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Review of glaucoma medication adherence monitoring in the digital health era

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Abstract

Current glaucoma treatments aim to lower intraocular pressure, often with topical ocular hypotensive medications. Unfortunately, the effectiveness of these medications depends on sustained patient adherence to regimens which may involve instilling multiple medications several times daily. Patient adherence to glaucoma medications is often low. Recent innovations in digital sensor technologies have been leveraged to confirm eyedrop medication usage in real-time and relay this information back to providers. Some sensors have also been designed to deliver medication reminders and notifications as well as assist with correct eyedrop administration technique. Here, we review recent innovations targeted at improving glaucoma medication adherence and discuss their limitations.

INTRODUCTION

Current glaucoma treatments lower intraocular pressure (IOP), the only proven modifiable risk factor which has been shown in multiple landmark clinical trials to reduce the risk of disease progression.[1–5] Despite increasing evidence to support the use of selective laser trabeculoplasty as first-line treatment,[6–8] lowering IOP with eyedrops remains the most common first-line therapy.[9] However, their effectiveness is based on sustained patient adherence to treatment regimens, which can involve instilling multiple medications several times daily.

Medication adherence is a major issue for all of medicine, and glaucoma management is no exception. One of the reasons why patients with chronic asymptomatic diseases like

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Contributors SLB conceived and designed the study. AE and BS conducted primary literature review. AE, BS and SLB drafted the manuscript.

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glaucoma are more prone to non-adherence is because they may not notice the benefits of medications.[10] Adherence rates for topical glaucoma medications range from 30% to 80%.[11–16] In a study of newly treated patients with glaucoma, more than 20% failed to obtain follow-up visits within at least 18 months of diagnosis,[17] as recommended by the American Academy of Ophthalmology's Preferred Practice Pattern guidelines.[18] Moreover, only 10% of patients refilled their prescription within 12 months, suggesting they are not taking glaucoma medications as prescribed.[1 17 19] Because poor medication adherence can hasten glaucoma progression and vision loss,[20] it is crucial to understand reasons for poor adherence, develop robust methods of measuring adherence and deploy interventions to improve adherence. Here, we have conducted a narrative review of recent advances in monitoring glaucoma medication adherence and novel patient engagement strategies that leverage innovations in digital health technologies.

REASONS FOR NON-ADHERENCE IN GLAUCOMA

Non-adherence to glaucoma medication is multifactorial. Robin and Muir grouped non-adherence to topical glaucoma medication into five dimensions: patient-related, social and economic, health-care system, therapy-related, and condition-related dimensions.[1] Patient-related barriers that negatively influence glaucoma adherence include insufficient knowledge about the risks of disease progression and the benefits of treatment, lack of self-efficacy and forgetfulness. In a study by Newman-Casey *et al* of both adherent and non-adherent patients, forgetfulness was ranked as the number one barrier to adherence, although among non-adherent patients, each of 11 commonly cited barriers was salient to greater than 30% of participants.[11] Other studies have also found that difficulties with glaucoma drop administration, costs and complex medication schedules were additional barriers.[21–24] Therefore, patients with glaucoma often face multiple barriers to medication adherence.

TRADITIONAL METHODS OF MONITORING ADHERENCE

Some traditional methods of monitoring medication adherence include patient self-report and analysing health insurance claims data or pharmacy claims data. Here, we review examples of how these methods are used.

Patient self-report

Patient self-report is one of the most commonly used measures of adherence.[25] Self-reported adherence is assessed through self-administered questionnaires or interviews by trained personnel. While simple and inexpensive, patient self-report commonly overestimates adherence when compared with electronic monitoring results.[26] According to the Glaucoma Adherence and Persistency Study, 95% of patients claimed they never missed taking their glaucoma medications despite clear evidence of poor adherence.[23] One potential factor cited by Sayner *et al*[10] in a study demonstrating patients over-reporting adherence compared with electronic monitors was social desirability bias, where patients' desire to please their physicians influences them to unconsciously over-report adherence.[27 28] Patient self-report is also subject to various biases like inaccurate memory and assumptions.[29]

Claims data

Health insurance claims data provide a complete list of reimbursed services for a large insured population, and pharmacy claims data are a subset of health insurance claims data specifically related to medications. In an analysis of claims data by Nordstrom *et al*, nearly half of patients who filled a glaucoma prescription discontinued all topical hypotensive treatments within 6 months.[30] Three years after the initial prescription, only 37% of patients had recently refilled their medication.[21 30] Several other studies have also used claims data to understand adherence rates in patients with glaucoma.[17 31 32] However, having a prescription alone does not equate to the patient successfully getting the medication onto the eye. Furthermore, some patients may have more than one health insurance, which leads to discrepancies in adherence using this method.

Claims data allow evaluation of large sample populations, but they demand a complex approach to measurement and interpretation. Pharmacy records have difficulty capturing the difference between the *addition* of a new medication and the *switch* to a new medication. In a study by Friedman *et al*, 17% of 174 patients were given a second medication for glaucoma, but only 10% of the added medications were correctly identified using pharmacy claims data. Moreover, 66.7% of the added medications were misclassified as switched medications, and 23.3% were misclassified as no change.[19] This suggests that misclassifications from pharmacy claims data can inflate adherence rates and obscure poor adherence. Additionally, pharmacy claims data cannot ensure patient usage of glaucoma medications at home, again resulting in overstatements of true adherence.

Pharmacy claims data can be used to assess the medication possession ratio (MPR), defined as the 'days of prescription supply dispensed divided by the number of days between the first and last prescription refill'.[19] MPR assesses the adherence of patients who are prescribed multiple medications and distinguishes between added and switched medications. Thus, MPR may be more comprehensive for patients who cycle off and back on medications.[19] However, MPR does not provide insight into timeliness and consistency of refilling. For example, a patient who struggles to properly instil an eyedrop will use more drops than prescribed and may request multiple bottles in early months of therapy, leading to a high MPR.[26]

In summary, traditional methods of monitoring can provide rough estimations of medication adherence but have major limitations, including mischaracterisation of adherence and lack of granularity. Thus, these methods are limited in accurately identifying non-adherent patients and facilitating interventions in real-time.

INNOVATIONS IN SENSOR TECHNOLOGY FOR ADHERENCE MONITORING

Given the potential inaccuracy of traditional methods of adherence monitoring, several digital sensor monitoring systems have been developed. Digital sensor monitoring systems have been referred to as the 'gold standard' for assessing medication adherence as they objectively quantify adherence, often in real-time, allowing clinicians to deliver personalised interventions and reminders targeting individual patient behaviours.[33–36] First, we will summarise developments for oral medications, where this technology is more well-developed. Then, we will specifically describe recent innovations in sensors for eye medication adherence monitoring.

Smart pill bottles

Several smart pill bottles have been developed to track medication usage. One example is the widely used Medication Event Monitoring Systems (MEMS) Smart Cap (AARDEX Group, rue bois St Jean, Seraing, Belgium), which is embedded with a sensor that records every time the pill bottle is opened and has been used in the field of ophthalmology among others.[10 37–42] This is assumed to correspond to patient consumption of a medication dosage. The MEMS Smart Cap can also alert a patient if he/she has already taken a dose that day. Similarly, the MedTracker is an instrumented 7-day pill reminder box that records each time the pillbox has been opened and closed.[43] Other smart pill bottles are able to detect when pills are removed and generate weekly patient feedback reports regarding adherence; they also glow, light up, buzz, sound alarms, and even send text and voice messages to remind patients to take medications (Vitality GlowCap, Vitality, Los Angeles, California, USA; AdhereTech, New York, New York, USA).[44] A randomised controlled trial using one such smart bottle, the Vitality GlowCap, found that daily alarms combined with individual or partner feedback reports improved statin medication adherence.[45]

Sensors for confirming medication ingestion

A notable limitation of smart pill bottles is that the sensors only measure when the bottle has been opened or when a pill has been removed, but not actual ingestion of the medication. One proposed way to overcome this is to supplement the smart bottle with a smart necklace capable of determining if medication ingestion has occurred based on skin movement of the neck during a swallow.[46] This smart necklace was able to correctly differentiate between chewable vitamins, saliva swallows, medication capsules, speaking and drinking water, with average precision and recall of 90.17% and 88.9%, respectively.[46] Alternatively, inertial sensors can be used to recognise the ‘twist cap’ and the ‘hand to mouth’ motions associated with pill taking.[47] Technology for inertial sensors has also been leveraged to measure adherence to home physiotherapy regimens.[48 49]

Ingestible biosensors are another digital method to directly assess medication ingestion. One of the most notable prototypes, Proteus Discover,[50] consists of ingestible sensors composed of copper, magnesium and silicon that are embedded within medication tablets. A signal is transmitted to the patient’s mobile phone when the tablets dissolve in the stomach, with an overall accuracy of 97.6%. Clinicians can then analyse patients’ adherence data through a secure web portal. Over 100 studies have investigated the use of these ingestible sensors to improve medication adherence for tuberculosis, diabetes, hypertension, psychiatric and post-transplant treatments, among others.[33 51–57] Other ingestible sensors like MyTMed and ID-Cap System (eTectRx, Newbury, Florida, USA) offer similar methods of monitoring adherence.[58–60]

Sensors for eye medications

The majority of digital sensor technologies have been studied and implemented to assist with oral medication adherence. In the early 1990s, C Cap (C Cap Compliance Cap, Allergan), was developed as the first medication cap with a memory aid to assess glaucoma medication adherence.[61] An early commercial device for monitoring eye drop adherence was the Travatan Dosing Aid (figure 1A), designed to assist patients in taking travoprost and record when drops were administered.[19 62] In a multifaceted programme to enhance glaucoma eyedrop usage, which included the device and patient education and reminders, mean adherence rate improved from 54% to 73% (p<0.001) in patients with <75% initial baseline drop-taking.[19 63] However, this dosing aid could not be used for other eye medications and was not widely adopted by patients or eyecare providers. In addition, the device was only available for a limited time.

Recently, others have innovated new ‘smart’ technologies designed for eyedrop bottles that are applicable across different medications. For example, E-Novelia (figure 1B) developed a custom, large bottle that encases eyedrop medication bottles which can detect wrong usage via location tracking and an inclination light used for electronic guidance, remaining volume of medication and drop dispensing while delivering reminders.[64] E-Novelia also contains sensors that can wirelessly transfer data to mobile phones. However, its large size makes it difficult for patients to carry and use, potentially posing a barrier to adoption. Kali Drop (Kali Care, Santa Clara, California, USA) is another smart eyedrop bottle designed to collect and record objective medication use data (ie, number of drops dispensed and the time and date taken), which can be analysed by patients and providers alike to track adherence. The Kali Drop device is compact and has 3G wireless sensors embedded in the base of the device capable of detecting whether the device was inverted at the time of use.[65 66] Embedded coloured lights are also employed to signal when a successful dose is recorded and transmitted. In a recent pilot study of the Kali Drop, the majority of patients found the device easy to use, that it did not interfere with medication-taking or their normal activities, and that they were not bothered by physicians tracking their adherence data.[65]

Several groups have developed less obtrusive sensors that can be adapted to various eyedrop medications. For example, Nishimura *et al* recently developed an eyedrop bottle motion sensor system to measure patient adherence with topical glaucoma medications.[67] Waveform data are automatically collected from the sensor and judged as a complete instillation via a deep learning model.[67] When evaluated, the sensor system successfully collected instillation data of 20 patients with glaucoma for 3 days with 100% accuracy.[67]

Similarly, Payne *et al* developed an intelligent sleeve for eyedrop bottles with a sensor capable of detecting eyedrop use, measuring fluid level and sending user information to providers to facilitate intervention (figure 1C). When tested, the smart sleeve successfully identified and time-stamped 94% of use events.[68]

Finally, Aguilar-Rivera *et al* developed a ‘smart drop’ bottle containing a thin electronic force sensor located under the label of the eyedrop medication bottle (figure 1D). This sensor detects and wirelessly transmits drop deliveries to a smartphone app with a 100% success rate of wireless communication over 75 feet and <1% false positive and false negative rates of single drop deliveries.[69]

The Hawthorne effect applies to the majority of the smart technology studies reviewed, given that patients were aware that their adherence to medication would be monitored while using the smart devices.[70 71] As a result, medication adherence may be overestimated with the use of smart technologies given the design of most of the studies. However, these eyedrop specific sensors offer a promising new avenue for generating glaucoma medication adherence data in real-time, which can help clinicians customise patient-specific interventions to improve adherence.

Similar to the use of smart pill bottles for monitoring oral medications, these sensors are focused on monitoring the medication dispensing event—that is, the transfer of medication from within the bottle to outside the bottle. They do not directly measure the instillation of medication in the eye itself. It is also important to note that storing of eyedrop medications outside of the smart sensor devices can lead to underestimations of adherence. Although there have been several studies regarding the use of contact lens biosensors to measure IOP[72–74] or to detect glucose levels,[73 75] our literature search did not yield formal assessments of using these devices for measuring medication adherence specifically. Evaluating the application of these devices for monitoring medication adherence in a more direct fashion (ie, instillation into the tear film) would be a promising avenue of future investigation. However, the current medication adherence sensors that are based on monitoring eyedrop bottles may have potential for broader deployment and acceptability due to their non-invasive design and reduced risk for side effects compared with devices that come into contact with the eye. Therefore, these sensors focused on medication dispensing still represent a worthwhile initial approach for measuring and monitoring eye medication adherence.

INNOVATIONS IN DELIVERY OF MEDICATION REMINDERS

Traditionally, patients are reminded to adhere to medication regimens during clinical encounters or phone calls. Some studies have shown that intensive educational and coaching programmes can improve adherence.[76–85] However, these approaches are labour-intensive and not easily scalable. Innovations in digital health technology—particularly the widespread adoption of smartphones, mobile apps and electronic health record (EHR) systems and their associated patient portals—offer novel modes of patient engagement around medication adherence.

Smartphones and mobile apps

Smartphone-based mobile apps are increasingly used to track adherence and deliver reminders, with 704 medication adherence-related apps available as of 2019.[86] The vast majority of sensor technologies for medication adherence monitoring are linked to mobile apps. In general, smartphones have been widely adopted, even among older adults who are more likely to be affected by glaucoma.[87 88] Lee *et al* found that patients with glaucoma were receptive to smartphone technology being used to monitor and improve glaucoma outcomes, with 26/43 (60%) study respondents reporting that they would use a medication adherence app.[89]

EHR systems and patient portals

EHR systems have also been widely adopted across the USA.[90 91] Boland *et al*[92] demonstrated that automated telecommunication-based reminders linked to medication data in an EHR improved patient adherence with once daily glaucoma medications. Patient portals linked to EHR systems have also recently become increasingly used, allowing patients to message clinicians, view laboratory testing and imaging results, and track medications.[93–95] These portals can also facilitate communication with patients and deliver automated medication reminders.

For instance, Varadaraj *et al* examined the feasibility and effectiveness of automated dosing reminders using an EHR-linked patient portal for glaucoma medication adherence and to assess patient satisfaction with EHR-linked reminders.[96] A web-based application was linked to the EHR patient portal, allowing patients to select medications from their medication list, format (via text or voice call), and timing of their automated, EHR-linked dosing reminders. Three months after initiation, 74% of participants found the reminders useful, and 42% reported they were very likely or likely to continue using EHR-linked reminders.[96]

Regardless of the source, long-term effects of automated reminders on patient behaviours require further study, as ‘alert fatigue’ may hinder effectiveness. Alert fatigue is a well-documented phenomenon among clinicians receiving alerts from EHR systems[97]; it is foreseeable patients may develop similar behaviours.

DISCUSSION

Glaucoma medication adherence is often undermined by the need for frequent and long-term use of medications which can be difficult to administer. Increased efforts are underway to better identify, monitor and address adherence (figure 2).

Innovations in sensor technology designed for eyedrop bottles offer a novel approach for assessing adherence. Connecting these data to smartphone-based apps and EHR systems can facilitate relaying adherence information back to both patients and clinicians in real-time. Despite the increasing use of alternative treatment to eyedrops, including selective laser trabeculoplasty,[6–8] minimally invasive glaucoma surgery,[98–100] and sustained release implants,[101 102] measuring and improving adherence to topical glaucoma medications remains an ongoing challenge.

There are several limitations of current strategies to enhance adherence with eyedrop administration. First, while several sensors detect eyedrop medication administration, they do not actually measure medication instillation into the eye itself. Similar to sensors specifically targeted at confirming oral medication ingestion, more work is needed to develop ocular sensors to confirm instillation of medications into the eye. Second, medication adherence affects racial minorities and individuals with less socioeconomic resources to a greater extent.[29 85 103] In a study by Sleath *et al*, African Americans were less likely to be educated about glaucoma by their providers and they were significantly less likely to be adherent to their glaucoma medications.[104] White patients were three times more likely to be 80% adherent or more to their glaucoma medications than non-white patients, mostly of whom were African Americans.[105] Thus, improving patient education and understanding of glaucoma and glaucoma medications could improve patient adherence and outcomes, particularly for racial minorities. Few studies have looked specifically at whether these new technological advancements can effectively be leveraged to address this health disparity. For example, the majority of participants in the study of EHR-linked reminders were white men with low risk for non-adherence.[106] Future studies should aim to have greater representation of women and minorities, who are disproportionately affected by glaucoma. Additionally, patients' digital literacy should be considered when designing and deploying these interventions.

Moreover, the majority of existing studies reviewed here had relatively small sample sizes and short follow-up periods. Because glaucoma is a chronic disease, longer follow-up periods are needed to establish whether patients can tolerate long-term granular medication adherence monitoring. Bias from the Hawthorne effect,[70 71] can also confound results, as adherence may have appeared to improve simply because patients knew they were being monitored. To establish efficacy, randomised controlled trials and masking procedures should be prioritised. Additionally, financial and economic considerations need to be addressed if these technologies are to be sustainable. Although decreased medication adherence incurs increased costs,[21] the vast majority of adherence technologies are still in development phases, and currently the published literature regarding novel sensors for eye medication adherence has not included detailed cost information. This may be due to these technologies being in very early stages of development, and costs might be anticipated to decrease as the technologies reach more widespread manufacturing and deployment that can leverage economies of scale. In the future, more rigorous economic analyses for the implementation of these sensor technologies will need to be conducted. Evaluating cost-effectiveness will be important given that low-cost alternatives such as educational videos to help patients improve their eyedrop administration technique have already been shown to be efficient avenues to address some of the barriers patients face in glaucoma medication adherence.[107]

Finally, ethical considerations must be at the forefront of all decisions to incorporate medication adherence technology into practice. Concerns about patient privacy, data sharing and adherence data becoming 'weaponised' to deny patients insurance coverage or increase premiums highlight some of the ethical issues that must be addressed.

In conclusion, the digital health era has brought multiple advancements in monitoring glaucoma medication adherence, such as improved sensor technologies and expanded modalities for communicating and engaging with patients in a widely scalable fashion. Increased focus on establishing efficacy with randomised controlled trials with long follow-up periods, rigorous economic analyses and addressing patient concerns about privacy and data sharing will be necessary to translate these technological innovations into clinical practice.

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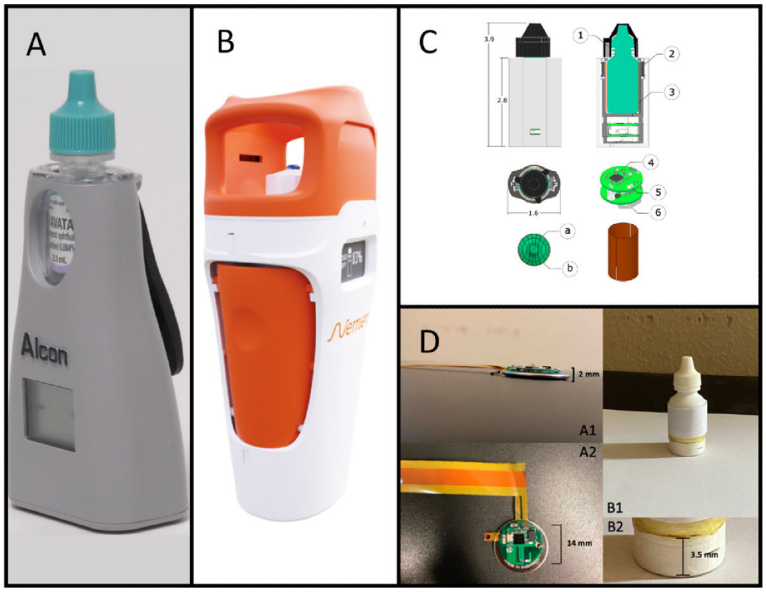

Figure 1.

Digital sensor technologies for glaucoma medication adherence monitoring. (A) The Travatan Dosing Aid. Reprinted from Friedman *et al*[108], Copyright (2007), with permission from Elsevier. (B) The e-Novelia Smart add-on for ophthalmic droppers. Available from: https://www.nemera.net/smart-ophthalmic-add-on-e-novelia/. (C) An intelligent sleeve with embedded sensors to quantify adherence and fluid level for glaucoma medication. Bar magnets (1) are placed in the cap, reed switches (2) in the sleeve sense cap removal, the two-part capacitive sensor (3) has two copper sheets (a) and (b) surrounding the bottle, electronics are embedded in an nRF51422 system-on-a-chip (4), Bluetooth low energy (5) is used for data transfer, and the system is powered with a single rechargeable coin cell battery (6). Reproduced with permission from Payne *et al*.[68] (D) A smart drop sensor system comprised a thin conductive pressure-sensitive electronic sensor, for bottle squeezing detection and an electronic circuit (<2 mm thick) for signal processing and wireless transmission, in lateral view (A1) and top view (A2). The flexible sensor is contained underneath the label (B1), with electronics at the base (B2). Reproduced with permission from Aguilar-Rivera *et al*.[69]

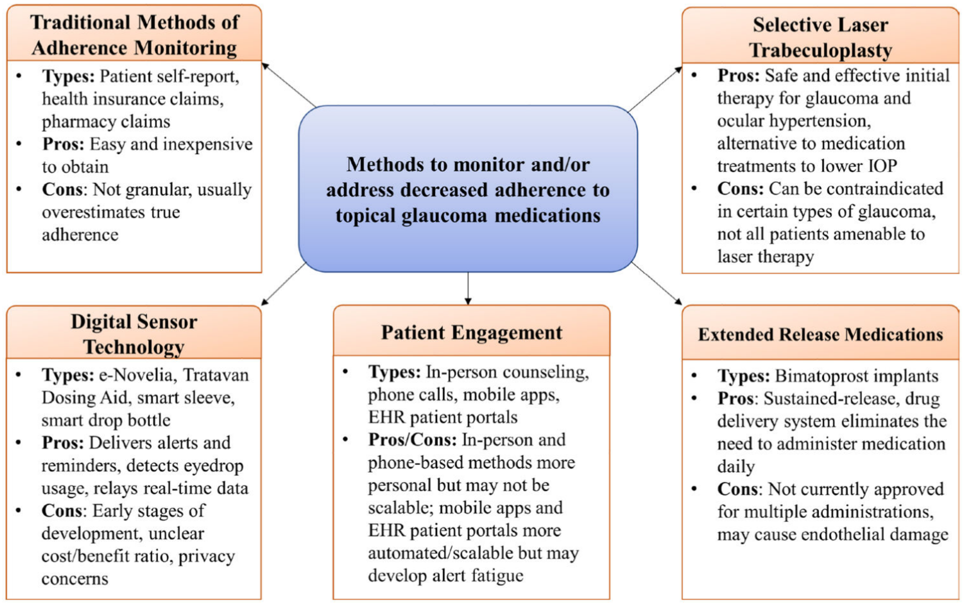

Figure 2.

Methods to monitor and/or address decreased adherence to topical glaucoma medications. Overview of developments in adherence monitoring and approaches. EHR, electronic health records; IOP, intraocular pressure.