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# A Synchronized Prescription Refill Program Improved Medication Adherence

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**ABSTRACT** Synchronizing medication refills—renewing all medications at the same time from the same pharmacy—is an increasingly popular strategy to improve adherence to medication regimens, but there has been little research regarding its effectiveness. In light of increasing policy interest, we evaluated the impact of a pilot refill synchronization program implemented by a large national insurer. A random sample of Medicare Advantage patients receiving mail-order refills for common maintenance medications (antihypertensive, lipid-lowering, or antidiabetic agents) were invited to join the program and followed for twelve months. On average, the absolute increase in the proportion of patients deemed adherent during follow-up was 3–10 percentage points for the intervention group, compared to 1–5 percentage points for the control group. Patients with poorer baseline adherence showed larger increases in the absolute proportion deemed adherent in intervention (23–26 percentage points) compared to a control group (13–15 percentage points). Synchronizing refills might be a promising intervention to improve adherence to maintenance medications, especially among Medicare patients with low baseline adherence.

Approximately 4.3 billion prescriptions were written in the United States in 2014,<sup>1</sup> but fewer than half of patients take medications as prescribed.<sup>2</sup> Efforts to boost adherence to medication regimens are important to a variety of stakeholders including patients, providers, and payers, as nonadherence can make it difficult to evaluate treatment effectiveness and can lead to compromised health outcomes and increased costs related to worsening of disease and complications.<sup>3–5</sup>

Because consistent adherence requires an adequate, continuous supply of medication, programs that ease access to medication are of particular interest. The logistical challenges involved with keeping track of remaining pills and obtaining timely refills and renewals are magnified for patients on multiple maintenance

medications, who often have the additional burden of refills coming due at different times. This might require keeping track of multiple renewal dates for mail-order pharmacies, making several trips to local retail pharmacies, or both. Each step of this process represents an opportunity for a supply problem, and thereby an adherence problem, to emerge.

Several groups have begun to examine the potential usefulness of synchronized prescription refill programs,<sup>6–8</sup> which adjust medication renewal dates so all prescriptions “come due” at once, as a strategy to reduce obstacles to optimal adherence. In the retail pharmacy setting, this permits patients to pick up all maintenance refills at the same time and place, thereby reducing the burden of remembering multiple refill dates and saving the time and inconvenience of multiple trips to the pharmacy. In the mail-order set-

ting, refill tasks are similarly clustered to be handled at one time. Medication synchronization programs have been widely adopted and are available at nearly two dozen pharmacy chains and approximately 2,000 independent pharmacies in the United States.<sup>9</sup>

Despite the popularity of these programs, very few peer-reviewed studies have evaluated adherence interventions that include synchronized refills. Two studies of appointment-based medication synchronization programs, in which synchronization was one component of a comprehensive approach that included in-person counseling and recommendations for extra adherence aids (for example, blister-pack service), have published positive results.<sup>6,10,11</sup> A 2013 evaluation of an appointment-based medication synchronization program implemented among new medication users in six chronic disease categories at a retail pharmacy chain in the rural Midwest found that enrolled patients had three- to sixfold greater odds of adherence over a one-year period compared with matched controls.<sup>6</sup> A subsequent study of commercially insured patients participating in a similar program in a retail pharmacy chain in Ohio found similar results among established medication users.<sup>10</sup> In addition to the appointment aspects of these programs, the specific intervention was personalized and involved face-to-face contact in small communities where established patient-pharmacist relationships were likely. As such, it is unclear to what extent synchronization of medication alone might boost adherence, without these additional program components.

Clarification of the pros and cons of synchronizing refills deserves continued exploration, particularly in light of substantial policy interest in implementing this strategy more broadly. Legislation requiring insurance plans to permit patients to obtain less than a one-month supply of a medication so that they can synchronize when their prescriptions will come due was proposed in thirteen states in 2014 and has been passed in Colorado, Connecticut, Oregon, and Utah.<sup>9</sup> Proposed California Assembly Bill 2418 would go further by mandating prescription synchronization and requiring prorated cost sharing for partial prescriptions,<sup>12</sup> but opponents cite insufficient evidence of effectiveness.<sup>13</sup> More recently, the 2015 *Medicare and You* handbook, sent by the Centers for Medicare and Medicaid Services (CMS) to all Medicare beneficiaries, explained the potential benefits of synchronizing prescriptions and notified members that they were entitled to request partial refills (with corresponding prorated copayments) to enable synchronization.<sup>14</sup>

We sought to add to the evidence base by ex-

amining changes in medication adherence associated with a synchronization program offered to Medicare patients receiving common maintenance medications through the mail-order pharmacy of a national insurer. This is a particularly relevant population for several reasons. First, 85 percent of US adults ages sixty-five and older have at least one chronic health condition, and 60 percent have at least two.<sup>15</sup> People of all ages struggle with medication adherence, yet forgetfulness, other memory problems, and transportation difficulties can pose additional prescription management challenges for older people. Second, we focused on beneficiaries receiving oral antihypertensives, lipid-lowering drugs, or antidiabetic agents, which treat three of the top five most prevalent conditions in Medicare.<sup>16</sup> In keeping with the fact that adherence is regarded as a marker of quality, these medications are also the focus of adherence criteria set by CMS's five-star quality rating system program for Medicare Part D prescription plans. Finally, mail-order pharmacies are becoming increasingly popular for maintenance medications since they typically offer a three-month supply at lower out-of-pocket expense and could aid adherence;<sup>17</sup> hence, it is important to learn more about the impact of adherence interventions for mail-order customers.

## Study Data And Methods

**STUDY DESIGN** This quasi-experimental study analyzed patients' adherence before and after participation in a pilot prescription synchronization program and compared changes to those found in a contemporaneous control group. The pilot program ran between September 2013 and December 2014 among beneficiaries enrolled in Medicare Advantage Prescription Drug (MA-PD) plans and participating in the Humana Pharmacy mail-order service. This population was chosen since the insurer had access to both medical and prescription records for these beneficiaries as well as the ability to synchronize their prescription refills.

First, 3,195 members were identified as eligible for the study based on Humana claims data (following selection criteria below). Second, 2,500 people were randomly assigned to an "intervention invitation" group, while the remaining 695 formed the control group. Intervention invitation members were contacted sequentially until 691 were reachable and agreed to enroll in the program. The control group was never contacted and continued to receive usual pharmacy services; their deidentified data were later analyzed as part of the evaluation. The study protocol was approved by the University of Pennsyl-

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vania Institutional Review Board.

**STUDY SAMPLE** Patients were eligible for the study if they were enrolled in a Humana MA-PD plan and using the Humana mail-order pharmacy; receiving two to six oral antihypertensives, lipid-lowering drugs, or antidiabetic agents (total number capped so as to limit the potential financial burden of synchronizing copayments); receiving these maintenance medications exclusively from the Humana mail-order pharmacy (to ensure complete refill information); not on a synchronized refill schedule already; not on a medication that could not be synchronized (for example, a drug with atypical refill schedules); and eligible for receiving communications from Humana, with a current mailing address on file.

**INTERVENTION** The Humana study team called intervention group members during the last four months of 2013 to invite them to join the synchronization program. Those who could not be reached after three follow-up calls were classified as unreachable. Those who accepted the invitation and enrolled had a brief (approximately ten-minute) phone consultation with a pharmacist or pharmacy technician, based on a standard script, which explained the potential benefits of synchronizing refills and confirmed that medications would be adjusted to come due on the same day. Every forty-five days before their next refills were due, a pharmacy technician interviewed participants by phone (again using a standard script) to check for any changes that would affect synchronization (that is, added or discontinued medications, dosage changes that would affect needed supply) and to obtain consent to send synchronized refills as scheduled. Participants were asked to check their medication supply so that refills would be sent only if needed. If participants expressed confusion about how to take their medication properly or reported a supply of medication that conflicted with the expected supply based on pharmacy records, they were transferred to a pharmacist for a brief review of the prescribed regimens. Participants were also encouraged to contact the pharmacy if they had any additional changes that would affect their need for refills.

The control group continued to receive usual care (that is, standard pharmacy services). They received automated calls prior to refill due dates to obtain their consent to send refills, in keeping with CMS policies regarding auto-refill programs;<sup>18</sup> they also had telephone access to a pharmacist if they had questions.

**OUTCOMES** Our primary outcome was medication adherence at the drug-class level, calculated as the proportion of days covered (PDC)<sup>19</sup> with a day's supply of a medication from at least one

## Synchronization programs help address logistical challenges involved with obtaining timely refills for multiple medications.

prescription in that drug class (antihypertensives, lipid-lowering agents, or antidiabetic agents), during the observation period. This approach is in keeping with CMS's technical guidance on measuring adherence.<sup>20</sup> We examined continuous PDC and a dichotomous measure of adherence ( $PDC \geq 0.80$ ), based on a common cutoff for classifying patients as adherent and used by CMS for star-rating calculations in Medicare Advantage.

All outcome variables were drawn from pharmacy claims data and calculated at the monthly level between June 2012 and December 2014, such that each member had twelve months of adherence scores both before and after the intervention start month. Control-group members were randomly assigned a pseudo-intervention start month to match the distribution of start months in the intervention group.

**STATISTICAL ANALYSIS** We used a difference-in-differences approach to compare before-and-after changes in medication adherence outcomes in the intervention group to before-and-after changes in the control group. Applying an intention-to-treat approach, we included all patients who enrolled in the intervention in the analyses, even if they disenrolled before the study period ended. Each analysis of drug class-level adherence outcomes was limited to the sample of patients taking medications from that drug class. Linear regressions were used for the continuous dependent variable of PDC, and logistic regressions were used for the dichotomous dependent variable of  $PDC \geq 0.80$ .<sup>21</sup> All regressions included an indicator for the postintervention period, an indicator for the intervention group, and their interaction. The interaction captures the difference-in-differences estimate of the intervention effect. Regression coefficients are reported for the continuous PDC outcome, while odds ratios are reported for the dichotomous measure of

adherence. All regressions also controlled for patients' age, sex, race, and marital status; a low-income subsidy indicator; health condition indicators; and the CMS Hierarchical Condition Categories score, which has been used to adjust for potential selection biases in studies among Medicare patients.<sup>22</sup>

In subgroup analyses, we further explored whether the effect of the intervention varied based on high (PDC  $\geq 0.80$ ) or low (PDC  $< 0.80$ ) baseline (preintervention) adherence. The low-adherence subgroup was further separated into those with baseline PDC ( $< 0.60$ ) and those with PDC between 0.60 and 0.80. In addition, we conducted extensive sensitivity analyses varying the analytic techniques, the time frame for adherence measurement, and the control variables, to check the robustness of our findings.<sup>23</sup>

**LIMITATIONS** Several study limitations should be noted. First, although eligible members were randomized to either the intervention invitation or the control group, this was not a randomized controlled trial; we compared people who accepted an invitation into the synchronization program with a sample of eligible controls who were not invited to join. Nonetheless, we compared the intervention and control groups on a wide range of characteristics, and they did not show differences in any of the observed demographic and clinical variables available from claims and enrollment files. In the subset (approximately 92 percent) of the sample that could be linked to additional consumer metadata variables, we also found no differences across the two groups. Since large-scale real-world implementation of the synchronization program would also involve offering plan members the option to join the program and self-selecting to participate, this design might actually have increased the study's external validity.

Second, nearly three-quarters of those who were invited to join the program declined or were unreachable. However, those who declined participation were remarkably similar to participants with regard to sociodemographic variables, health status, and past adherence, as can be seen in online Appendix Exhibit A2.<sup>24</sup> In addition, the intention-to-treat approach used in our analyses means that those who disenrolled from the program before the twelve-month study period ended were included in the analysis even though they did not experience the full intervention; hence, our results are likely an underestimate of the full potential of the synchronization program.

Third, our sample population consisted of Medicare Advantage members who exclusively used mail-order pharmacy services for their maintenance medications. Since there is some

evidence that mail-order pharmacy use is associated with better adherence,<sup>25,26</sup> our eligibility criteria might have increased our likelihood of sampling adherent patients and thus led to a ceiling effect (that is, less room to improve adherence given the already high baseline adherence levels) for some participants. Our findings might not extend to non-Medicare patients or those using alternative pharmacy arrangements (such as retail pharmacies).

Finally, PDC is a validated claims-based adherence measure that is associated with clinical outcomes,<sup>27</sup> yet it is possible that some patients might not have been taking all of the medications they received. As such, there is the possibility that our PDC results overestimate true adherence.

## Study Results

Twenty-eight percent (691 of 2,500) of those invited to participate agreed to enroll in the synchronization program. A flow chart showing the path to enrollment in the program is available in Appendix Exhibit A1.<sup>24</sup> Patients who agreed to participate were similar in observed characteristics to those who declined (Appendix Exhibit A2).<sup>24</sup> Ninety-eight percent of both the intervention (678 of 691) and control (679 of 695) groups had no missing data on key baseline variables and were included in the final analysis.

The intervention and control groups were well balanced in terms of demographic and clinical characteristics (Exhibit 1). Mean age was approximately seventy-five years, just below half were female, and approximately half were married. Fewer than 10 percent received Part D low-income subsidies. More than 90 percent had a cardiovascular condition, and a little more than one-third had diabetes. Fifteen percent of the intervention group disenrolled from the prescription synchronization program before the study period ended (Appendix Exhibit A1).<sup>24</sup> Although many (40 percent) did not give a reason, others cited a change in insurance plans (34 percent), a preference for calling in refills (13 percent), or the end of multiple maintenance medications prescribed (7 percent; data not shown).

Compared to the control group, the intervention (synchronized refills) group had larger absolute increases in PDC scores and adherence rates after the intervention (Exhibit 2). For instance, among the intervention subgroup using antihypertensives, mean PDC increased from 0.86 to 0.89, and the adherence rate increased from 83 percent to 86 percent, compared with no increase in mean PDC and a 1-percentage-point increase in adherence rates in the corresponding control subgroup using antihypertensives. Syn-



EXHIBIT 1

Baseline sample characteristics of synchronized prescription refill and control groups

| Characteristic                                       | Synchronized refills group (n = 679) | Control group (n = 678) | p value |
|------------------------------------------------------|--------------------------------------|-------------------------|---------|
| Age in years, mean (SD)                              | 74.5 (6.6)                           | 74.9 (7.2)              | 0.40    |
| Female                                               | 48.3%                                | 47.1%                   | 0.64    |
| Race                                                 |                                      |                         |         |
| White                                                | 85.7%                                | 86.3%                   | 0.76    |
| Black                                                | 10.4                                 | 9.9                     | 0.73    |
| Other                                                | 3.9                                  | 3.8                     | 0.99    |
| Married                                              | 54.6%                                | 50.9%                   | 0.16    |
| Part D low-income subsidy                            | 6.5%                                 | 6.8%                    | 0.82    |
| CMS-HCC score, mean (SD)                             | 56.8 (15.4)                          | 58.5 (21.1)             | 0.09    |
| Health conditions                                    |                                      |                         |         |
| Cancer                                               | 8.2%                                 | 10.3%                   | 0.19    |
| Cardiovascular                                       | 91.0                                 | 91.9                    | 0.57    |
| Diabetes                                             | 35.7                                 | 36.0                    | 0.94    |
| Chronic kidney disease                               | 6.5                                  | 8.7                     | 0.12    |
| Respiratory diseases                                 | 31.1                                 | 28.6                    | 0.32    |
| Baseline use of selected medications                 |                                      |                         |         |
| Percent filling antihypertensives                    | 96.2%                                | 97.3%                   | 0.25    |
| No. of antihypertensive drug subclasses, mean (SD)   | 3.3 (1.6)                            | 3.4 (1.8)               | 0.26    |
| Percent filling lipid-lowering drugs                 | 80.9%                                | 79.1%                   | 0.41    |
| No. of lipid-lowering drug subclasses, mean (SD)     | 1.01 (0.1)                           | 1.01 (0.1)              | 0.34    |
| Percent filling antidiabetic agents                  | 31.7%                                | 31.1%                   | 0.81    |
| No. of antidiabetic agent subclasses, mean (SD)      | 1.56 (0.6)                           | 1.52 (0.7)              | 0.56    |
| Total no. of drugs in these three classes, mean (SD) | 4.5 (1.7)                            | 4.6 (1.9)               | 0.38    |

**SOURCE** Authors' analysis of Humana claims data, June 2012 to December 2014. **NOTES** SD is standard deviation. CMS-HCC is Centers for Medicare and Medicaid Services Hierarchical Condition Category score. N = 1,357 members.

chronization was also associated with statistically significant absolute increases in mean PDC for lipid-lowering agents (+0.04) and for antidiabetic agents (+0.05). On average, the absolute increase in the proportion of patients who achieved adherence (defined as PDC  $\geq$  0.80) dur-

ing the twelve-month follow-up period was 3–10 percentage points for the intervention group compared to 1–5 percentage points for the control group. The odds of achieving adherence were also higher for the intervention group compared to control, ranging from 1.31 for lipid-low-

EXHIBIT 2

Descriptive and regression-adjusted outcomes for synchronized prescription refill and control groups

|                                       | Synchronized refill group |        |       | Control group |        |       | Unadjusted                             | Regression adjusted   |            |
|---------------------------------------|---------------------------|--------|-------|---------------|--------|-------|----------------------------------------|-----------------------|------------|
|                                       | N                         | Before | After | N             | Before | After | Difference-in-differences <sup>a</sup> | Estimate <sup>b</sup> | 95% CI     |
| Continuous proportion of days covered |                           |        |       |               |        |       |                                        |                       |            |
| Antihypertensives                     | 653                       | 0.86   | 0.89  | 660           | 0.84   | 0.84  | 0.03**                                 | 0.03**                | 0.02, 0.04 |
| Lipid-lowering drugs                  | 549                       | 0.71   | 0.78  | 536           | 0.66   | 0.69  | 0.04**                                 | 0.04**                | 0.03, 0.06 |
| Antidiabetic agents                   | 215                       | 0.70   | 0.80  | 211           | 0.72   | 0.76  | 0.05**                                 | 0.05**                | 0.03, 0.08 |
|                                       |                           |        |       |               |        |       | Difference-in-differences <sup>a</sup> | Odds ratio            | 95% CI     |
| Adherent                              |                           |        |       |               |        |       |                                        |                       |            |
| Antihypertensives                     | 653                       | 83%    | 86%   | 660           | 80%    | 81%   | 3%**                                   | 1.32**                | 1.16, 1.51 |
| Lipid-lowering drugs                  | 549                       | 67     | 75    | 536           | 62     | 66    | 4%**                                   | 1.31**                | 1.17, 1.48 |
| Antidiabetic agents                   | 215                       | 67     | 77    | 211           | 68     | 73    | 5%**                                   | 1.37**                | 1.12, 1.68 |

**SOURCE** Authors' analysis of Humana claims data, June 2012 to December 2014. **NOTES** Adherent is defined as proportion of days covered (PDC)  $\geq$  0.80. CI is confidence interval. <sup>a</sup>Absolute difference (for example, 3 percent indicates 3 percentage points). <sup>b</sup>Difference-in-difference estimate from regression. \*\*p < 0.05

**EXHIBIT 3**
**Descriptive and regression-adjusted continuous proportion of days covered (PDC) outcomes for synchronized prescription refill and control groups, by baseline adherence status**

|                              | Synchronized refills group |        |       | Control group |        |       | Unadjusted                             | Regression adjusted   |             |
|------------------------------|----------------------------|--------|-------|---------------|--------|-------|----------------------------------------|-----------------------|-------------|
|                              | N                          | Before | After | N             | Before | After | Difference-in-differences <sup>a</sup> | Estimate <sup>b</sup> | 95% CI      |
| Baseline PDC ≥0.80           |                            |        |       |               |        |       |                                        |                       |             |
| Antihypertensives            | 465                        | 0.94   | 0.92  | 450           | 0.93   | 0.89  | 0.03**                                 | 0.03**                | 0.02, 0.04  |
| Lipid-lowering drugs         | 236                        | 0.91   | 0.85  | 174           | 0.90   | 0.83  | 0.01                                   | 0.01                  | −0.01, 0.03 |
| Antidiabetic agents          | 97                         | 0.91   | 0.89  | 98            | 0.91   | 0.86  | 0.03                                   | 0.03                  | −0.00, 0.06 |
| Baseline PDC <0.80           |                            |        |       |               |        |       |                                        |                       |             |
| Antihypertensives            | 188                        | 0.65   | 0.81  | 210           | 0.63   | 0.73  | 0.06**                                 | 0.06**                | 0.03, 0.09  |
| Lipid-lowering drugs         | 313                        | 0.55   | 0.73  | 362           | 0.54   | 0.62  | 0.09**                                 | 0.10**                | 0.07, 0.12  |
| Antidiabetic agents          | 118                        | 0.53   | 0.72  | 113           | 0.55   | 0.68  | 0.07**                                 | 0.07**                | 0.02, 0.11  |
| Baseline PDC ≥0.60 and <0.80 |                            |        |       |               |        |       |                                        |                       |             |
| Antihypertensives            | 137                        | 0.72   | 0.84  | 142           | 0.71   | 0.79  | 0.05**                                 | 0.05**                | 0.02, 0.09  |
| Lipid-lowering drugs         | 155                        | 0.71   | 0.80  | 162           | 0.71   | 0.73  | 0.07**                                 | 0.07**                | 0.03, 0.11  |
| Antidiabetic agents          | 54                         | 0.71   | 0.83  | 56            | 0.71   | 0.80  | 0.03                                   | 0.03                  | −0.03, 0.09 |
| Baseline PDC <0.60           |                            |        |       |               |        |       |                                        |                       |             |
| Antihypertensives            | 51                         | 0.47   | 0.71  | 68            | 0.45   | 0.60  | 0.09**                                 | 0.09**                | 0.03, 0.16  |
| Lipid-lowering drugs         | 158                        | 0.40   | 0.66  | 200           | 0.40   | 0.53  | 0.13**                                 | 0.13**                | 0.09, 0.17  |
| Antidiabetic agents          | 64                         | 0.37   | 0.62  | 57            | 0.40   | 0.56  | 0.10**                                 | 0.10**                | 0.03, 0.16  |

**SOURCE** Authors' analysis of Humana claims data, June 2012 to December 2014. **NOTE** CI is confidence interval. <sup>a</sup>Absolute difference. <sup>b</sup>Difference-in-differences estimate from regression. \*\*p < 0.05

ering agents to 1.37 for antidiabetic agents.

As shown in Exhibits 3 and 4, subgroup analyses revealed that prescription refill synchronization had the largest effects among the subgroup with the lowest baseline (PDC <0.60). In this subgroup, there were statistically signifi-

cant, larger absolute increases in the proportion of the intervention group deemed adherent compared to the control group (23 versus 14 percentage points for antihypertensives, 26 versus 13 percentage points for lipid-lowering drugs, and 25 versus 15 percentage points for anti-

**EXHIBIT 4**
**Descriptive and regression-adjusted categorical adherence outcomes for synchronized prescription refill and control groups, by baseline adherence status**

|                              | Synchronized refills group |        |       | Control group |        |       | Unadjusted                             | Regression adjusted     |            |
|------------------------------|----------------------------|--------|-------|---------------|--------|-------|----------------------------------------|-------------------------|------------|
|                              | N                          | Before | After | N             | Before | After | Difference-in-differences <sup>a</sup> | Odds ratio <sup>b</sup> | 95% CI     |
| Baseline PDC ≥0.80           |                            |        |       |               |        |       |                                        |                         |            |
| Antihypertensives            | 465                        | 91%    | 90%   | 450           | 90%    | 86%   | 3%**                                   | 1.30**                  | 1.08, 1.56 |
| Lipid-lowering drugs         | 236                        | 87     | 81    | 174           | 86     | 79    | 1                                      | 1.03                    | 0.82, 1.29 |
| Antidiabetic agents          | 97                         | 88     | 86    | 98            | 87     | 83    | 2                                      | 1.18                    | 0.83, 1.68 |
| Baseline PDC <0.80           |                            |        |       |               |        |       |                                        |                         |            |
| Antihypertensives            | 188                        | 61     | 78    | 210           | 59     | 70    | 6**                                    | 1.40**                  | 1.15, 1.70 |
| Lipid-lowering drugs         | 313                        | 52     | 70    | 362           | 50     | 59    | 10**                                   | 1.64**                  | 1.42, 1.89 |
| Antidiabetic agents          | 118                        | 49     | 69    | 113           | 52     | 64    | 7**                                    | 1.42**                  | 1.10, 1.82 |
| Baseline PDC ≥0.60 and <0.80 |                            |        |       |               |        |       |                                        |                         |            |
| Antihypertensives            | 137                        | 68     | 81    | 142           | 67     | 76    | 5**                                    | 1.35**                  | 1.07, 1.70 |
| Lipid-lowering drugs         | 155                        | 67     | 76    | 162           | 67     | 69    | 7**                                    | 1.48**                  | 1.20, 1.82 |
| Antidiabetic agents          | 54                         | 67     | 79    | 56            | 67     | 76    | 3                                      | 1.15                    | 0.80, 1.66 |
| Baseline PDC <0.60           |                            |        |       |               |        |       |                                        |                         |            |
| Antihypertensives            | 51                         | 44     | 67    | 68            | 42     | 56    | 9**                                    | 1.62**                  | 1.15, 2.30 |
| Lipid-lowering drugs         | 158                        | 37     | 63    | 200           | 37     | 50    | 13**                                   | 1.84**                  | 1.52, 2.23 |
| Antidiabetic agents          | 64                         | 35     | 60    | 57            | 37     | 52    | 10**                                   | 1.69**                  | 1.19, 2.41 |

**SOURCE** Authors' analysis of Humana claims data, June 2012 to December 2014. **NOTES** PDC is proportion of days covered (PDC) ≥ 0.80. CI is confidence interval. <sup>a</sup>Absolute difference (for example, 3 percent indicates 3 percentage points). <sup>b</sup>Difference-in-differences estimate from regression. \*\*p < 0.05

diabetic agents, respectively) (Exhibit 4). There were minimal or no effects of program participation among the subgroup with high baseline adherence ( $PDC \geq 0.80$ ).

Sensitivity analyses using fixed effects to address time-invariant patient-specific unobservable characteristics, using quarterly data instead of monthly data for adherence outcomes and controlling for additional consumer variables, produced results similar to those of our main analyses and confirmed the robustness of our findings (Appendix Exhibit A3).<sup>24</sup> A final sensitivity analysis implementing propensity score matching further confirmed this (Appendix Exhibit A4).<sup>24</sup>

## Discussion

In this study we found that voluntary enrollment in a synchronized refill program was associated with significantly improved adherence in Medicare patients receiving three common classes of maintenance medications: antihypertensives, lipid-lowering agents, and antidiabetic agents. The intervention group showed statistically significant absolute increases in mean proportion of days covered of 0.03–0.05 as well as absolute increases of 3–5 percentage points in the proportion of patients achieving an adherence benchmark of  $PDC \geq 0.80$  relative to the control group. Since the mean baseline adherence in our sample was remarkably high to begin with, especially among patients using antihypertensives and lipid-lowering agents, this might have resulted in a ceiling effect for some patients. Indeed, improvements in adherence were even greater for intervention subgroups with poorer baseline adherence defined as  $PDC < 0.60$ , with increases in the proportion of these patients deemed adherent greater than 9–13 percentage points relative to the control group.

It is perhaps not surprising that prescription synchronization alone did not appear to lead to the same magnitude of improvement that has been reported in studies of appointment-based medication synchronization programs, which typically offer face-to-face contact with a pharmacist and a more comprehensive set of services, such as troubleshooting of adherence issues that are not solely related to medication supply (for example, grouping doses in labeled blister packs to help patients remember which doses are to be taken at which time).<sup>6,10</sup> Synchronization is able to target many of the logistical issues related to medication supply, but it is not able to target other common roots of nonadherence (for example, forgetting of doses or ambivalence about taking medications). Nevertheless, synchronization can be easily combined with other types of

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interventions, based on a patient's specific adherence challenges.

In addition, our findings suggest that the medication synchronization program we examined compares favorably to other widely adopted systems-level interventions to improve medication adherence. For instance, the Center for Medicare and Medicaid Innovation recently announced the test of a Medicare Advantage Value-Based Insurance Design Model<sup>28</sup> that has already been widely adopted by insurers and employers.<sup>29–32</sup> Despite their popularity, a 2013 review of interventions using value-based insurance design, which typically involve reducing or eliminating patients' prescription copayments as a way of increasing medication adherence, found average adherence improvements of 3 percent at one year.<sup>29</sup> The literature on whether such modest improvements in adherence translate into a positive impact on health outcomes or economic savings is limited. However, two seminal studies have indeed found that even modest differences in adherence levels for cardiovascular and diabetes medications are associated with changes in physiological outcomes and cardiovascular events.<sup>33,34</sup> Also, there is evidence that boosting adherence to cardiovascular medications to or above an 80 percent cutoff (as used in our study) is indeed associated with lower risk of adverse cardiovascular events.<sup>27</sup>

While our study examined Medicare beneficiaries in MA-PD plans, our results likely apply to the Medicare fee-for-service population as well, since prescription synchronization would still be expected to alleviate logistical challenges associated with managing multiple refills. In addition to reducing these burdens, synchronization programs also facilitate budgeting since there is greater predictability in the timing of refill copayments. In our study this benefit was cited by 85 percent of participants as a helpful component of the program (data not shown). It should be noted that we examined maintenance medi-

cations that are typically associated with low out-of-pocket expense, thereby mitigating any potential negative impact of consolidating payments. For patients with significantly greater out-of-pocket spending or strict fixed incomes, paying for all medications at once could present financial hardship. This once again underscores the fact that there is no one-size-fits-all solution for adherence challenges.

More research is warranted, but our findings offer several important insights for synchronization program design. First, it is sensible to target less adherent patients first since they benefited most from the program we examined. Moving patients from being classified as less adherent (PDC <0.80) to adherent (PDC ≥0.80) is also one of the quality targets highlighted by the Medicare Part D star ratings for the medication classes we examined.<sup>13</sup>

Second, although this program was free, it had a relatively low participation rate. One explanation could be “status quo bias,” wherein people tend to continue with their current choice, even when better alternatives exist, because it is the “path of least resistance.”<sup>35</sup> Future programs may wish to try an opt-out or enhanced active choice

policy to increase enrollment.<sup>36</sup> Enhanced active choice is an approach to making the decision between alternatives more salient by presenting it at the time of another point of intersection with the consumer—for example, when doing a refill—and highlighting the advantages such as convenience to signing up for a program versus the downside of doing this manually. The framing of these programs can be created as either a strong or a weak nudge, depending on the context.<sup>36</sup>

Finally, since adherence is a dynamic process that requires sustained attention, member retention strategies for medication synchronization programs could also be helpful in maximizing participation and potential gains.

In summary, our findings suggest that a prescription refill synchronization program for Medicare beneficiaries using a mail-order pharmacy was associated with improvements in adherence to antihypertensives, lipid-lowering agents, and antidiabetic agents, particularly in patients with low baseline adherence. Further studies are needed to examine the economic impact of such programs and whether they are associated with changes in health outcomes. ■

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## NOTES

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