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REVIEW

Adherence and Persistence to Medical Therapy in Glaucoma: An Overview

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ABSTRACT

Glaucoma is a group of progressive optic neuropathies characterized by loss of retinal ganglion cells and visual field deterioration. Despite the fact that the underlying pathophysiology of glaucoma remains unknown, elevated intraocular pressure (IOP) is a well-established risk factor, and the only factor that can be modified. Robust evidence from epidemiological studies and clinical trials has clearly demonstrated the benefits of IOP control in reducing the risk of glaucoma progression. IOP-lowering therapy by the means of eye drops remains a first-line treatment option. However, like other chronic and asymptomatic conditions, many patients with glaucoma have difficulties in maintaining high rates of adherence persistence to prescribed medications. On average, patients with chronic medical conditions take 30–70% of the prescribed medication doses, and on average 50% discontinue medications in the first months of therapy. The ophthalmic literature shows similarly low rates of adherence to treatment. Indeed, poor adherence is associated with disease progression and increased complication rates, as well as healthcare costs. The present review analyzes and discusses the causes of variability of the adherence to the prescribed drugs. The education of patients about glaucoma and the potential consequences of insufficient adherence and persistence seems fundamental to maximize the probability of treatment success and therefore prevent visual disability to avoid unnecessary healthcare costs.

Keywords: Glaucoma; Therapy; Progression; Adherence; Persistence

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Key Summary Points

Adherence to therapy is defined as the degree to which patients follow the prescribed therapy in a defined period.

Persistence describes the time in which the patients fill the prescribed therapy until the first discontinuation.

There are multiple reasons for poor adherence or insufficient persistence, including forgetfulness, the large number of drugs prescribed, and the virtual absence of immediate benefits.

It is evident that there is a need for education and tailoring of the therapeutic scheme for each patient with glaucoma.

Poor adherence is associated with disease progression and increased complication rates, as well as healthcare costs.

INTRODUCTION

Adherence and persistence to the prescribed therapy in patients with chronic diseases such as primary open-angle glaucoma (POAG) is of utmost importance for the success of the treatment and to avoid unnecessary healthcare costs. The terms to describe patient medication-taking behaviors became more precise over time. Adherence to therapy is defined as the measure to which patients follow the prescribed therapy in a defined period of time. On the other hand, persistence describes the time in which the patients fill the prescribed therapy, until the first discontinuation [1]. To the best of our knowledge, the first to describe the importance of "compliance" of patients to therapy was Hippocrates, who stated: "Keep a watch…on the faults of the patients, which often make them lie about the taking of things prescribed." Adherence in glaucoma is comparable to several chronic diseases with few or no symptoms at initial stages, e.g., diabetes and hypertension, which require oral medication [2]. In this regard, according to Brown and Bussell [3] a large proportion of patients with hypertension, between 50% and 80%, are non-adherent to their therapeutic regimen. The insufficient adherence is associated with poor efficacy of therapy, disease progression, complication, and hospitalization [4]. It was estimated that poor adherence increased healthcare costs by approximately 3–10% [5]. For what concerns specifically glaucoma, the insufficient adherence may often be erroneously considered as treatment failure, inducing unwarranted modifications of hypotensive drugs, unnecessary surgical interventions, and increased costs for the health systems. Indeed, as demonstrated by Newmann-Casey et al. [6], adherence to prescribed glaucoma medication resulted in an improved quality of life associated with a relatively low increase of costs over the course of a lifetime. Overall cost for adherent patients was estimated at approximately $62,000, compared with $52,000 for non-adherent patients. In terms of quality-adjusted life years (QALYs) over a period of 60 years, non-adherent patients had a mean loss of 0.34 QALYs with respect to adherent patients, and the consequent cost-effectiveness ratio was $29,600 per QUALY gained.

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

REASONS FOR POOR ADHERENCE OR INSUFFICIENT PERSISTENCE

The reasons for poor adherence or insufficient persistence are multiple, including forgetfulness, the large number of drugs prescribed, insufficient disease awareness about pathophysiology of glaucoma, and the virtual absence of immediate benefits. It is also worth noting that compliance to topical ophthalmic drugs is hampered by physical impedance and disability, such as movement disorders that hinder eye-drop administration, poor hand–eye coordination, and insufficient visual acuity [7]. Moreover, POAG is a chronic disease that often

results in visual field loss that the patient does not detect until it is advanced. Therefore, adherence to therapy is often hindered by the fact that patients with glaucoma hardly recognize a notable improvement of symptoms. On the other hand, disease progression is closely related to the degree to which the patients adhere to their therapy. Past literature illustrates that, among patients still alive at 90 years old with a history of glaucoma, the prevalence of profound vision loss (monolateral or bilateral) is 42.6% among non-adherent patients compared with 19% among adherent subjects.

A Cochrane review recently illustrated that there are several techniques to improve adherence among patients with glaucoma, but those with the highest success rates employed personalized counseling strategies [8]. Intriguingly, knowledge of glaucoma among patients was found to be significantly associated with increased self-reported adherence [9] and persistence to glaucoma medication [10]. Educational videos [11] as well as educational sessions with nurses [12] on the importance of correctly following the prescribed therapeutic regimen were demonstrated to be useful in improving medication adherence in a follow-up of up to 6 months. Moreover, the simplification of the therapeutic schemes for the hypotensive drugs, explanation of proper instillation technique, and other educational interventions may help patients to adequately adhere to the prescribed eye drop regimen. Indeed, monotherapy is usually the first choice of treatment. The need to simplify the treatment regimen leads to the introduction of fixed combination eye drops when multiple therapy is required. However, even the simplest regimens are associated with poor adherence rates [8].

METHODS TO MEASURE ADHERENCE

The most frequent methods utilized to measure patient adherence to therapy are self-reports, pharmacy dispensing records, and electronic systems linked to drops bottles, which can assess the frequency of use. For what concerns self-reports, it has been demonstrated that patients usually overestimate their adherence to the prescribed therapy; about 95% of patients with glaucoma report to be perfectly adherent and persistent with the eye drops, despite clear evidence of lower objective rates as illustrated by the Glaucoma Adherence and Persistency Study (GAPS) [13]. GAPS was carried out to develop methods for investigating adherence to glaucoma medications by using a modified claims data-based measure of adherence, validation by chart review, and patient and physician interviews. The GAPS evidenced that large pharmacy databases offer insight into medication usage but are vulnerable to errors from free sampling (since patients who receive free samples will be considered to have poor adherence), misidentification of newly treated patients, and misclassification of added versus switched medications. Moreover, as a large proportion of patients stop and restart medications, medication possession ratio (MPR) is a robust measure of adherence over time that reflects the resumption of medication after a gap in adherence. The data of GAPS confirm that adherence to treatment with glaucoma medications is poor, similar to adherence in patients with other chronic diseases. Moreover, self-reports may be affected by the cyclic behaviors that are associated with white-coat syndrome, which typically shows a strict adherence to therapy for 5 days prior to a scheduled visit followed by a decline in compliance over the next month [13]. In this regard, it should be noted that this behavior may induce practitioners to erroneously consider the patient as having a well-controlled IOP. Therefore, in cases of progression of the visual field loss, it would be impossible to discern whether the IOP target should be further lowered or if the disease is progressing due to the insufficient adherence of the patient in the time between scheduled visits. Large pharmacy dispensing reports help to avoid the above-described problems associated with self-reports.

Various techniques have been described to measure the adherence of patients with glaucoma to prescribed therapy, with varying degrees of success. These include subjective grading based on questionnaires and objective measurements such as pharmacy dispensing

records or insurance claims databases. The introduction of medication monitors allowed for even more precise quantification of the adherence of patients with glaucoma. Considering that insufficient adherence to therapy represents an important health and economic issue, it is important to use the appropriate technique to quantify medication-taking behaviors.

Questionnaires

Self-reported questionnaires (SRQs) are one of the most common techniques utilized to investigate adherence to therapy among patients with glaucoma. SRQs are easy to use and are relatively affordable. However, the reliability of this method is impaired by a possible overestimation by patients in self-assessing their ability to follow the prescribed regimen [14]. In this regard, it is known that SRQs reported higher adherence rate in comparison with other methods, such as electronic monitoring devices [15]. Indeed, the average difference between these two methods was estimated to be between 9% and 14% [4]. In this regard, Kass et al. [16] reported that patients missed 24% of their prescribed drops using a gyroscopic sensor associated to pilocarpine bottles. When asked, the same patients reported that they missed only 3% of the doses.

There are two questionnaires that are commonly used for assessing adherence: the Frequency of Missed Dose (FMD), which is a one-item questionnaire investigating the number of doses missed by the patients each month, and the modified version of Morisky, Green and Levine Medication Adherence Questionnaire (MGL) [17]. The McClelland group [18] developed a questionnaire tailored to patients with glaucoma, based on the already existing MGL, that is used to investigate adherence to therapy in the diabetic population and in those with high blood pressure. The nature of the questions evaluates the knowledge of the patient concerning:

(1) their own disease
(2) the importance of following a regular treatment
(3) the relationship of trust established with the referring physician

Using this questionnaire it was shown that 41.4% of subjects referred complete adherence to the prescribed therapy and 53.9% referred partial adherence, while low adherence was reported by 4.7% [18, 19]. The three major reasons for incomplete adherence were forgetfulness, changes in the daily routine, and tiredness linked to the administration of drops later in the evening. Furthermore, using questionnaires it was demonstrated that only 55% of patients were aware of the names of the drugs they used. This incomplete awareness was associated with low adherence rates [19].

Pharmacy Dispensing Records

Another instrument for investigating adherence is the MPR. This method utilizes the official registers of pharmacies or administrative data to measure the drug refill patterns, and it was used for investigating adherence in several chronic diseases, including glaucoma. MPR could be considered as the quantity of prescription supply dispensed divided by the amount of medication required during a defined period of time [19]. For population health researchers, administrative claims databases present many benefits, including sample size, real-world utilization information, and generalizability [20]. These data aim to investigate the relationship between adherence to therapy with economic and health outcomes. MPR is also useful when studying persistence to therapy among patients with glaucoma.

Using this method the GAPS demonstrated that 59% of patients with glaucoma withdrew their medication within 12 months, and only 10% kept following the prescribed therapy after 1 year [13]. In a study conducted by Fehaam et al., using a chain composed of two retail pharmacies (64 stores) in the USA collecting data over a period of 24 months, it was shown that at 12 months MPR was 37%, demonstrating insufficient persistence to glaucoma therapy [21]. However, MPR could be considered more as an indicator of drug consumption rather than adherence or effective medication use.

Indeed, GAPS showed that a possible bias stems from the utilization of free samples received from their physicians, an event described in about 20% of patients, which may increase the time between two consecutive refills. Another source of error may be represented by the introduction of a second drug, which could be interpreted by registers as a switch, or an interruption, of the drug used, an event that was estimated to occur in about 17% of the patients. Moreover, the time that an eye-drop bottle lasts a given patient does not necessarily reflect the amount of liquid effectively administered. For example, if a patient recognizes having missed the eye, another drop would be subsequently applied, resulting in an increase of the estimated administration [13].

Medication Monitoring Systems

Electronic monitoring devices associated to drop bottles were proposed to objectively quantify the true instillation rate. These systems are expensive and easy to use. These systems are powerful tools for measuring frequency of eye-drop administration, highlighting irregular treatment patterns and the potential increased rate of administration approaching scheduled visits. It was not until 1974 that development of the first electronic monitoring sensor capable of detecting the frequency at which the bottle was lifted from the eye drop bottle container was achieved [22, 23]. More recently, Norrel et al. [24] proposed an electronic sensor able to register the cap removal from an eye drop bottle, that could be also associated to a unit recording the inversion of the bottle; bulkiness of the devices and high costs represented some of the main reasons for the limited diffusion of these systems. However, the most important issue associated with the utility of these methods is that these devices are able to report the frequency in which the patient uses their eye drops, but they do not provide information about the volume of the liquid appropriately instilled on the ocular surface [25].

In the following years, further systems were proposed. Some of them provided built-in electronic sensors; an example of this is represented by Kali drop device (Aptar Group, Aptar Pharma). The electronic sensor of Kali drop device is able to detect when the eye-drop bottle is used by the patient, recording the movements of the bottle, cap removal, and the number of drops that leave the bottle [26]. Through this device, an adherence rate of 82% was recorded, which slightly decreased over a 1-month period.

FACTORS DETERMINING ADHERENCE AND PERSISTENCE

Several barriers for low adherence and persistence with topical glaucoma therapy were identified in many studies. Tsai et al. [27] using patient interviews identified many obstacles to compliance, and the majority of them were either social/environmental factors or were linked to the prescription itself, such as adverse events, complexity of drug regimens, and cost of medications. Taking into account that patients with glaucoma are usually elderly and are often alone, social/environmental barriers gain importance. These barriers were suggested to be related to the lack of support during instillation of drops, forgetfulness, major life events, and travel issues.

Additionally, Konstas et al. [28] investigated compliance with topical glaucoma therapy, detecting two categories of obstacles to adherence: involuntary (forgetfulness or difficulty administering drops) and voluntary (medication side effects).

Moreover, the factors for low adherence and persistence in glaucoma therapy were investigated by Gelb et al. [29] in the Glaucoma Adherence and Persistence Study (GAPS) through structured interviews. Many factors and co-factors were identified by physicians such as cost (55%), forgetfulness (32%), fear or denial (16%), lack of understanding about glaucoma (16%), and regimen complexity (15%).

From their own perspective, investigators detected lack of patient motivation to use drops (50%), insufficient understanding about the pathophysiology of glaucoma (41%), and ineptitude to convey why adherence and persistence

are crucial in the treatment of a chronic condition [29].

Another important barrier for poor adherence is white-coat syndrome, which is associated with a strict adherence to the therapy for 5 days prior to a scheduled visit and then a decline over the next month [30–32].

Cost, Variability by Drug Class and Tolerability

One of the main reasons for the insufficient adherence to therapy could be linked to problems with eye-drop administration and the complex dose regimens prescribed [33]. In a survey in four geographically distinct ophthalmology practices in the USA, 62% of patients with glaucoma reported having problems in following the prescribed therapy. The most common obstacle referred by patients was drop administration (44%), followed by cost (41%) and adverse events (16%). In addition, several patients needed carers and declared that a relative or another person administered their drops [33].

The number of drops prescribed seems an important issue in determining the compliance of the patients [34]. Robin and Cover illustrated that patients with multiple medications had more problems than patients on monotherapy. Indeed, patients who were prescribed an adjunctive ocular hypotensive drug refilled their first-prescribed medication less frequently [35].

Moreover, in a systematic review, Claxton et al. observed that fewer doses per day were associated with better adherence [36].

Indeed, it should be also noted that scarcely adherent patients may hardly reach the target IOP. The insufficient IOP reduction may be erroneously considered treatment failure, inducing physicians to prescribe additional drops and therefore further reducing the patient adherence [36].

Differences in adherence and persistence by class of ocular hypotensive drugs have been shown in many studies. Furthermore, variability by drug class is related to adverse events/tolerability, cost, and dose regimen of the medication [8, 32].

For what concerns the role of the drug class in determining patient adherence, several studies suggested a better adherence and persistence with prostaglandins than other types of drugs [37–39].

The importance of prostaglandin analogs in increasing adherence and persistence was shown also in other studies. Indeed, it was illustrated that nearly half of patients who were diagnosed with glaucoma or were considered as glaucoma suspect discontinued the hypotensive therapy within 6 months. By 3 years following the initial prescription, only 37% of patients had recently refilled the prescription. However, prostaglandin therapy was associated with better adherence and persistence rates with respect to the other classes [40]. In this regard it has been demonstrated that only 33–39% of patients with glaucoma were persistent with initial glaucoma prescription of timolol at 1 year, while persistence increased to 70% in patients treated with a prostaglandin analog [1, 41]. It is worth noting that both these aspects were found to be higher in patients with diagnosed open-angle glaucoma than glaucoma suspects [39].

Little is known about the effect of drug cost. A survey of patients with glaucoma in the USA showed that 41% of patients had problems paying for their medications [33], while another study, also conducted in the USA, illustrated that 11.5% of the patients considered their medication too expensive and for this reason avoided properly refilling their prescription [42].

Healthcare in European Union (EU) is publicly funded for all residents by the National Health Systems (NHS), irrespective of social class or employment, and each resident has a general practitioner (GP), and thus this aspect related with persistency has a marginal impact in European Union countries. For what concerns the side effects related to the hypotensive therapy, Gelb et al. noted a difference between

mild and more disturbing adverse events in terms of adherence. Interestingly, some patients reported a better adherence when they experienced minor adverse events, such as itching and burning. These symptoms seemingly attest that the patient was adherent to the prescribed treatment [29]. Indeed, about 30% of patients who referred these side effects had better adherence rate than those who did not [14]. On the other hand, conjunctival hyperemia was the most common side effect and frequently mentioned by patients as the primary cause for stopping or switching their medication [29].

Comorbidity and Difficulty Administering Drops

The effect of age on the adherence rate is still debated; however, it could be envisaged that older patients with glaucoma may be less compliant to their treatment due to age-related comorbidities [30, 43]. In this regard, the ability to adhere to the therapy could be hindered by physical (e.g., arthritis, tremor) or mental (e.g., memory problems) dysfunctions [44].

Physical or functional disabilities (such as manual dexterity, hand–eye coordination, and sufficient visual acuity[7]) may prevent the patient to adequately administer eye drops, and it was demonstrated that older patients needed auxiliary support from carers [45].

Moreover, for what concerns social/environmental factors, it was illustrated that patients who depended on carers to instill their prescriptions were associated with a decreased ability to remember their drops [33]. On the other hand, Tsai did not find a reduction in the adherence rate among patients living in nursing homes [46].

Little is known about the effect of comorbidity in adherence and persistence. In the GAPS study it was analyzed how concomitant medical diseases influenced adherence rate, using the Deyo-Charlson comorbidity scoring index. In this paper it was shown that there is an indirect relationship between comorbidities and adherence rates [47, 48].

Other papers suggested that poor adherence was associated with systemic multiple therapies and complex regimens. However, the sense of illness perception in patients with co-occurring diseases was found to increase adherence to therapy [49].

Lastly, adherence deteriorates as therapy duration increases. In this regard, Robin and Grover noted that in the second year the risk of non-adherence increased up to 20%, while in the third year it increased to more than 28.5% [7].

Denial, Lack of Education, and Lack of Patient Understanding about Glaucoma

The lack of education about the glaucomatous pathophysiology is correlated with poor adherence [1]. Busche and Gramer noticed a direct relationship between MPR rates and the patient's knowledge about the importance of the therapy in determining disease progression [34]. Past literature also shows lower adherence rates in patients whose awareness about glaucoma depends exclusively on the physician compared with patients informed by friends, printed material, or the internet [1, 34].

Since glaucoma is a chronic asymptomatic disease, such as diabetes or hypertension, patients hardly recognize the importance of their daily therapy. For this reason, the constant monitoring performed by physicians seems critical to increase the adherence to therapy [7]. In this regard, several studies argue that is important to plan follow-up visits, since doing this on a discontinuous basis is correlated with low adherence rates [50–53].

A paper compared patients with glaucoma who had programmed follow-up visits every 6 months and those who had intervals in follow-up of more than 6 months. In that paper the adherence to therapy was investigated through telephone interviews, and the group of patients who had a gap of more than 6 months in follow-up presented a poorer adherence [52]. Also the role of the physician in determining adherence to therapy was demonstrated by the

GAPS study. In this regard, patients with the follow-up visit planned and reminded by the physicians had higher MPR [14].

INTERVENTIONS FOR IMPROVING ADHERENCE AND PERSISTENCE TO THE PRESCRIBED THERAPY

The solution to the compliance challenges in all medical branches is complex and passes through a multilevel approach [1] (involving patients, healthcare providers, healthcare organizations), and each strategy must be integrated.

Regarding the strategies for increasing adherence, single-focus interventions did not prove effective [3]. In chronic therapies, a multifaceted and individual approach is recommended [2] and multiple interventions must be combined; the same all-around and patient-tailored strategy could be suggested for glaucoma therapy [4, 5]. Indeed the 2013 Cochrane review [6] about adherence in glaucoma showed that it is not possible to recommend any single-focus intervention due to the heterogeneity of the strategies and the lack of high-quality studies in this field. The above-mentioned paper reported that those studies that merged the educational/informative intervention with other counseling interventions (such as daily routine planning) appear to be more successful. The reason why this multifaceted approach in some glaucoma studies [7] did not give significant results compared with the control group often lies in the "study participation awareness" effect aroused in these patients, which made them more aware since they were recruited. Intervention options available with the aim to improve adherence are analyzed below.

Considering that patients with glaucoma are supposed to be tested with periodic functional assessments (e.g., visual field examination), the first intervention in favor of adherence on therapy could simply be regular ophthalmological examinations, during which it is possible to reinforce the recommendations regarding use of prescribed eye drops.

INDIVIDUALIZING THERAPY, EDUCATIONAL, AND MOTIVATIONAL INTERVENTIONS

It was already evident in the 1970s [8] that there was a need for education and tailoring of the therapeutic scheme for each patient. Monitoring aids capable of recording information about the use of eye drops cannot improve compliance if they are not supported with patient education and a tailoring of the therapy based on the patient's routine. In 2013 Waterman et al. [8] showed the efficacy of an individualized-patient care program in improving adherence in patients with glaucoma. Individualized care programs assume a good doctor–patient relationship and include educational intervention, giving motivation, counseling, and keeping the attention of the patients on the importance of the adherence and persistence [10, in addition to discussing with the patient (and caregivers) the best planning of the therapy into their routine, simplifying eye-drop schedule, teaching instillation technique, and training the correct technique for eye-drop administration.

Among patients with glaucoma there is often poor perception of the disease and of the benefits of therapy. Several papers [4, 8, 11, 12] showed that patient education is an important factor in adherence to glaucoma therapy, particularly if delivered over multiple sessions [54] and especially in newly diagnosed patients [14]. Knowledge of glaucoma (and of the risks in avoiding eye drops) can be improved by informative material, videos [4, 13], slideshow [8], meetings, didactic presentation, or interactive session [14].

Education alone seemed insufficiently effective in changing behavior; indeed, it was shown that it could be disappointing for patients with glaucoma [13]. A 2016 systematic review on educational intervention found [11] that only interventions with a relevant amount of face-to-

face counseling improved glaucoma adherence. The majority of effective educational interventions were based on the framework of behavioral theory (e.g., adult learning theory, health motivation theory, motivational interviewing, self-determination theory). Motivational counseling (as also for other clinical issues) [15] has proved to be useful in the case of glaucoma treatment adherence [4, 16], but only if the counseling time was not too short [11, 12, 17]. Communication was reported [18] to be a key factor in glaucoma compliance: although it is often an obstacle especially in patients with glaucoma [19], doctor–patient relationship can be a significant resource for improving adherence. Friedman et al. [14] highlighted the importance of this relationship and of the health-related beliefs coming from it. Indeed, these authors suggested that it is essential to establish a doctor–patient alliance to engage the patient with the chosen strategies. In this relationship there would be a place to discuss clearly that vision can be lost if eye drops are not used, talk about strategies, plan the routine, and tailor therapy [4]. Patient-centered communication also helps physicians in exploring patients' firmer individual barriers and confronting them [21].

It was shown that patients with glaucoma need motivation [22] to constantly take the prescribed eye drops. To be motivated the patient must have a strong belief that the therapy works and that it is suitable for their case, with the hopeful conviction that eye drops are the best care for their eyes and visual function. It is documented that, compared with adherent patients, among nonadherent ones the belief that someday their eyesight will be affected by glaucoma is more common [23]. The importance of the right motivational inputs from the medical staff (tailored approach, education about clinical consequences of non-adherence) [2, 5] and the support by caregivers and family has been demonstrated. In this regard, in 2016 Dreer et al. [55] showed the efficacy of a multifaceted therapy program (a combination of education, motivational interviewing, and problem-solving training).

ACCESS TO THE EYE DROPS, INSTILLATION AIDS, AND DRUG COSTS

The physical limitations, including the inability to visualize the dropper tip or to identify correct bottle, could be an obstacle to the correct instillation of eye drops. Poor proficiency in self-administering eye drops is a significant impediment to glaucoma therapy efficacy [25] and is a consistent barrier to adherence [18]. Patients need their doctors to teach them (as well as their caregivers) how to correctly instill eye drops [18], and providing these practical instructions is an essential step to increase adherence [26]. In a 2017 study, Atey et al. [56] calculated that 77.2% of evaluated patients with glaucoma administered drops inappropriately, mostly because they closed their eyes. Note that the proficiency to instill eye drops is associated with adherence: in fact, when non-adherent patients instill eye drops, they are seemingly less able to instill them due to insufficient practice.

There are numerous instillation aids [57] now on the market: AutoDrop (Owen Mumford), AutoSqueeze (Owen Mumford), Eyedrop device (Vanguard Design), Eyot (Spruyt Hillen), Mirror-hat device (Strungaru MH), Opticare drop dispenser (Cameron Graham), Opticare Arthro (Cameron Graham), Upright Eyedrop Bottle (EG Glero), Xal-Ease (Pfizer). These aids are often an underutilized resource that doctors could encourage patients to buy if necessary.

There is evidence [58] that lowering drug costs is a good strategy for increasing adherence to therapy in patients with chronic conditions. In interviews with patients with glaucoma in the USA, cost did not seem to be a specific compliance factor [45, 59]. Some of these findings must be taken with caution because the interviews were taken in focus-group settings (structured discussion group, which aims to gather critical information) and not in single settings (an in-depth exploration of what is taking place and allows individual participants more privacy in their responses). A 2016 study protocol [60] concerning the effect of value pricing of glaucoma medications was published,

but the results have yet been published. The potential "economic barrier" is difficult to detect and seems invisible if the issue is not directly discussed with the patient [60].

RELIEVE EYE-DROP-RELATED STRESS

In recent years, many efforts have been made by pharmaceutical companies to produce eye drops with milder side effects. A significant step forward has been made thanks to the introduction of preservative-free eye drops. It is currently possible to give patients a therapy with no/minimal expected adverse effects [61].

Complexity of medication regimen can be a significant barrier, especially in elderly patients who are already taking many other drugs and struggle to remember to take them all every day at the established times. The effectiveness of increasing therapy adherence by reducing the number of daily doses has been demonstrated for various medical branches [62]. Even in patients with glaucoma, receiving multiple medication is a demonstrated non-adherence factor [32]. Simplifying therapeutic strategies (dosing demands) is probably the most effective intervention on improving glaucoma eye-drop adherence [54].

Forgetfulness, reported by patients with glaucoma, is the primary reason for noncompliance [18].

Tools that remind the patient to take the eye-drop dose and tools that can both encourage assumption of the dose as well as electronically store delivery data (adherence aids, see below) have been tested, although for now they are not very common.

A basic intervention in elderly patients is to help them remember the tablets by utilization of the daily blister packs [63]; in the case of eye drops, the unit-of-use packaging could be useful, but only if single-dose eye drops are used. A memory aid tested in 1991 (C Cap, Allergan) seemed useful (patient requested more refills after receiving the aid) [64]. A 2015 study evaluated an audiovisual reminder system (Eye Drop Chart), but the results reported no significant difference in adherence before and after using the aid [65]. Other tested reminder systems are alarm devices [66, 67], while telephone calls and SMS have been tested solely as clinical appointment reminders [68]. With the advent of smartphones/tablets and smartwatches, effective eye-drop-reminder/alerts applications have also been developed [69].

MONITORING EYE-DROP DELIVERY (ADHERENCE AIDS/MONITORING AIDS)

Electronic adherence monitoring devices [12] can store data in an internal chip and retrospectively help doctors in identifying deficiencies of administration. In this case the corrective intervention is of course postponed and occurs in the future (while they could also be immediately useful to the patient—as a reminder—if also equipped with a display with the current drop delivery status). Other new wireless devices also guarantee real-time monitoring by remote (Kali Drop, Kali) [26]. The Travatan Dosing Aid (TDA; Travalert; Alcon) [53] combines the three characteristics of dosing, memory (visual and audible) and monitoring aid [66], but it is shaped to accommodate only one single type of bottle (Travatan®).

Note that dosing and monitoring aids (monitoring aids only if they are visible as a distinct object from the eye-drop bottle, or if they can make alarm sounds), could act as reminder/memory aids simply by their presence, more so than the eye-drop bottle alone. This would be relevant for both patients and for caregivers.

ADHERENCE-FREE THERAPEUTIC STRATEGIES

One of the solutions to the challenge of adherence is working around the problem, focusing on care strategies independent of patient compliance. Adherence-free approaches are realistically one of the possible future paths for glaucoma treatment. Adherence-free therapeutic options range from early glaucoma surgery (laser trabeculoplasty, minimally invasive surgery with implantable drainage devices) to

intraocular or para-ocular positioning of implantable devices with slow release of hypotensive drug.

Regarding surgery, while it showed efficacy, it cannot be an answer for all types of glaucoma as it responds to specific indications and contraindications. Regarding implantable devices, in recent years a biodegradable intracameral plant (Sustained-Release-Bimatoprost, Bimatoprost SR; Allergan) has been tested [70] that delivers slow-release bimatoprost; the administration (by injection) occurs every 4–6 months, and after the first doses it can also be extended to 12 months. The first tests showed Bimatoprost SR to be safe and effective [70] in lowering IOP; it also reduced drug adverse effects since the prostaglandin injected is isolated from the ocular surface [71]. Another option are rings to be inserted in the conjunctival fornix (Bimatoprost ring, BIM Ring; Allergan), which have demonstrated safety, comfort, and retention and seem capable of reducing the IOP; compared with eye drops it seems that the incidence of adverse effects does not increase [72].

CONCLUSIONS

Insufficient adherence to therapy among patients with glaucoma is a widespread problem and represents an important health, social, and economic issue. Indeed, poor adherence is associated with disease progression and increased complication rates, as well as healthcare costs. The variability of the adherence to the prescribed drugs may stem from several factors including age, multimorbidity, the elevated number of medications to take, and insufficient knowledge about the disease. In this regard, there are several techniques available to improve patient adherence that should be tailored to patient needs, by reducing the number of drugs and avoiding unnecessary treatments. The profound education of the patient about glaucoma pathophysiology and the potential consequences of insufficient adherence and persistence seems fundamental to maximize the probability of treatment success and therefore to avoid unnecessary healthcare costs.

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

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