. The study participants who completed the program demonstrated a statistically significant improvement in adherence compared to the participants who did not finish the program.

Eye drops will continue to occupy an essential role in glaucoma treatment, so personalized medicine and motivational interviewing are critical factors in improving adherence and outcomes. Patients will only use their medications if they understand the importance of adherence and feel personally invested in their treatment regimens. Therefore, patient-centered communication strategies and individualized health behavior models will remain cornerstones of effective patient care for years to come.

Conclusion

One of the biggest factors contributing sub-optimal outcomes in chronic diseases is the necessity for steady, regular use of medications over many years. Taking glaucoma medications inconsistently hastens disease progression. Fixing this complex issue is a burden that both patients and their providers share, and improved adherence is likely to come from a multifaceted approach to patient care. The first step is accurate monitoring of adherence in order to identify at-risk patients. More consistent medication use can then be addressed via an individualized approach, utilizing a combination of education, improved eye drop administration, and dose reminders. Lastly, issues with adherence are not limited to glaucoma. Other areas of medicine struggle with this same challenge and have employed creative techniques for improving adherence. Eye care providers should remain aware and receptive to what other areas of medicine are doing to improve adherence.

Compliance with Ethical Standards

Conflict of Interest Michael J Gale: none.

Robert M Kinast: Universal Adherence (Co-owner); Bedo Solutions (Co-owner).
Facundo G Sanchez: none.
Steven L Mansberger: Universal Adherence (Co-owner); Allergan/Abbvie (Research); Thea (Consultant).

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- •• Of major importance

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