Short Communication

The effect of interactive reminders on medication adherence: A randomized trial

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1. Introduction

The low rate of medication adherence in the United States is estimated to cost Americans between $100 billion and $289 billion annually (Viswanathan et al., 2012). Forgetfulness is considered to be a key contributor to patients’ failure to take their medications as prescribed (Gadkari and McHorney, 2012). To overcome forgetfulness, a number of recent studies have examined whether devices that remind people to take their prescribed medication improve medication adherence. We conducted a large randomized controlled trial (RCT) to examine the efficacy of not only basic reminders that simply tackle forgetfulness but also reminders that are designed to tackle another barrier of adherence—procrastination and lack of motivation (George et al., 2006; Israni et al., 2016). We evaluated their impact on medication adherence over a three-month intervention period and three-month post-intervention period using data on prescription refills. Our basic reminders tackle forgetfulness by simply encouraging people to take pills regularly. Inspired by the potential of behavioral science for promoting health behavior (Mogler et al., 2013; Li and Chapman, 2013), our interactive reminders are designed to leverage several behavioral science principles that may increase patients’ motivation to refill prescriptions and take medicines as prescribed. First, past research has shown that merely asking people about their intentions and plans to engage in a behavior (e.g., to make blood donations, to get vaccinations) can increase actual engagement (Godin et al., 2008; Milkman et al., 2011). One explanation for this effect is that people prefer to behave consistently with intentions that they have stated, even when their intentions are private (Milkman et al., 2011; Cialdini, 2006). Second, research has shown that setting specific goals motivates people to work harder and achieve better performance than they would in the absence of such goals (Locke and Latham, 1990). Building on these insights, we...
designed two types of interactive reminders that prompted people to form intentions about taking medications and encouraged them to set specific adherence goals. One type of reminder prompted participants to predict their future medication adherence levels, and another type of reminder prompted participants to commit to a medication adherence level. Our RCT compares receiving no reminders with receiving reminders and explores whether interactive reminders are particularly impactful.

2. Methods

2.1. Study design, population, and procedures

In November 2014, 46,581 participants with employer-sponsored commercial or Medicare Advantage insurance from Humana were deemed eligible for inclusion in our randomized controlled trial. These participants were taking oral medication for cholesterol, diabetes, or blood pressure control, were expected to refill their medication every 30 days, and had 40–80% medication adherence in the 12 months prior to randomization (Fig. 1). Participants were enrolled by Humana.

This study involved four primary experimental conditions. After consulting with Humana, we set our intervention period to three months—a reasonable starting point for examining the impact of our intervention on adherence among participants with 30-day scripts. Participants in the usual care condition received standard engagement messages that the insurer regularly sends. Participants in the other three conditions received three additional reminder mailings, with each mailing sent around the 15th of each month from November, 2014 through January, 2015. In the basic reminder condition, these mailings simply reminded participants to take a target medication (for cholesterol, diabetes, or blood pressure) (Szilagyi et al., 2000). In the prediction condition, our mailings prompted participants to predict the number of days in the next 30 when they would take their medication (Godin et al., 2008; Milkman et al., 2011; Cialdini, 2006; Locke and Latham, 1990). In the commitment condition, the mailings prompted participants to commit to a self-determined number of days over the next 30 to take their medication (Godin et al., 2008; Milkman et al., 2011; Cialdini, 2006; Locke and Latham, 1990). All reminder mailings included a sticky note that participants could place somewhere (e.g. on a refrigerator) as a reminder, and those in the prediction and commitment conditions were encouraged to record their prediction or commitment on the sticky note.

Furthermore, inspired by past research showing that people are more likely to follow through on plans that are made public (Cialdini, 2006), we randomly assigned half of the participants in the prediction and commitment conditions to receive encouragement to share their prediction or commitment with Humana online, via text, or via postcard. Thus, both the prediction and commitment conditions consisted of two sub-groups. After institutional review board waiver of informed consent, researchers at the University of Pennsylvania used R, version 3.1.1 (R Core Team) to randomly assign participants in a 1:1:1:1:1:1 ratio to one of six groups, without blocking or other restrictions (Fig. 1).

2.2. Study outcomes and statistical analysis

We used pharmacy claims data to calculate each participant’s proportion of days covered (PDC), defined as the number of days when he/she had any pills in the medication category listed on his/her mailing divided by the number of days in the observation period. In our primary analysis, we use PDC as our proxy for adherence, a continuous measure that is widely used by researchers to measure medication adherence (Lee et al., 2006; Lin et al., 2006; Osterberg and Blaschke, 2005; Choudhry et al., 2011). We used ordinary least squares regressions in STATA, version 14 (StataCorp) to predict PDCs on an intent-to-treat basis, controlling for PDC during the six months prior to the start of our experiment (May 15, 2014 to November 14, 2014), gender, ethnicity, the linear and squared terms of age, log-transformed income, and the type of medication that was listed on the reminders. The regressions had an 80% power to detect a minimum of a 1.2-percentage-point difference between the usual care and each treatment condition with \( \alpha = 0.05 \). We also evaluated adherence using a binary measure of optimal adherence which was set equal to one if a patient’s PDC in a given period was equal to or >80%, and zero otherwise. This less sensitive measure of adherence has also been widely used in past research, and we used logistic regressions to predict...
this secondary outcome variable (Osterberg and Blaschke, 2005; Choudhry et al., 2011).

3. Results

3.1. Main results

All conditions were balanced on available demographic variables (age, gender, ethnicity, income) and adherence prior to our randomized control trial, suggesting that our randomization was successful. Encouraging participants to publicly share their prediction or commitment (i.e., by conveying it to Humana) did not significantly influence adherence rates (see supplemental materials for details). Thus, we focus on the differences between our usual care, basic reminder, prediction, and commitment conditions below.

During the mailing period (November 15, 2014 to February 14, 2015), mean PDC in the usual care condition was 60.69%. The three reminder conditions, combined, increased PDCs by 0.95 percentage points (95% confidence interval [CI], 0.26% to 1.65%)—a significant but small amount. This effect was driven by prediction and commitment reminders, which increased PDCs by 1.07 percentage points (95% CI, 0.30% to 1.85%) and 1.00 percentage point (95% CI, 0.22% to 1.77%),

### Table 1
Baseline characteristics and medication adherence results.

<table>
<thead>
<tr>
<th>Reminder conditions</th>
<th>All conditions combined*</th>
<th>Usual care</th>
<th>Basic reminder</th>
<th>Interactive reminder: prediction</th>
<th>Interactive reminder: commitment</th>
<th>Reminder conditions, combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>46,581</td>
<td>7812</td>
<td>7766</td>
<td>15,500</td>
<td>15,503</td>
<td>38,769</td>
</tr>
</tbody>
</table>

#### Baseline sample characteristics

| % Male | 46.31% | 45.66% | 47.64% | 46.23% | 46.04% | 46.44% |
| % Caucasian | 54.20% | 54.81% | 54.00% | 53.74% | 54.45% | 54.07% |
| % Black | 19.04% | 18.79% | 18.90% | 19.32% | 18.97% | 19.10% |
| Mean age (SD) | 69.32 (11.49) | 69.21 (11.56) | 69.38 (11.59) | 69.32 (11.52) | 69.36 (11.37) | 69.35 (11.47) |
| Mean income (SD) | $54,621 (47,983) | $54,692 (46,974) | $54,720 (46,974) | $54,644 (48,226) | $54,512 (48,054) | $54,606 (47,908) |

#### Mean adherence (PDC) during the six-month pre-mailing period: May 15, 2014 to November 14, 2014 (SD)

| All conditions combined | 55.36% (23.73%) | 55.33% (23.48%) | 55.18% (23.83%) | 55.37% (23.85%) | 55.45% (23.67%) | 55.37% (23.78%) |

#### Results - overall analysisb

During the three-month mailing period: November 15, 2014 to February 14, 2015

| Mean medication adherence (PDC) | 61.49% | 60.67% | 61.16% | 61.76% | 61.79% | 61.65% |
| Unadjusted increase | N/A | N/A | 0.50% | 1.12%* | 1.09%* | 0.98%* |
| OLS regression-adjusted increasec | N/A | N/A | 0.64% | 1.07%** | 1.00%* | 0.95%** |

During the three-month post-mailing period: February 15, 2014 to May 14, 2015

| Mean medication adherence (PDC) | 59.01% | 58.17% | 59.26% | 58.94% | 59.39% | 59.18% |
| Unadjusted increase | N/A | N/A | 1.09% | 0.78% | 1.22%* | 1.02%* |
| OLS regression-adjusted increase | N/A | N/A | 1.21%* | 0.76% | 1.09%* | 0.98%* |

#### Results - subgroup analysisd

Participants with above-median baseline PDC

During the three-month mailing period: November 15, 2014 to February 14, 2015

| Mean medication adherence (PDC) | 76.68% | 76.16% | 76.36% | 76.89% | 76.87% | 76.78% |
| Unadjusted increase | N/A | N/A | 0.21% | 0.74% | 0.71% | 0.62% |
| OLS regression-adjusted increase | N/A | N/A | 0.11% | 0.45% | 0.60% | 0.46% |

During the three-month post-mailing period: February 15, 2014 to May 14, 2015

| Medication adherence (PDC) | 71.43% | 70.95% | 71.52% | 71.38% | 71.68% | 71.53% |
| Unadjusted increase | N/A | N/A | 0.57% | 0.43% | 0.73% | 0.57% |
| OLS regression-adjusted increase | N/A | N/A | 0.51% | 0.24% | 0.62% | 0.45% |

Participants with below-median baseline PDC

During the three-month mailing period: November 15, 2014 to February 14, 2015

| Mean medication adherence (PDC) | 46.32% | 45.29% | 46.01% | 46.76% | 46.56% | 46.53% |
| Unadjusted increase | N/A | N/A | 0.72% | 1.47%* | 1.27%* | 1.24%* |
| OLS regression-adjusted increase | N/A | N/A | 1.20%* | 1.73%** | 1.41%* | 1.50%** |

During the three-month post-mailing period: February 15, 2014 to May 14, 2015

| Medication adherence (PDC) | 46.62% | 45.47% | 47.04% | 46.62% | 46.98% | 46.85% |
| Unadjusted increase | N/A | N/A | 1.57%* | 1.15% | 1.50%* | 1.37%* |
| OLS regression-adjusted increase | N/A | N/A | 1.95%* | 1.33%* | 1.56%* | 1.55%* |

Standard deviations in parentheses.

+ p < 0.1.
* p < 0.05.
** p < 0.01.
*** p < 0.001.

a Our full sample involved participants in the United States with commercial or Medicare Advantage insurance with Humana from November 15, 2014 to May 14, 2015.

b Increases are relative to the usual care condition.

c Our regression controlled for PDC during the six months prior to the start of our experiment (May 15, 2014 to November 14, 2014), gender, ethnicity, the linear and squared terms of age, log-transformed income, and the type of medication that was listed on the reminders.

d We separated our sample by median PDC during the six-month pre-mailing period (57.07%) and estimated the effect of our intervention for each subgroup.
respectively. Basic reminders insignificantly increased PDCs by 0.64 percentage points (95% CI, 0.26% to 1.53%)

During the post-mailing period (February 15 to May 14, 2015), mean PDC in the usual care condition was 58.20%. The three reminder conditions, combined, increased PDCs significantly by 0.98 percentage points (95% CI, 0.15% to 1.81%). This was driven by basic and commitment reminders, which increased PDCs by 1.21 percentage points (95% CI, 0.14% to 2.28%) and 1.09 percentage points (95% CI, 0.16% to 2.02%), respectively. Prediction reminders insignificantly increased PDCs by 0.76 percentage points (95% CI, 0.17% to 1.69%). Table 1 summarizes these results. Our secondary analyses considering “optimal” adherence (PDC ≥ 80%) as a binary outcome measure yield directionally similar results, though statistical significance is weaker for this less sensitive outcome (Supplementary Table 1).

3.1. Subgroup analysis

We separated our sample by median PDC during the six-month pre-mailing period (57.07%) and estimated the effect of our intervention on each subgroup (Choudhry et al., 2017). Among the participants whose PDC was above median prior to the mailing period, the three reminder conditions, combined, did not significantly improve medication adherence during the mailing period (mean difference from the usual care condition = 0.46 percentage points, 95% CI, −0.40% to 1.31%) or during the post-mailing period (mean difference from the usual care condition = 0.45 percentage points, 95% CI, −0.68% to 1.58%). Among participants whose PDC was below median prior to the mailing period, the three reminder conditions, combined, significantly improved medication adherence by 1.50 percentage points (95% CI, 0.41% to 2.58%) during the mailing period and 1.54 percentage points (95% CI, 0.33% to 2.76%) during the post-mailing period, compared to the usual care condition. We observed similar patterns when we compared different types of reminders with the usual care condition (rather than pooling all reminders before making this comparison). Participants with above-median baseline PDC did not statistically significantly benefit from any type of reminder during the mailing or post-mailing period; participants with below-median baseline PDC benefited significantly from prediction and commitment reminders during the mailing period, and from basic reminders and commitment reminders during the post-mailing period. Table 1 summarizes these results. However, note that in our OLS regressions to predict PDCs, the interaction terms between indicators for our reminder conditions and an indicator for having a below-median (vs. above-median) baseline PDC are not statistically significant, indicating that the qualitatively better adherence observed among those with relatively lower PDCs described above is not significant.

4. Discussion

We show that reminders, especially interactive ones, improve medication adherence and that the effects persist even after mailings stop. Our subgroup analysis suggests that reminder mailings may be more effective for those who have lower prior adherence.

Overcoming low medication adherence is a challenge. Even RCTs that test expensive, aggressive reminders (e.g., pill bottle caps with a digital timer) show null effects (Choudhry et al., 2017). The effects of our intervention are small in terms of absolute magnitude, and if implemented alone, reminder mailings would have limited clinical impact. However, mailed reminders can easily supplement more intensive adherence interventions at very low cost. They scale easily and are inexpensive; in contrast, methods that have been shown to successfully improve medication adherence to a substantial degree are often complex to scale, labor-intensive, and expensive (Lee et al., 2006; Osterberg and Blaschke, 2005).

As an example, we compare our intervention with a highly-cited program that reduced medication copayments and significantly increased adherence by 5.4 percentage points. We calculate the increase in medication adherence per dollar spent using the following formula: (the average increase in PDC per person due to an intervention) × (the number of days in the observation period) / (the cost of the intervention per person). In our study, reminders increased the average PDC by 0.95 percentage points during our 92-day mailing period and by 0.98 percentage points during our 89-day post-mailing period. Thus, our reminder intervention was estimated to produce an average increase of 0.02 pills per dollar spent over 394 days (Choudhry et al., 2011). We use the median observation period (394 days), average cost ($926), and average increase in PDC (5.4 percentage points) in our estimate (i.e., (5.4% × 394) / 926).

4.1. Limitations

Several limitations of this study should be acknowledged. First, once a month, on average, all of our study participants received usual care mailings from their insurer, which sometimes contained medication adherence reminders, and participants may also have received reminders from other sources (e.g., the pharmacies where they refilled prescriptions). Thus, our observed reminder effect reflects the benefits of adding an (interactive) reminder to standard reminders from Humana and other sources, and our study may underestimate the impact that reminders could have on people who do not already receive any form of reminder.

Second, limited by the data that the pharmacy benefit manager (PBM) had, we calculate medication adherence based on prescription refills. While prescription refill patterns are often used as a proxy for medication adherence (Osterberg and Blaschke, 2005; Choudhry et al., 2017), they do not measure actual pill intake. Changing medication intake is psychologically different than changing prescription refills. Unfortunately, it is extremely challenging, if not impossible, to measure actual medication intake, especially in large populations.

Third, while our choice of tracking PDCs for three months during the post-mailing period is consistent with the length of the follow-up periods in many other RCTs examining medication adherence (Simoni et al., 2007; Murray et al., 2007), the long-term effects of our interventions beyond our follow-up period are unknown. Finally, we only examined customers with 30-day refill frequencies, and reminders may work differently for customers on different refill schedules.

5. Conclusion

Our randomized controlled trial reveals that reminders – particularly interactive ones – have a positive and persistent, although modest, effect on medication adherence. Given the large challenge of overcoming poor medication adherence, a multifaceted approach seems necessary (Osterberg and Blaschke, 2005). Future investigations of how to use reminders as a supplement to other medication adherence programs would be valuable.

Conflict of interest disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Dai reports funding in part by grants from Human (10046498 and 10047966) during the conduct of the study. Mr. Mao reports funding in part by grants from Human during the conduct of the study. Dr. Volpp reports grants from Human during the conduct of the study as well as grants from Hawaii Medical Services Agency (10051742), Discovery (South Africa) (10042481), Merck (10042345 and 10042350), Weight Watchers (10033966), and CVS (10041902) outside of the submitted work; he has received consulting income from CVS and VAHealth and is a principal in VAHealth, a behavioral economics consulting firm. Dr. Pearce reports employment by Human, the funding organization, during the course of the study.
Mr. Relish reports employment by Humana, the funding organization, during the course of the study. Dr. Lawnicki reports employment by Humana, the funding organization, during the course of the study. Dr. Milkman reports grants from Humana during the conduct of the study and personal fees from serving on the Health Prize Academic Advisory Board, outside the submitted work. No other disclosures were reported.

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Role of the funder/sponsor

The funding organization, in collaboration with the academic investigators, provided input on the design and conduct of the study; oversaw the collection and management of the data; and contributed to the preparation, review, and approval of the manuscript, as well as the decision to submit the manuscript for publication. The funding organization had no role in the analysis or interpretation of the data.

Additional contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2017.07.019.

References