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Glaucoma Adherence – from Theriac to the future

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Patients must administer glaucoma eye drops every day to be effective. However, patients struggle adhering to prescribed glaucoma treatments, and poor adherence is arguably the largest contributor to vision loss from glaucoma. In this opinion for the Centennial Year of the American Journal of Ophthalmology (AJO), we will provide historical highlights to glaucoma adherence through four epochs: ancient history, modern history beginning with the advent of AJO in 1918, our contemporary understanding since the turn of the millennium, and the future. This opinion will describe the advances in the science of adherence, and the future work needed.

Since the beginning of medical care, physicians have recognized the difficulty with medication adherence. More than 2000 years ago, Hippocrates famously stated, “*Keep a watch...on the faults of the patients, which often make them lie about the taking of things prescribed.*” The Greeks created one of the first eye drops called theriac¹, a concoction to treat various illnesses including ‘piercing and pressing’ of the eyes from glaucoma. A key component of theriac was snake viper’s flesh! Unsurprisingly, theriac caused eye irritation. Physicians recognized an early lesson in eye drop adherence: pain is a barrier to adherence. They ‘improved’ theriac by adding opium to the concoction. In addition, physicians of the time often recommended an authoritarian patient-doctor relationship to improve patient adherence.

A second epoch from the advent of AJO until 2000 ushered several changes to the science of adherence. This epoch included the development of multiple classes of effective and tolerable glaucoma eye drops. However, adherence remained poor. In 1966, Riffenburgh emphasized the importance of a cooperative doctor-patient relationship. He argued that patient drop-taking behavior responds best to shared patient-physician decision-making and mutual participation rather than an authoritarian relationship.² This epoch also introduced electronic dosing monitors, which documented patients’ poor adherence and physicians’ difficulty recognizing it. Kass and colleagues’ groundbreaking study in 1986 in AJO used a custom-made pilocarpine bottle eye drop monitor with an integrated circuit containing a gyroscopic sensor. They found that patients missed 24% of their pilocarpine doses; their adherence improved just prior and after a recent visit; their physicians were unable to estimate their adherence; and patients over-reported their adherence stating that they missed only 3% of doses.³ However, this device was not able to be mass produced because of FDA guidelines for drop administration (see below).

A third epoch from 2000 until present day has shown a dramatic increased number of publications regarding glaucoma adherence (see Figure). This epoch has demonstrated that glaucoma adherence ranges between 50–60% when defined as using less than 80% of expected doses using self-reporting, pharmacy claims, chart reviews, and electronic dose-monitoring devices. However, these methods of measuring adherence can be inadequate because patients routinely overstate their level of adherence using self-reporting³, and pharmacy records and chart reviews may be incomplete, inaccurate, and difficult to obtain.⁴ Researchers have also explained factors related to poor adherence using health behavior models. These models suggest that physicians may identify barriers to adherence by inquiring how patients view the severity of their glaucoma; their attitudes to susceptibility to vision loss; the potential benefits and disadvantages of eye drop medications; and their self-perceived ability to demonstrate excellent adherence (i.e. “self-efficacy”).⁵ Physicians benefit from patient-centered communication strategies, which may improve their diagnostic ability to detect poor adherence.⁶ Common reasons for poor adherence include medication cost, symptomatic side effects, forgetfulness, poor health literacy, limited trust in health care, busy schedules, and physical or mental limitations.⁷ Small adjustments like simplifying dosing schedules, using eye drops with milder side effects, or adding medication reminders can improve adherence.⁸ Studies from this epoch also helped researchers understand the visual impact and economic costs of poor adherence.⁹

This epoch also documented the challenge of eye drop administration. Instilling eye drops requires fine-motor dexterity and spatial awareness to gently compress a bottle while maintaining its tip above, but not against, the ocular surface. Gupta and colleagues found that more than 90% of glaucoma patients instill their eye drops incorrectly. Thirty percent of patients missed the eye, and 75% of patients contaminated the bottle against the ocular or periocular surface.¹⁰ In a study using video recordings, 60% of patients reported never missing an eye drop, but less than 30% successfully instilled an eye drop on video review.¹¹ Like the Kass article referenced above, patients routinely overestimate their ability to administer eye drops.

The last epoch, the Future, may hold promise for improving the science of glaucoma adherence. As stated above, eye care providers have been unable to satisfy one of the tenets of epidemiology: to measure eye drop adherence accurately and reliably. Eye drop adherence would benefit from a universal device that provides visual and audio alerts when an eye drop medication is due and accurate adherence data to patients, physicians, researchers, and pharmacies. Eye drops, however, present unique challenges for measuring adherence. The FDA approves an eye drop medication only after its delivery bottle shows suitable sterility, drop quantity, and drop volume. A dose monitor for eye drops must utilize the FDA-approved bottle for that medication, without modification, and without interfering with eye drop delivery. Eye drop bottles vary in shape and form. Further, unlike oral pill bottles and caps, patients cannot reuse eye drop bottles because of sterility issues. However, two wireless smart monitors are in development for eye drops. The Kali Drop device attaches to the body of an eye drop bottle and uses a combination of motion and tactile sensors to track eye drop usage.¹² The authors have developed the Devers Drop Device, which is a reusable, silicone monitor and alert system that couples to any eye drop bottle cap

while permitting normal functioning of the bottle cap. Monitors may become mainstream instruments for measuring and improving eye drop adherence, or research tools only.

The future will also include improved delivery of ocular medications. Several manufactures have created delivery aids to increase the success rate of eye drop administration. These aids seem to go in and out of fashion and patients underutilize them.¹³ New aid and bottle designs, such as the nose-pivoted sleeve and bottle (Bedo Solutions, Portland, OR) may improve medication delivery. Future bottles may also use sensors and/or mists to verify medication reaches the ocular surface. Non-eye drop medication delivery, including subconjunctival or anterior chamber injections, punctual plugs, and contact lenses, can guarantee adherence once placed. Sustained release delivery systems hold promise for a non-drop future.

Despite the advances in the past century, eye drop adherence remains inadequate. In the future, we may even have an ingestible monitor, which documents adherence to a psychiatric medication.¹⁴ Similar ingenuity is needed in ophthalmic care. Still, even if technology improves, patients will only use their eye drops if they are motivated to do so, and must believe in their health care in order to adopt a change a behavior. Physicians can help understand these motivations using a health behavior model. They can help with self-efficacy of eye drop dosing using a delivery aid. Finally, dose monitors may provide key information that is currently lacking to improve the science of eye drop adherence in the future.

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Figure.

The number of publications have increased steeply since the year 2000 in Pubmed (using the search terms 'glaucoma adherence' OR 'glaucoma compliance').