**Automated Telecommunication-Based Reminders and Adherence With Once-Daily Glaucoma Medication Dosing**

The Automated Dosing Reminder Study

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**IMPORTANCE** Topical glaucoma medications lower intraocular pressure and alter the course of the disease. Because adherence with glaucoma medications is a known problem, interventions are needed to help those patients who do not take their medications as prescribed.

**OBJECTIVE** To assess the ability of an automated telecommunication-based intervention to improve adherence with glaucoma medications.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a prospective cohort study of medication adherence, followed by a randomized intervention for those found to be nonadherent, of individuals recruited from a university-based glaucoma subspecialty clinic. A total of 491 participants were enrolled in the initial assessment of adherence. Of those, 70 were nonadherent with their medications after 3 months of electronic monitoring and randomized to intervention and control groups.

**INTERVENTIONS** A personal health record was used to store the list of patient medications and reminder preferences. On the basis of those data, participants randomized to the intervention received daily messages, either text or voice, reminding them to take their medication. Participants randomized to the control group received usual care.

**MAIN OUTCOMES AND MEASURES** Difference in adherence before and after initiation of the intervention.

**RESULTS** Using an intent-to-treat analysis, we found that the median adherence rate in the 38 participants randomized to the intervention increased from 53% to 64% ($P < .05$). There was no statistical change in 32 participants in the control group. To assess the real efficacy of the intervention, the same comparison was performed for the participants who successfully completed the study after randomization. Analyzed this way, the adherence rate in the 20 participants in the intervention group increased from 54% to 73% ($P < .05$), whereas there was again no statistical change in the 19 participants in the control group. Eighty-four percent of the participants who received reminders agreed they were helpful and would continue using them outside the study.

**CONCLUSIONS AND RELEVANCE** Automated telecommunication-based reminders linked to data in a personal health record improved adherence with once-daily glaucoma medications. This is an effective method to improve adherence that could realistically be implemented in ophthalmology practices with a minimum amount of effort on the part of the practice or the patient.
The barriers to medication adherence by patients with glaucoma are complex. Tsai et al reported 71 obstacles that could be categorized as situational or environmental factors, medication regimen, patient factors, and practitioner factors. Another study identified lack of education regarding glaucoma, lack of faith in drops, problems with drop administration, forgetfulness, and the practical issues of medication administration (eg, timing, location, and packaging) as important barriers to adherence.2

Because lack of patient adherence with medications is a known problem in a number of diseases, including glaucoma, there is a body of work on improving adherence. One systematic review,3 including 8 studies of interventions applied to patients with glaucoma, found heterogeneity in terms of both the measure of adherence (7 by self-report and 2 with an electronic monitor) and interventions evaluated. Because the interventions spanned approaches that ranged from education to individualized care planning to automated reminders, the authors of the review were unable to recommend a single intervention.

Another systematic review4 included studies that addressed interventions to improve medication adherence and was not limited to glaucoma. Because of the heterogeneity of the included studies the authors were unable to recommend a single intervention. They were able to suggest, however, that some combination of the following was likely beneficial: a simplified drug regimen, instruction and counseling, dosing reminders, more frequent office visit follow-up, supervised self-monitoring, patient rewards, family therapy, psychological therapy, and telephone follow-up.

These reviews predate 3 randomized studies of glaucoma adherence interventions. The first of these studies5 assigned non-adherent participants to a control group or to an intervention that included an educational video, discussion of adherence barriers with a study coordinator, regular telephone calls, and an electronic reminder connected to the medication bottle. Adherence was unchanged in the control group but increased from 54% to 73% in the intervention group. A second study6 randomized patients new to treatment to a control or customized educational intervention with frequent follow-up. The primary outcome was adherence based on refills with secondary measures related to self-report of adherence, glaucoma knowledge, beliefs about illness and medications, intraocular pressure (IOP) fluctuations, and changes in management. The intervention group displayed more knowledge, reported better adherence, had lower IOP fluctuations, and had fewer changes in management. A third recent study7 also identified nonadherent participants and then randomized them to an educational intervention using telephone calls and printed materials or to usual care. This study assessed adherence using a combination of self-report, refill history, missed appointments, and medical record review. Using these metrics, medication adherence increased for both groups after randomization.

One important drawback to the adherence interventions studied thus far for glaucoma is that they are difficult to implement because they are labor intensive and therefore not cost-effective for clinics operating in the current fee-for-service system in the United States. We therefore set out to evaluate an intervention that could be placed under patient control and would also require little or no ongoing work by clinic staff. Because personal health records and patient portals into electronic health records are increasingly common and now required,8 we elected to use one such system as the basis of an intervention to improve adherence. In addition, because of the presence of telephones everywhere, both wired and wireless, we used telecommunication-based reminders as the means of intervention. This approach has been reported to improve medication adherence in patients with human immunodeficiency syndrome9 and in those using long-term medications in general.10

To assess the ability of automated reminders to improve adherence with once-daily glaucoma medications, the Automated Dosing Reminder Study (ADRS) was designed with 2 phases: (1) an observational stage to identify participants who were nonadherent with their once-daily prostaglandin therapy and (2) a study of a telecommunication-based intervention to improve adherence.

Methods

The ADRS was reviewed and approved by The Johns Hopkins University School of Medicine Institutional Review Board. Patients provided written informed consent. The baseline characteristics and adherence of the participants enrolled in the observational phase are reported elsewhere.11 Those participants determined to have poor adherence with their medications were then transitioned to the intervention phase of the study.

Adherence Monitoring

The methods for participant recruitment, assessment of baseline characteristics, and measurement of adherence are described elsewhere.11 After 3 months of monitoring participants' use of daily prostaglandin medications using an electronic bottle cap (MEMSCap, MedWestvaco Corp), adherence was assessed in 3 ways: (1) as the percentage of days on which a dose was taken within 4 hours of the mean dosing time for that patient, (2) as the percentage of the total number of prescribed doses taken, and (3) as the percentage of days on which the correct number of doses was taken. If any of these numbers were below 75% or if the second value was above 125%, the participant was determined to be nonadherent (only 2 participants were labeled nonadherent by the latter criteria alone). Study participants who were nonadherent by this definition were then assigned to a control or intervention group using assignments randomized equally in blocks of 10 and placed in envelopes.

Intervention

Participants in the intervention group were registered for a HealthVault account (Microsoft Corp). HealthVault is a personal health record designed to allow patients to accumulate and manage their medical data. Study personnel were available to help with account creation. A customized HealthVault application was used to enter each participant's prostaglandin medication (bimatoprost, latanoprost, or travoprost) into the personal health record (eFigure 1 in the Supplement). Study personnel then worked with each participant to specify when
they wished to be reminded about their medication dosing and whether those reminders should be via telephone or text message (Figure 1). At any point during this phase of the study, participants could contact study personnel to modify or disable the reminders. Participants randomized to the control group did not receive any additional intervention, and both groups were again instructed to use the MEMSCap to monitor their medication use.

Once a participant’s medication and desired reminder time were entered into HealthVault, that information was transmitted securely as structured data to Memotext (Memotext LLC), where their preferences were used to generate daily reminders by telephone or text message (eFigure 2 in the Supplement). In either case, the reminders informed each participant in the intervention group that it was time to take his or her medication. The interactive voice response system also allowed participants to reset the reminder and receive it again in 1 hour: “Hello, this is your automated reminder to take your [drop name] eye drop. Press 1 if you have or are about to take your [drop name]. If you are not able to take your eye drop right now and would like a second reminder in 1 hour, please press 2 now.”

At 3 months after randomization, participants were again asked questions by the study coordinator about the monitoring device, their drop use, and the reminders (intervention group only):

- I find the device easy to use when I put in my drops (strongly agree to strongly disagree).
- I feel that using the monitor is causing me to take my drops less than I would if I were not using the dosing monitor (strongly agree to strongly disagree).
- I have used my drops without using the device during the study (strongly agree to strongly disagree).
- In the past 3 months, I used my glaucoma drops (every day, all but 1 or 2, more than half, about half, less than half, almost never).

Some days, I forget to take one of my doses of glaucoma medications (strongly agree to strongly disagree).
I found the reminders helpful (strongly agree to strongly disagree).
If reminders were available, I would continue to use them outside the study (strongly agree to strongly disagree).

The MEMSCap was collected, and the adherence rate was again calculated.

Statistical Analysis
Descriptive statistics were tabulated for each treatment group: number and percentage for categorical variables, mean and SD for continuous variables that appeared to be normally distributed, and median and range for other continuous variables. These statistics were compared for intervention and control participants using the Fisher exact test, the t test, or the Wilcoxon rank sum test, respectively. Differences in responses to the Likert-scale questions were assessed with the Mann-Whitney test. The primary outcome for the study was change in percentage of adherence from before to after intervention, measured as median percentage point change, and was evaluated for significance using the Wilcoxon signed rank test. Associations among change in percentage of adherence and demographic variables were explored using the Wilcoxon rank sum test for 1 binary variable and 1 continuous variable and the Spearman rank correlation coefficient for 2 continuous variables. Least squares means and P values from general linear regression models were used to estimate change in adherence in each group while adjusting for covariates. Analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc), and R, version 3.0.2 (cran.r-project.org).

Results
The flow of participants through the study is depicted in Figure 2. The baseline characteristics of the entire ADRS cohort and a comparison of the groups that successfully completed the 3-month assessment of adherence and those that were lost to and unavailable for follow-up are reported...
Participants again had their medication dosing monitored using MEMS caps for an additional 3 months after randomization. The reasons for randomized participants not completing the study included 16 who could no longer be contacted, 2 who disliked the monitor, 2 who disliked the reminders, 2 who transferred to other clinics for care, 1 due to cost, and 8 for other reasons. Potential risk factors for not completing the study, including age, sex, race, educational level, and baseline adherence, were compared between the groups who completed the intervention phase and those who did not. No statistical differences were found between these 2 groups for any of these variables (P > .05, data not shown).

Because of the large percentage of participants lost to and unavailable for follow-up (Figure 2), the effect of the intervention was evaluated in 2 ways. First, we analyzed the prerandomization and postrandomization adherence rates using an intent-to-treat analysis in which participants who were lost to and unavailable for follow-up had their baseline adherence assigned as their final adherence. With this approach, there was an increase of 11 percentage points in median adherence rates for the intervention group. The tendency for individual changes in adherence to be positive in the intervention group paired analysis was statistically significant (P = .04). A decrease in median adherence of 5 percentage points observed in the control group was not statistically significant (Table 2). Second, we assessed the real efficacy of the intervention by restricting the data to those participants who successfully completed all phases of the study. When analyzed in this way, the intervention resulted in an increase of 19 percentage points in median adherence. Individual changes again tended to be positive in the intervention group (P = .003), whereas the control group remained statistically unchanged (Table 2 and Figure 3).

Because the 2 randomized groups were significantly different in terms of age, MMSE score, and educational level, additional analyses were performed to assess potential confounding in the reported results. The association between adherence and age, sex, MMSE score, and educational level was assessed using both intervention and postrandomization adherence rates using an intent-to-treat analysis, so we opted to use sex and age as potential confounders. Sex was not related to either age or MMSE score, and educational level was assessed using both age, MMSE score, and educational level was assessed using both postrandomization adherence rates using an intent-to-treat analysis, and the Wilcoxon rank sum test for continuous variables not normally distributed (those with median and range). Because of the large percentage of participants lost to and unavailable for follow-up (Figure 2), the effect of the intervention was evaluated in 2 ways. First, we analyzed the prerandomization and postrandomization adherence rates using an intent-to-treat analysis in which participants who were lost to and unavailable for follow-up had their baseline adherence assigned as their final adherence. With this approach, there was an increase of 11 percentage points in median adherence rates for the intervention group. The tendency for individual changes in adherence to be positive in the intervention group paired analysis was statistically significant (P = .04). A decrease in median adherence of 5 percentage points observed in the control group was not statistically significant (Table 2). Second, we assessed the real efficacy of the intervention by restricting the data to those participants who successfully completed all phases of the study. When analyzed in this way, the intervention resulted in an increase of 19 percentage points in median adherence. Individual changes again tended to be positive in the intervention group (P = .003), whereas the control group remained statistically unchanged (Table 2 and Figure 3).

Because the 2 randomized groups were significantly different in terms of age, MMSE score, and educational level, additional analyses were performed to assess potential confounding in the reported results. The association between adherence and age, sex, MMSE score, and educational level was assessed using both the control and intervention groups. Because increased adherence was significantly associated with female sex, older age, and lower MMSE score, we considered these variables as potential confounders. Sex was not related to either age or MMSE score, but age and MMSE score are significantly inversely related in both the intent-to-treat and real efficacy analyses (P < .001 and P = .002, respectively). The MMSE score also had a stronger association with adherence in both analyses, so we opted to use sex and MMSE score as adjustment variables. These models produced results with statistically significant increases in adherence in the intervention group for both the intent-to-treat (8 percentage points, P = .03) and real efficacy (16 percentage points, P = .004) analyses, whereas there was no statistically significant change in the control group.

Study participants were asked about their experience with the electronic dosing monitor and to assess their adherence at their 6-month visit. No statistically significant differences were found between the 2 groups (eTable in the Supplement).
intervention group was asked about the reminders, and 84% of them strongly or somewhat agreed that the reminders were helpful and that they would like to continue using them.

Discussion

We found that a telecommunication-based reminder linked to a personal health record can increase adherence with once-daily glaucoma medications. This finding is important because it supports an intervention that is feasible in terms of time and cost for a typical ophthalmology practice. Our collaborator, Memotext, estimates that this particular kind of intervention could be implemented for approximately US $20 per patient. Furthermore, the automated reminders were well received by the study participants.

Because only a few patients appear to be nonadherent with their medications based on the initial phase of the ADRS, it will be important to identify those at highest risk of nonadherence to target any adherence interventions. A tool to identify those at highest risk that can be easily applied in a clinical setting has been developed and validated. Taken together, we believe this risk calculator, or one like it, and the automated reminders described represent a practical means of improving adherence.

Although nonadherence may arise from multiple underlying factors, forgetting to take medications is chief among them. Because automated reminders directly target this mechanism of nonadherence, they are a prime candidate for investigation. Furthermore, reminders may prove useful for patients whose nonadherence is due to other causes. In other words, if reminders can be shown to prompt drop administration even for patients with cognitive or situational limitations, there may be no need to design interventions to address those other barriers.

The complexity of glaucoma medication adherence is reinforced by the discrepancy between the results of the ADRS and

### Table 2. Change in Adherence Rate in the Intervention and Control Groups*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence rate</td>
<td>$n = 38$</td>
<td>$n = 32$</td>
</tr>
<tr>
<td>Initial</td>
<td>53 (0 to 100)</td>
<td>51 (5 to 83)</td>
</tr>
<tr>
<td>Final</td>
<td>64 (1 to 100)</td>
<td>46 (5 to 98)</td>
</tr>
<tr>
<td>Change</td>
<td>0 (~39 to 95)</td>
<td>0 (~43 to 89)</td>
</tr>
</tbody>
</table>

* The intent-to-treat analysis includes all participants randomized in both groups, and the real efficacy analysis includes those who successfully completed the study.

### Figure 3. Change in Adherence

Distribution of changes in adherence for the control and intervention groups between the 3- and 6-month study visits for participants completing all phases of the study. Change in adherence is defined as the final (6-month visit) adherence minus the initial (3-month visit) adherence. The count in a particular bin includes values of adherence change less than or equal to the value of the midpoint to the right and greater than the midpoint to the left (ie, the bars between −20 and 0 include no change).

Travatan Dosing Aid (Alcon Inc) studies, which reported some improvement with interventions, and the results of the Interactive Study to Increase Glaucoma Adherence to Treatment Trial, which reported no differential change in adherence. One obvious area of difference between our studies and the Interactive Study to Increase Glaucoma Adherence to Treatment Trial is in the monitoring of adherence, which we performed as directly as possible, whereas they performed with indirect measures, such as interviews, missed appointments, and clinic notes.

In addition to demonstrating the efficacy of this particular approach to reminders, our results also clearly point out the difficulty of studying and intervening with nonadherent patients. This is most evident in the high rate of patients who were lost to and unavailable for follow-up, suggesting that keeping nonadherent patients in the practice and using their medications is a challenge. If these patients are indeed less likely to follow up with their glaucoma care, a correlation that is supported by a prior study at our institution, then there will need to be additional intervention to deal with that aspect of their beliefs and behaviors.

The high rate of participants being lost to and unavailable for follow-up after randomization is both a significant finding and a significant limitation in terms of our ability to assess the intervention. Loss of participants after randomization, coupled with the fact that the original cohort was significantly more adherent than a similar group in a prior study at our institution, resulted in a smaller than expected number of participants completing the intervention phase of the study. The differences in the characteristics of the control and intervention groups (Table 1) are therefore likely an artifact of the small sample size and a couple of participants with outlier values (eg, the participant with an MMSE score of 13). Because of these differences and the small sample size, we performed multivariate analysis with an intent-to-treat approach in which we assigned the baseline adherence as the final adherence for all participants lost to and unavailable for follow-up.
up. In both of these analyses, the intervention had an effect on adherence not seen in the control group. The intent-to-treat analysis continued to show an effect of the intervention despite being biased against finding such an effect by assuming no change in adherence in those participants who did not complete the study. We believe the conservative nature of the intent-to-treat analysis is appropriate to overcome the likelihood of bias that is inherent in any study with a high rate of participant dropout.

Also of note is the fact that even in the intervention group, the median adherence rate after the reminders were implemented (73%) was still below the cutoff we have defined for being adherent. There are also clearly some participants for whom the intervention had no effect on their adherence (Figure 3). Although it seems reasonable to conclude that some improvement in adherence is desirable, the answer to how much adherence must increase to be clinically meaningful will require additional studies looking specifically at measures of optic nerve structure and function and 24-hour IOP. It is also of interest to link adherence and the effect of interventions to these clinical outcomes for a longer period given the slowly progressive nature of the disease.

Conclusions

The combination of an electronic health record portal for patients and telecommunication-based reminders is likely to be one important method of addressing adherence with glaucoma medications. This contention is based on the rapid adoption of electronic health records by ophthalmology practices and the fact that it will be required that patients can have remote access to their own records. On the other hand, the multifactorial nature of medication nonadherence will require the development of additional interventions that will work for those patients with barriers not overcome with this approach.