Glaucoma Treatment: A Closer Look at Non-Adherence

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Student Name: Sumir Pandit

Scholarly Report Title: Glaucoma Treatment: A Closer Look at Non-adherence

Mentor Name and Affiliation: Teresa Chen, MD, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary

Abstract

TITLE: Glaucoma Treatment: A Closer Look at Non-adherence

Purpose: The health and economic impacts of non-adherence to glaucoma treatment are profound. If adherence were increased, even marginally, the occurrence of severe complications such as blindness may be reduced. This study sought to understand which factors contribute to glaucoma patients' failure to properly take their medication and elicit how these reasons can be remedied.

Methods: Patients from a single physician's clinic, who had both a diagnosis of glaucoma and a prescription for one or more pressure-lowering eye drops, comprised the eligible population. These patients were recruited from a convenience sample in the waiting room. Patients who consented to participate (99 patients of 121 patients approached, or 82%) took a written paper survey, which asked patients questions about their medication taking habits, their technology usage, and their preferred medication-reminder methods. Independent sample t tests and chi square tests were performed to find correlations between variables isolated from the surveys.

Results: 99 patients completed surveys. For the survey question, "Do you take your medicated eye drops at approximately the same time (within an hour) every day?" 86 of 95 respondents (91%) replied in the affirmative. There was a statistically significant difference ($p = .04611$) observed between the mean ages of those who responded yes (67 years old) and no (55 years old). This indicates that older patients tend to take their medication closer to the same time every day than do younger patients. Interestingly, a similar correlation between reported number of missed doses and age was not seen. According to the survey, those who take their medication within the same hour every day tend to use many medication-reminder methods - friends, family, and written notes - in addition to themselves to remember their medication. Meanwhile, those who take their medication less consistently during the day used fewer medication-reminder methods - mainly their spouses. At this time, there appears to be no statistically significant correlation between a patient's "tech-savviness" and his/her self-reported level of adherence.

Conclusions: Patients who take their medications at consistently the same time every day tended to be older and used many medication-reminder methods compared to patients who take their medications less consistently. Better knowledge of the role of technology, reminders, and timing habits as they are related to adherence is integral to improving patient adherence - and thus health - overall.

My Contribution to the Project

The original idea behind the project was mine, borne from an interest in bridging the gap between the care that is prescribed by the physician and the care that is administered by the patient. As such, I did not join an existing project or work off of an existing data set; rather, I built the project from the ground up, and was very grateful to have the support of my mentor Dr. Chen along the process.

I initially approached Dr. Chen with my idea for the project, the survey for data collection, and the end-points I sought to study. Following her approval and incorporating her suggestions, I moved forward to **design** the project in a way that reinforced my goals for the study.

Following my conceptual planning of the project, I undertook to write the Institutional Review Board application. The IRB process included multiple phone calls and in-person meetings to discuss particulars of the project with various administrators at both Mass Eye and Ear and Harvard Medical School. Over several weeks, I received revision requests from the IRB and submitted several iterations of revised applications.

At the conclusion of the IRB process, I met with the Information Technology officers at Mass Eye and Ear to work out the logistics of my technology and data usage during the project. Over the course of several meetings, I negotiated concessions appropriate for my project needs. In line with IT requirements, I acquired a separate research computer and encrypted it myself, such that it was up to standards for PHI data storage and analysis.

Following the administrative groundwork which took place over several weeks, I began the steps of carrying out my project. I created and iterated the survey for data collection, and reviewed the final wording with Dr. Chen. I completed EMR and computer training such that I could access patient records online. Dr. Chen assisted and arranged the clinic logistics such that I would have space in the clinic to carry out the surveys. She also instructed me on optimal chart navigation so that I could appropriately include/exclude patients from the study.

Subsequent to these preparations, over approximately two months, I personally chart reviewed and flagged over 300 patients, with a final tally of 99 patients who completed the study in full. I entered the data I collected into a secure encrypted computer, and I subsequently **analyzed** the data over the following months and years. I was the only study coordinator **executing** these tasks for my project.

I submitted an abstract of my initial findings at the Association for Research in Vision and Ophthalmology (ARVO) national conference, where it was accepted. I presented a poster at that conference in Seattle Washington in May 2013.

Subsequently, I continued work on a full manuscript of my study, which I recently completed and is the work that follows.

Appendix 1: Full Manuscript

Introduction:

In the practice of medicine, the therapeutic chain of action—examination, evaluation, diagnosis, treatment—is fraught with many factors impeding its realization, none more so than the breakdown between diagnosis and treatment. Indeed, even the most carefully crafted treatment plan is made less effective when that treatment—the medications prescribed—are improperly or incompletely administered. Patient adherence to medication—and strategies to boost it—has been studied as a means to improve the overall delivery of care. In this study, we examine this issue in the field of ophthalmology from a unique viewpoint.

In glaucoma especially, where the progression of disease is slow and insidious, the dissociation between the importance of medication and the absence of apparent symptoms may heighten the problem of non-adherence. Previous studies have established that low adherence rates are associated with poor clinical outcomes, establishing a concrete reason to investigate and ultimately remedy reasons for non-adherence.[i] Literature on this topic, as related to ophthalmology, has extensively detailed potential reasons for non-adherence, including lack of disease education, inability to afford medication, simple forgetfulness, among many others.[ii,iii] Indeed, one study strongly linked poor patient-physician rapport with decreased adherence, indicating that physician factors may influence this critical outcome as much as the patients themselves.[iv] Ophthalmologists have previously designed elaborate interventions aimed at providing multi-faceted approaches to improving adherence, including patient education, medication subsidization, and electronic monitoring. To be sure, these interventions have in some cases resulted in significant improvements in adherence. However, these multi-faceted approaches have high costs of implementation and may be impractical on a large scale.[v] Approaches in which single interventions have been attempted are relatively less commonly seen. Notably, one study demonstrated the positive role of improved patient education in improving adherence to medication.[vi]

Looking more broadly outside of ophthalmology, the literature on medication adherence has numerous associations and causal links between interventions and increased medication adherence. One meta-analysis examined multiple interventions across a range of disorders including hypertension, asthma, COPD, HIV, diabetes, among others.[vii] In this analysis, short term effects in acute illness were examined based on the interventions of warnings of adverse effects and a medication-dispensing chart with home follow-up; neither intervention either positively or negatively affected adherence rates relative to the control groups within five days (all groups had very high adherence). The hypothesis was that mere

inclusion in the study involved discussion of adherence importance, whose effects persisted over the relatively short study duration. Once again, the effect of patient education on adherence is clear.

In the same study, longer-term effects were examined via a variety of ways. The most unified strategy attempted to modify dosing schedules by switching medications to extended release formulae and decreasing the frequency of administration each day. The effect on improved adherence was significant when fewer pills were required each day, though notably there was no effect on clinical outcomes associated with improved adherence. Nonetheless, this substantiation of a reasonable intervention suggests that ease of administration is in itself a goal of medication prescription. However, the implications on ophthalmology—where the chronicity of glaucoma obviates any short-term effects of one-time patient education, and the route of administration of eye-drops limits the utility of extended release formulae—remain unclear.

The same study examined various technology solutions, including automated telephone reminders and personalized phone calls and pill reminder notifications, each of which resulted in statistically significant improvements in adherence. Indeed, the potential of technology as a remedy for non-adherence is alluring, particularly in an era where the cost of employing dispersed technology is ever-decreasing.

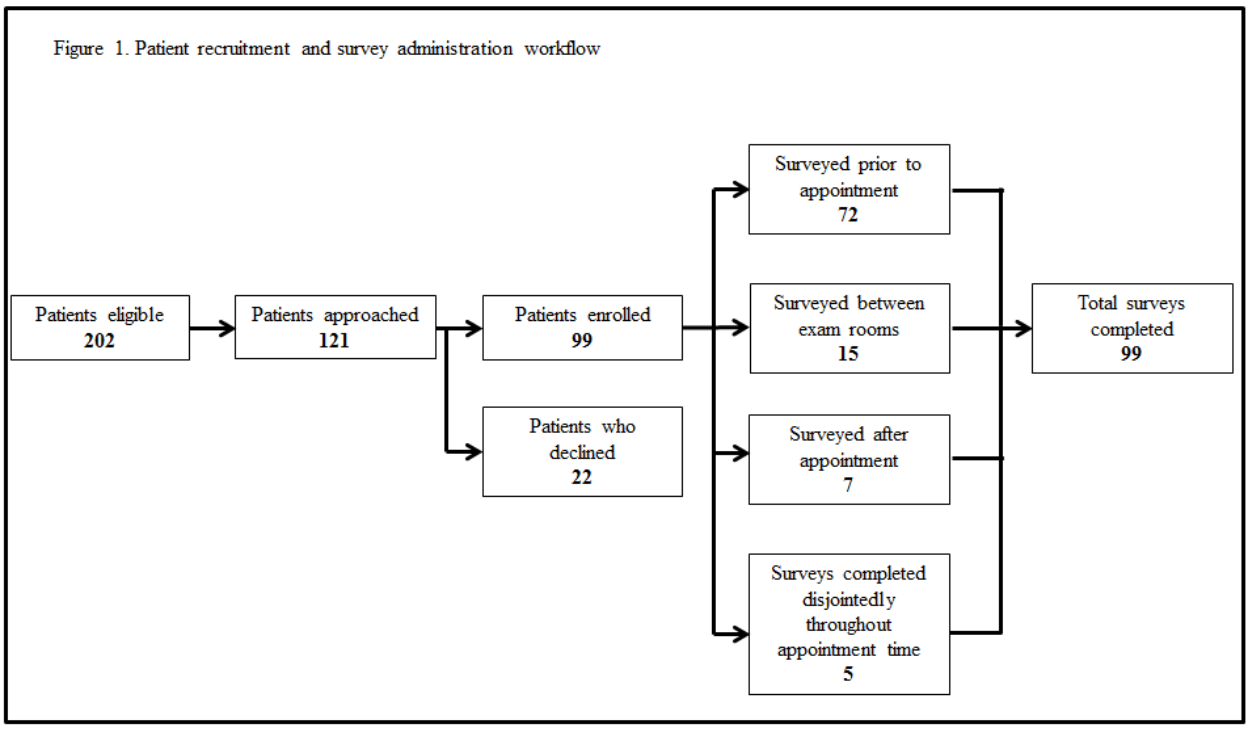
A particularly relevant recent study attempted to create a predictive model of non-adherence in a low-income, minority population of patients being treated for hypertension.[viii] The eight-question survey queried self-reported rates of recent non-adherence and various reasons for non-adherence. Surveys were linked to clinical blood pressure outcomes and the subsequent analysis demonstrated 83% predictability between the survey answers and true clinical markers of non-adherence. This study's focus on the reliability of self-reported metrics is relevant, though the use of clinical outcomes as well as its patient population substantially differentiates it from our current study.

Our study builds on the work of these previous studies by including many of their factors influencing adherence as items of observation. At the same time, this study is unique because it seeks to understand more broadly how a patient's home milieu affects his or her medication habits. By means of a survey administered to patients in a single ophthalmology practice, we gathered information to better understand how much non-adherence was due to lapses in memory, what techniques patients are already using to combat them, and what interest/utility patients see in technological aides to these strategies.

Methods:

The study, approved by the Massachusetts Eye and Ear Infirmary and Harvard Medical School Institutional Review Boards, was designed as a cross-sectional patient survey. Potential subjects were recruited from the practice of a single physician at Mass Eye and Ear Infirmary. Inclusion criteria included (1) the diagnosis of glaucoma and (2) a prescription for at minimum a once-daily eye drop for a chronic eye condition. Eligibility was determined through a review of the patient's electronic medical record and a list of their current medications.

From June 2012 to August 2012, 202 patients were deemed eligible for the study. All eligible patients received an informational flyer about the study upon checking in to the clinic. Of those, 121 potential subjects were approached in MEEI while waiting for their appointments with a glaucoma specialist and asked to participate in the survey prior to their appointments. A private room was made available for both the informed consent process and survey administration. Survey administration was carried out either before the appointment, between different components of the appointment, or after the appointment that day, at the patient's preference (Figure 1).



All subjects were approached, and all surveys were conducted by the same investigator. The survey included questions about the patient's demographic data, medication-taking habits, current and preferred medication-reminder methods, and technology usage.

Statistical methods: Initially, descriptive statistics were collected on each survey question, including means, standard deviations, and ranges for continuous variable responses, and frequencies for categorical variable responses. Next, independent sample t tests were performed to assess correlations between continuous data and categorical data, for example, between medication cost and self-reported inability to pay for the medication. Chi-squared analysis was performed to assess relationships between two sets of categorical data, for example, between use of text messaging and preference for automated reminder text messages. Significance was determined by a p value of 0.05. Statistical analysis was performed with the statistical software R (version 2.2.0).

Results:

99 of the 121 patients approached ultimately participated in the study and completed the survey; their demographics are presented below in Table 1 and their responses are presented below in Table 2. Note: because subjects were often permitted to mark more than one choice per question, the sums of responses are often greater than 99.

Table 1. Demographics				
		All	**Non-consistent Medication Takers**	**Consistent Medication Takers**
Total patients		99	9	86
Education Level				
	Didn't graduate high school	7	0	6
	High school/GED/equivalent	33	5	28
	Associate's degree	16	0	16
	Bachelor's degree	17	2	13
	Master's degree	12	0	12
	Doctorate	12	2	10
	Did not respond	2	0	0
Race/Ethnicity				
	White	68	6	61
	Black or African-American	12	0	12
	Hispanic or Latino	5	1	4
	American Indian or Alaska Nat	0	0	0
	Indian subcontinent	0	0	0
	Asian	9	2	6
	Did not respond	5	2	3
Age				
	Mean	66	55	67
	Quartile 1	59	48	61
	Median	69	55	69
	Quartile 3	78	74	79
Transportation to clinic that day				
	Driven by someone	47	5	41
	Public transit only	20	1	18
	Drove themselves	22	1	20
	Senior Shuttle	6	0	6
	Other	4	2	1

Table 2. Results			
Note: because subjects were often permitted to mark more than one choice per question, the sums of responses are often greater than 99			
		Responses	***As a % of total***
"If you have a cell phone, how do you use it?"		99	
	Do not own a cell phone	18	*18%*
	Phone calls only	46	*46%*
	Text messaging	27	*27%*
	Internet	14	*14%*
"On a regular computer or iPad, how do you use the internet?"		99	
	No internet use at all	32	*32%*
	Email account	54	*55%*
	News and current events	46	*46%*
	Maps and directions	46	*46%*
	Social media	23	*23%*
"In the last six months, have your missed taking any dose of medicated eye drops that you were supposed to take?"		98	
	Have not missed a single dose	62	*63%*
	Have missed at least one dose	36	*37%*
"Overall, compared to the number of medicated eye drop doses you are supposed to take, what percent of those doses do you ultimately end up taking?"		98	
	Reported 100% adherence overall	54	*55%*
	Reported 75-99% adherence overall	36	*37%*
	Reported less than 75% adherence overall	9	*9%*
"What are the main reasons you typically miss a dose?"		71	
	Simple forgetting	38	*54%*
	Inconvenient timing of medication	14	*20%*
	Cannot afford medication	7	*10%*
	Feel they do not need medication as often as prescribed	7	*10%*
	Do not understand instructions for medication	5	*7%*
"Who or what usually reminds you to take your medication?"		98	
	Totally self-reliant	61	*62%*
	Spouse	15	*15%*
	Other family members	11	*11%*
	Written reminders	3	*3%*
	Other memory tricks	7	*7%*
"With your usual reminder system in place, when you take your drops, do your take your drops at approximately the same time (within an hour) every day?"		95	
	Take medication within same one hour window every day	86	*91%*
	Do not take medication within same one hour window every day	9	*9%*
"If Mass Eye and Ear Infirmary started a program to help remind you to take your medication at the right time, which method would you prefer?"		89	
	Personal phone calls	28	*31%*
	Automated phone calls	27	*30%*
	Personal text messages	21	*24%*
	Text message to family members	3	*3%*
	Personal email	14	*16%*
	Did not want any assistance	13	*15%*
"What is the approximate cost of your medications per month out of pocket?"			
	Eye Medications only		
	Mean	$ 49.86	
	Median	$ 20.00	
	All Medications		
	Mean	$ 88.23	
	Median	$ 50.00	
	Outlier (not included in analysis)	$ 1,700.00	

Qualitatively, the technology usage statistics provide insight into how patients consume electronic content, with implications for possible venues for patient education. Notably, 46% of this population used a cell phone only for the phone call feature, and a further 32% endorsed having no internet use at all. To characterize a substantial portion of this population as limited in technological capability would be accurate. Indeed, the preferred reminder methods mirror this finding, where amid multiple more targeted and technological options available, 61% of patients stated they would prefer a reminder method that involved phone calls.

The most significant findings are seen in the area of dose consistency, where 91% of patients report taking their medication within the same hour each day. However, the disparity in characteristics between that "consistent" population and the "inconsistent" population were highly significant and will be discussed below.

Overall, self-reported adherence figures were extremely high, with 63% of patients denying missing even a single dose within the last six months, and 55% of patients reporting 100% lifetime adherence. As discussed below, there is precedent for doubting the veracity of these figures.

Discussion:

The issue of adherence to medication has plagued physicians even pre-dating the recent rise of technology, but this increasing influence of technology has brought to light potential low-cost ways to improve adherence. Indeed, this study's focus was aimed at discovering how much non-adherence was due to lapses in memory, what techniques patients are already using to combat them, and what interest/utility patients see in technological aides to these strategies.

In this study, because patient non-adherence was self-reported, we acknowledge the limitations of those data as standalone figures. Indeed, 91% of patients surveyed reported high adherence, defined here as over 75% of prescribed doses taken. Self-reported adherence is known to be poorly correlated with true adherence.[ix,x] Therefore, this metric—while helpful in understanding patients' perceptions of their own adherence—was deemed unhelpful in establishing true trends and was not used in further analysis. Instead, this study focuses on the more descriptive factors revolving around adherence and medication-taking habits. Those findings are highlighted below.

In terms of reasons for non-adherence, a plurality (39 among 71 episodes, or 54%, of reported non-adherence) were attributed to simply forgetting. A further 14 episodes (20%) of non-adherence were attributed to inconvenient timing of medication for non-adherence; for the purposes of this investigation, this reason was also included in the overall "forgetting" category. Otherwise, 14 episodes (20%) of non-

adherence were due to education issues, and a further 7 (10%) were due to medication costs. Despite our broader focus on memory lapses causing medication adherence, these episodes of non-adherence were included in a later analysis since patients were able to mark more than one reason for non-adherence.

Another goal of this study was to determine how tech-savviness plays into patients' medication-taking routine. Tech-savviness was defined in this study as (1) using the internet at all, (2) using a personal cell phone for anything in addition to phone calls, and (3) having a personal email account and using it at least monthly. Although the technology use questions in insolation yielded valuable information about patients' technology use habits, no statistically significant correlations were identified between technology usage and self-reported adherence, medication consistency, or reminder methods. Nevertheless, a large proportion of patients (86 of 99) stated they would consider using technology reminder solutions if they were offered by the clinic, and all but 28 of those supported solutions that could be automated and sent en-masse.

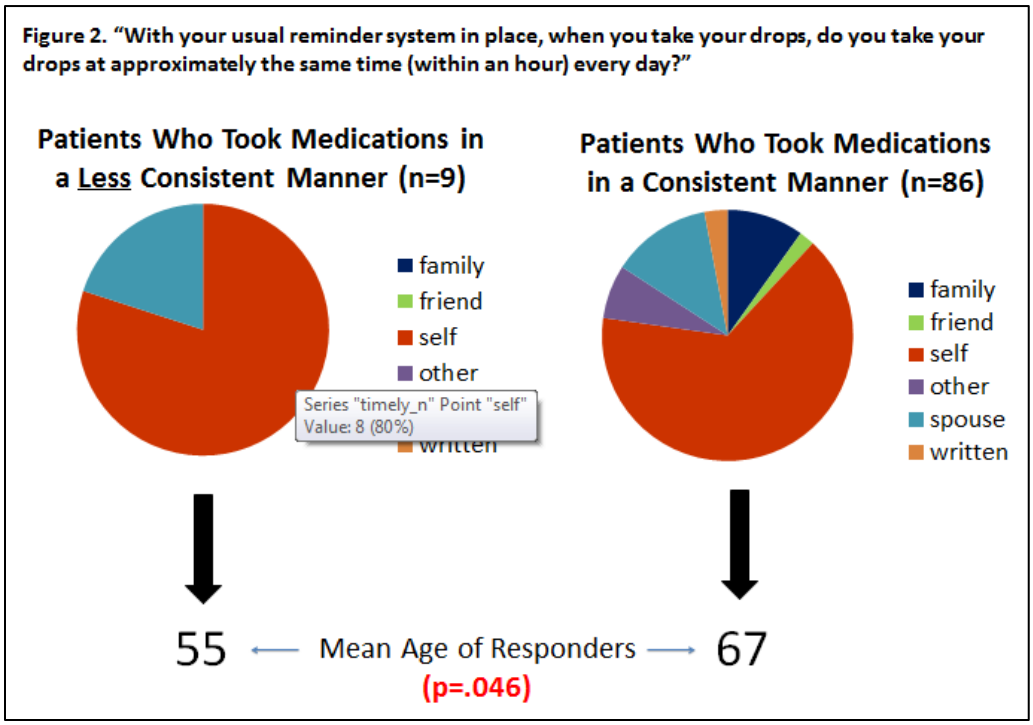
As is discussed further below, multiple reminder methods have high utility in improving patients' consistency in medication administration, and thereby their overall adherence. We see the use of technology as a supplementary reminder technique—an inexpensive and easily deployed method of many reminder methods patients also use.

Among all patients, we examined consistency of daily doses—defined as taking drops at approximately the same time (within an hour) every day—as a factor in adherence. Here, we observed our study's most significant findings.

Those reporting consistency of daily doses were seen to employ significantly more reminder methods—examples of such include reminders from family, friends, self, written notes, etc. The more consistent group was seen to use up to six different methods, versus two among the less consistent group. We find the implications of this to be quite substantial: those who recruited more individuals and techniques for reminding themselves took their medication more consistently. Whether this is due to the confounding of more fastidious individuals both installing more fail-safes and also being more consistent, or whether it is indeed causative—that more reminders caused the greater consistency— is unclear from this study.

We also observed a correlation of greater consistency and age—mean age of 67 among the consistent group versus mean age of 55 among the less consistent group ($p=0.046$) (Figure 2). The age correlation is perhaps easier to trace, wherein older patients may have older children who are capable and willing to be additional reminder tools, and older patients have similar-aged peers for whom the medication reminder is mutual. Anecdotal evidence obtained during data collection suggested both are true for many patients in

this study. Once again, any correlation between consistency and adherence were not established due to the self-reported nature of adherence metrics; however, the strong endorsement of "inconvenient timing" as a reason for non-adherence among this population suggests that consistent administration would help remedy a major contributor to memory lapses.



Limitations:

This study was carried out by one investigator in one ophthalmology clinic over a span of three months, with the intent of minimizing confounders and inconsistency in survey administration. As such, however, the sample size was ultimately 99 patients, which carries with it the limitations of any small-sized study. Those limitations are threefold: (1) there is concern that the sample size is not large enough to sufficiently answer all the questions of interest, (2) that any discovered statistically significant findings are in fact artifacts of sampling bias in a small population, and (3) that some true findings are hidden by the low power of the study. These are legitimate limitations of the study and were anticipated before initiation of data collection; this study was intended to be a pilot, whose subsequent investigations would be more targeted based on pilot findings and be more highly powered.

The relatively high recruitment yield (82%) for a study of this size mitigates somewhat the risk of response bias and indicates a relatively representative sample from the data obtained. Nevertheless, the

risk remains that those who declined participation in the survey may represent an especially non-adherent or otherwise skewed portion of the population, whose results are not captured by the survey.

As with any study that invites self-reporting of habits, there lies a risk of inaccurate reporting. However, the investigator who approached the patients attempted to mitigate the risk of deliberate misreporting by emphasizing that he was not involved in the patients' care, would not report the patients' answers (or participation at all) to their physician, and that their data would be aggregated and anonymized before it was seen by anyone else. Further toward the goal of anonymity, patients were given room to complete the survey without the investigator seeing their individual responses. Nevertheless, the risk of social desirability bias—over-reporting socially desirable behaviors in oneself— persists. Recollection bias, wherein the patient unintentionally skews his or her reporting based on inaccurate memory, as well as recency bias, where recent behavior is disproportionally reporting as reflecting all behavior—are also risks in such any such study.

In any study of association, the risk of confounding variables influencing correlations exists. In this study, the major finding—that those who take their medication more consistently each day tend to have more reminder methods—was examined through stratification based on education level, where those with bachelor's, master's, or doctorate degrees were grouped as "more educated" and the rest were grouped as less well educated. No significant difference in proportion of medication habits was observed. Gender might be another possible source of confounding, though survey data did not capture this variable in order to stratify results accordingly.

The population in this study was drawn from the practice of a single provider at Massachusetts Eye and Ear Infirmary. Table 1 indicates the demographic composition of this group. These results are most applicable to a New England-based population of patients, though the generalizability could extend to any older, predominantly white and well-educated US population of glaucoma patients.

Conclusion:

In summary, this investigation substantiated the oft-held assertion that more reminder methods are correlated with more consistency in medication administration, with strong implications for reverberations on adherence as well. As demographic shifts (i.e. a technologically-aware baby boomer population reaching old age) and technology trends (i.e. ever-less-expensive technology integrating ever-more into daily life) move towards more glaucoma patients using more technology in the near future, we see an openness to technological reminders as a low-cost way to supplement patients' arsenals of reminder techniques.

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