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Osteoporosis Telephonic Intervention to Improve Medication Regimen Adherence

A Large, Pragmatic, Randomized Controlled Trial

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Background: Multiple studies demonstrate poor adherence to medication regimens prescribed for chronic illnesses, including osteoporosis, but few interventions have been proven to enhance adherence. We examined the effectiveness of a telephone-based counseling program rooted in motivational interviewing to improve adherence to a medication regimen for osteoporosis.

Methods: We conducted a 1-year randomized controlled clinical trial. Participants were recruited from a large pharmacy benefits program for Medicare beneficiaries. All potentially eligible individuals had been newly prescribed a medication for osteoporosis. Consenting participants were randomized to a program of telephone-based counseling (n=1046) using a motivational interviewing framework or a control group (n=1041) that received mailed educational materials. Medication regimen adherence was the primary outcome compared across treatment arms and was measured as the median (interquartile range) medication possession ratio, calculated

as the ratio of days with filled prescriptions to total days of follow-up.

Results: The groups were balanced at baseline, with a mean age of 78 years; 93.8% were female. In an intention-to-treat analysis, median adherence was 49% (interquartile range, 7%-88%) in the intervention arm and 41% (2%-86%) in the control arm ($P=.07$, Kruskal-Wallis test). There were no differences in self-reported fractures.

Conclusion: In this randomized controlled trial, we did not find a statistically significant improvement in adherence to an osteoporosis medication regimen using a telephonic motivational interviewing intervention.

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ADHERENCE WITH MANY long-term medication regimens is poor and appears worse for conditions that do not produce daily symptoms.¹ A meta-analysis involving more than 50 000 patients found that patients with osteoporosis demonstrate adherence for 48% of days with a prescribed treatment during the first year of therapy.² More than 2 million fractures associated with osteoporosis or osteopenia occur annually in the United States at an estimated medical cost of \$19 billion.³ Medications have been shown to reduce fracture risk in many populations⁴; thus, improving adherence to osteoporosis drug regimens is a public health priority.⁵

Nonadherence is a complex behavior with many potential causes,⁶ including concerns about medication safety, lack of confidence in a medication's benefits or in the

patient's ability to adhere to a regimen, forgetfulness, complexity of the treatment regimen, and drug affordability.^{1,7-9} The multitude of reasons underpinning nonadherence to a medication regimen and the failure of many unidimensional programs suggest that a successful intervention needs to be multifaceted and tailored for a given individual.¹⁰ These features are characteristic of one-on-one counseling interventions. Several medication adherence interventions using counseling based on motivational interviewing have been successful in other clinical areas.^{11,12}

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Motivational interviewing is a client-centered counseling method based on the stages-of-change model of health behavior.^{13,14} The counselor interacts with the pa-

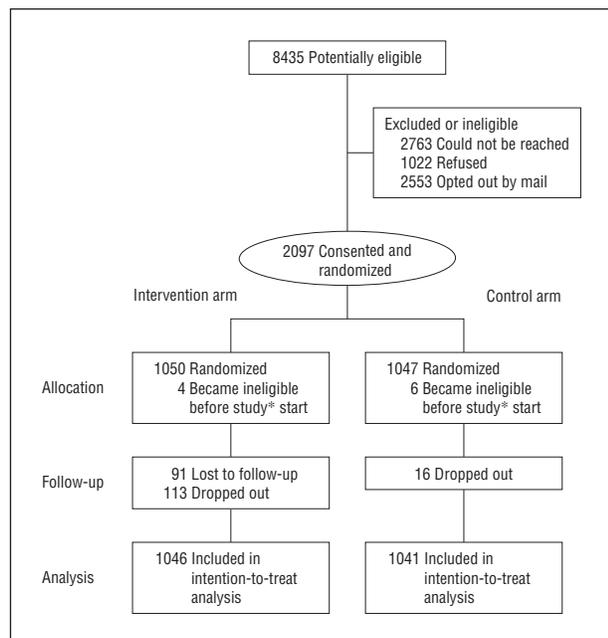


Figure 1. The Consolidated Standards of Reporting Trials diagram illustrating the assembly of the study cohort and its follow-up through the trial procedures. *Indicates died between recruitment and the start of follow-up 30 days later and were excluded from analyses.

tient to identify the reasons for problematic health behaviors and then shapes the counseling to address the issues most likely to help that particular person. We developed a motivational interviewing program that could be delivered by health educators via the telephone. Medicare beneficiaries starting prescription osteoporosis medication regimens were recruited and randomized to receive motivational interviewing counseling sessions (intervention arm) or mailed educational materials (control arm).

METHODS

STUDY DESIGN AND OVERSIGHT

The Osteoporosis Telephonic Intervention to Improve Medication Adherence (OPTIMA) trial was a large, pragmatic, randomized effectiveness trial, which has been described in detail previously.¹⁵ The trial was conducted in accordance with the trial protocol, which was reviewed by the Partners Healthcare institutional review board. The study was deemed exempt from institutional review board oversight; however, a safety officer appointed by the National Institutes of Health (the funding agency) reviewed safety data during the course of the trial. The study was designed by the authors; data were collected in a blinded fashion and analyzed by a statistical programmer (J.L.) blinded to treatment assignment.

STUDY PARTICIPANTS

We collaborated with a state-run pharmacy benefits program for low-income older adults residing in the state of Pennsylvania.¹⁶ More than 200 000 state residents are enrolled annually and receive medications for a nominal copayment. Monthly administrative claims files identifying beneficiaries receiving new prescription medication for osteoporosis (eg, estrogen replacement therapy, a bisphosphonate, teriparatide acetate, calcitonin, or raloxifene hydrochloride) were transferred se-

curely to the study team. Subjects received a letter inviting them to participate in the program and providing them the opportunity to opt out of further contact. Potentially eligible subjects who did not opt out were contacted, and recruitment was attempted if they met additional study eligibility criteria, including living in the community and being able to understand spoken English. Subjects gave verbal consent to be part of a program for osteoporosis and were then randomized to the intervention or control arm (**Figure 1**). Because all subjects in both arms received enhanced care, they were not aware of their treatment arm allocation.

INTERVENTION

Approximately 30 days after randomization, all subjects in both arms began to receive mailings regarding osteoporosis. During the course of the study, all subjects received 7 informational mailings covering topics such as exercise, fall prevention, and recommended calcium intake (see eMaterials, available on request from the authors). The subjects in the intervention arm also received motivational interviewing counseling sessions via telephone with 1 of 7 health educators. We aimed for 10 counseling sessions per subject during the course of the study. Each session had a specific educational topic (eg, discussing medications with your physician, calcium and vitamin D supplementation, fall prevention, managing adverse effects of medication) and included a series of open-ended questions to elicit subjects' attitudes toward medication adherence and to determine barriers to long-term osteoporosis medication use. The health educators received training in motivational interviewing through a half-day training program at study initiation that included role-playing, lecture, and discussion. The motivational interviewing counseling was reinforced through telephone conferences 1 to 2 times per month with a behavioral scientist (M.D.I.) and clinical expert (D.H.S.). In addition, 3 times during the course of the 2.5-year study period, health educators recorded client telephone calls (with the subject's consent) that were then reviewed and graded by a motivational interviewing trainer. The trainer gave structured feedback to each health educator using an assessment tool.¹⁷

OUTCOMES

The primary outcome of the study was adherence to prescription osteoporosis medication regimens, as measured by the medication possession ratio (MPR) during the 12 months of follow-up.¹⁸ The MPR can be measured using different methods; we calculated it as the number of days with filled prescriptions during the observation period \times 100 divided by the number of days in the observation period.¹⁹

We used pharmacy claims data from the collaborating state-run pharmacy benefits program to calculate the MPR. Paid medication claims based on filled prescriptions form the basis of these data. The MPR is widely recognized as a valid measure of adherence.¹⁸

Secondary outcomes included persistence with prescription osteoporosis medication, defined as days from initial prescription until the first period during which the subject experienced an interruption in prescription filling lasting longer than 60 days.¹⁸ We also assessed self-reported fractures, falls, depression, and satisfaction with the program using an exit survey.

STATISTICAL ANALYSIS

Primary Analysis

The analysis was performed according to a predetermined statistical analysis plan. We compared the baseline characteris-

tics of the 2 treatment arms using the unpaired *t* test for continuous variables and a Kruskal-Wallis test for categorical items. The primary analyses of outcomes used an intention-to-treat approach in which all subjects in the assigned treatment arms underwent evaluation until the completion of the 12-month follow-up without regard to dropout (unless subjects died or lost eligibility for the state-run pharmacy benefits program, in which case they were censored at the time of these events). The distribution of MPRs was not normal; thus, we compared the median (interquartile range [IQR]) MPR across the 2 treatment arms. For each treatment arm, we also compared the distribution of MPRs, calculated as the percentage of patients in each decile of MPR.

The sample size was chosen to ensure 90% power to detect an absolute difference of 10% in adherence (measured by MPR) between the 2 arms.

Secondary Analyses

We examined the secular trends of MPR by treatment arm across the study follow-up period, assessing whether the effect of the intervention varied during the course of the 12-month follow-up. Follow-up time was partitioned into 60-day increments, and an interaction term between follow-up time and treatment arm was tested in a linear regression model, with the MPR as the dependent variable.

We also compared the intervention's effects in subgroups, such as participants aged 65 to 74 years vs 75 years or older, those with a previous fracture vs none, white subjects vs non-white, and married subjects vs not married.

During the study period, Medicare Part D was introduced. Some pharmacy claims were unavailable from Medicare prescription drug plans that did not share complete data with the state-run pharmacy benefits program. We conducted sensitivity analyses to determine the potential effects of incomplete data. Subjects were censored when the state-run pharmacy program noted that a beneficiary entered a nonparticipating Medicare prescription drug plan.

Persistence with prescription osteoporosis treatments was illustrated using Kaplan-Meier survival curves and compared across study arms using the log-rank test. The proportions of subjects in each treatment arm reporting fractures, falls, and poor or fair health were compared using the Kruskal-Wallis test.

The statistical analysis was performed using commercially available software (SAS Institute, Inc, version 9.1).

RESULTS

PATIENTS

We recruited and enrolled 2097 subjects into the trial (Figure 1). Ten subjects died between enrollment and the start of follow-up and were excluded, leaving 2087 available for analysis. The recruited subjects closely resembled the total eligible pool (see the eTable; <http://www.archinternmed.com>). As noted in **Table 1**, the baseline characteristics of subjects in the 2 arms were similar. Across both study arms, the mean age was approximately 78 years, and 93.8% were female. Most subjects were single or widowed. The mean number of comorbid conditions was 5.2, and the mean number of different medications used in the year before the trial was 10.4. Previous fractures, falls, activity limitations, and poor eyesight were common, with a similar incidence across treatment arms. The most common prescription osteo-

Table 1. Baseline Characteristics of the Study Population^a

Characteristic	Treatment Arms	
	Intervention (n = 1046)	Control (n = 1041)
Female sex	986 (94.3)	971 (92.8)
Age, mean (SD), y	77.8 (6.4)	77.7 (6.6)
Race		
White	942 (90.1)	909 (87.3)
Nonwhite	104 (9.9)	132 (12.7)
Marital status		
Married	228 (21.8)	231 (22.2)
Divorced or separated	103 (9.8)	124 (11.9)
Widowed or single	715 (68.4)	686 (65.9)
No. of medications, mean (SD)	10.2 (6.0)	10.6 (6.0)
No. of comorbidities, mean (SD)	5.2 (3.4)	5.3 (3.3)
Comorbidity		
Prior fracture	303 (29.6)	285 (29.2)
Poor eyesight	210 (20.4)	208 (20.7)
Activity limitation	730 (70.9)	709 (70.7)
≥1 Prior fall	412 (40.2)	378 (38.3)
Osteoporosis medication		
Bisphosphonate, intravenous	2 (0.2)	2 (0.2)
Bisphosphonate, oral, daily	7 (0.7)	4 (0.4)
Bisphosphonate, oral, weekly	664 (63.5)	666 (64.0)
Other, oral or intranasal ^b	355 (33.9)	358 (34.4)
Other, injectable ^b	18 (1.7)	11 (1.1)

^aUnless otherwise indicated, data are expressed as number (percentage) of subjects. Sample sizes of several variables differ because of missing data.

^bIncluded raloxifene hydrochloride, calcitonin, teriparatide acetate, and estrogen replacement therapy.

porosis treatment in both arms consisted of weekly bisphosphonates. The only statistically significant difference across the arms was in the distribution of races, with slightly more white subjects in the intervention arm. Thirty-six subjects in the intervention arm and 39 in the control arm died during follow-up.

In the intervention arm, the median number of completed calls was 8 (IQR, 6-9), and the median duration of a counseling session was 14 minutes (IQR, 10-19).

PRIMARY END POINT

During the 12 months of follow-up, the median MPR was 49% (IQR, 7%-88%) in the intervention arm and 41% (IQR, 2%-86%) in the control arm (Kruskal-Wallis test, *P* = .07) (see **Table 2**). There was a suggestion of a difference in MPR between the intervention and control groups at the extremes of the distribution: 34.4% of the intervention groups vs 39.1% in the control group had an MPR of less than 20%, whereas 32.8% in the intervention group vs 30.3% in the control group had an MPR of more than 80%, but this difference was small and did not reach statistical significance (χ^2 trend test across all deciles, *P* = .08) (**Figure 2**). The trend in the median medication possession ratios for six 60-day intervals during the follow-up year is shown in **Figure 3**.

The sensitivity analyses performed to test the effect of data dropout through enrollment in nonparticipating Medicare Part D plans showed higher median MPRs for both groups than in the primary analysis (intervention arm, 61%; control arm, 54%).

Table 2. Median MPR in Entire Cohort and Subgroups

Variable	Intervention Arm		Control Arm		P Value
	No. of Subjects ^a	MPR, Median (IQR), %	No. of Subjects ^a	MPR, Median (IQR), %	
Intention to treat ^b	1046	49 (7-88)	1041	41 (2-86)	.07
Subgroup analysis ^c					
Age, y					
65-74	346	48 (7-87)	362	31 (0-80)	.045
>75	700	49 (6-88)	679	46 (2-90)	
Sex					
Female	986	50 (7-88)	971	41 (2-86)	.27
Male	60	20 (0-81)	70	38 (0-83)	
Prior fracture					
Yes	303	46 (7-87)	285	51 (12-85)	.07
No	723	50 (7-88)	708	35 (0-86)	
Marital status					
Married	228	52 (7-90)	231	32 (0-83)	.17
Other ^d	818	48 (7-87)	810	44 (3-87)	
Race					
White	942	50 (7-90)	909	40 (0-87)	.07
Nonwhite	104	35 (4-76)	132	43 (11-79)	

Abbreviations: IQR, interquartile range; MPR, medication possession ratio.

^aSample sizes of several variables differ because of missing data.

^bP value is calculated using the Wilcoxon rank sum test.

^cP values are calculated for interaction.

^dIncludes widowed, divorced, or single.

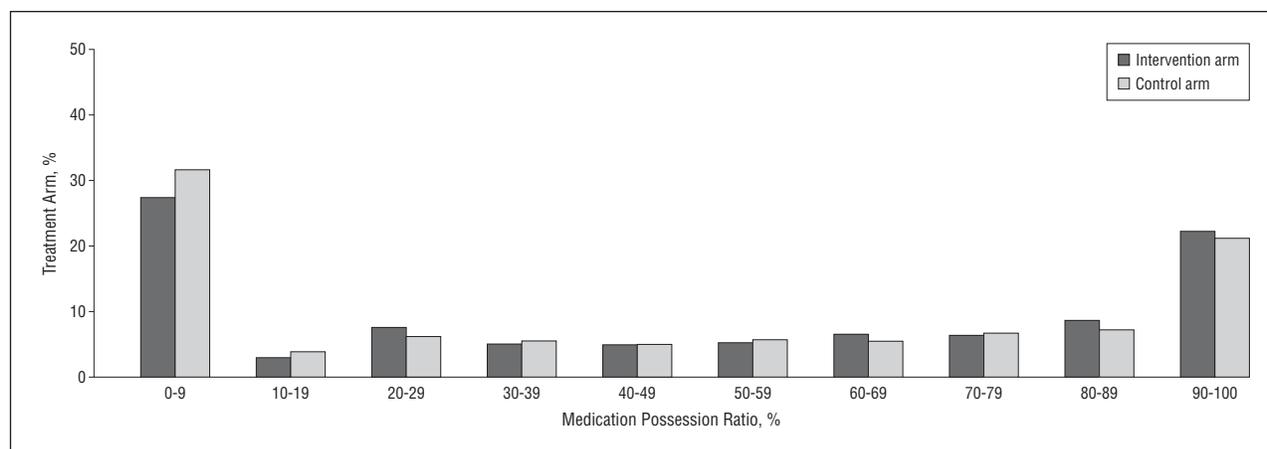


Figure 2. Histogram displaying the distribution of adherence for the intervention and control arms by decile of medication possession ratio.

SECONDARY END POINTS

There were no statistically significant differences noted in secondary outcomes, including self-reported fractures (intervention arm, 10.9%; control arm, 11.2%), self-reported falls (intervention arm, 38.1%; control arm, 35.7%), or poor or fair general health (intervention arm, 40.2%; control arm, 40.9%). In addition, persistence with osteoporosis medication regimens appeared similar across the 2 groups (**Figure 4**) (log-rank $P = .34$).

SUBGROUP ANALYSES

The effectiveness of the intervention appeared to differ modestly across several of the subgroups (Table 2). The intervention was associated with improvement in MPR for subjects aged 65 to 74 years (median MPR for the in-

tervention arm, 48%; for the control arm, 31%) compared with little improvement in those 75 years or older (median MPR for the intervention arm, 49%; for the control arm, 46%; $P = .045$ for interaction). Among those without a previous fracture, the intervention appeared more effective (median MPR for the intervention arm, 50%; for the control arm, 35%) compared with those with a previous fracture (median MPR for the intervention arm, 46%; for the control arm, 51%; $P = .07$ for interaction). In addition, the intervention produced somewhat larger effects among white subjects (median MPR for the intervention arm, 50%; for the control arm, 40%) compared with nonwhite subjects (median MPR for the intervention arm, 35%; for the control arm, 43%; $P = .07$ for interaction). In the latter 2 subgroup analyses (by fracture history and race), the interactions terms did not reach statistical significance.

The per-patient intervention costs were \$280.94, including training of the health educators, recruitment of subjects, telephone calls, mailings, and data storage.

COMMENT

Nonadherence to medication regimens results in suboptimal clinical outcomes and excess health care costs in many chronic conditions, including osteoporosis.²⁰⁻²³ We attempted to improve prescription medication adherence for osteoporosis through a pragmatic randomized controlled trial in collaboration with a public prescribing benefits program. The intervention used principles of motivational interviewing and was delivered by telephone. Subjects in the intervention arm did not experience a statistically significant increase in median MPR, a well-accepted measure of adherence, compared with controls.

We used motivational interviewing as the behavioral framework for the medication adherence counseling. Interviewing was performed by health educators who underwent extensive training and who used regular feedback and structured assessments.¹⁷ Motivational interviewing has been widely used for addiction counseling and more recently has been adopted for other health care settings.¹⁴ It formed the basis for a successful intervention that improved adherence with antihypertensive therapy by 14% and produced reductions in blood pressure.¹² Adherence to antiretroviral therapy improved by 4.5% using a motivational interviewing-based counseling program.¹¹ However, not all similar programs have been successful.²⁴ Our intervention was the first telephone-based motivational interviewing program targeting adherence to a medication regimen of which we are aware. Although our intervention did not achieve a statistically significant improvement, these prior studies and the effects seen in select prespecified subgroups in our trial suggest that motivational interviewing shows promise as a counseling model for medication adherence and should be investigated further.

We had estimated the sample size of this trial based on a 10% increase in medication regimen adherence, which was deemed to be clinically important. We observed an increase in adherence of 8%. Thus, the trial did not document a statistically significant difference between randomization groups and did not achieve the clinically important increase in adherence we sought to identify. Our follow-up may have been inadequate to detect a change in fracture rate attributable to a modest change in medication use. The a priori power calculation for the trial was based on the adherence end point and not the fracture end point because detecting a difference in fractures was unlikely based on our hypothesized 10% improvement in adherence.^{23,25,26}

These findings have several important implications. First, although our results were not statistically significant, we demonstrated that a relatively simple intervention has the potential to achieve modest improvements in medication adherence, particularly in select prespecified subgroups. Second, the intervention's structure has relevance for other programs that aim to improve adher-

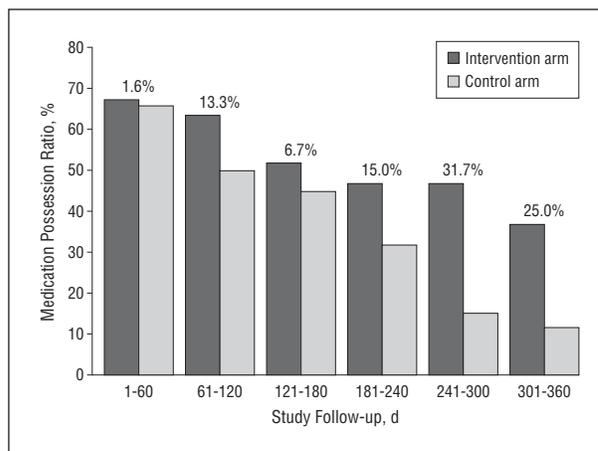


Figure 3. Histogram displaying the median medication possession ratios for six 60-day intervals, by treatment assignment. The interaction effect between treatment arm and sequential 60-day periods during follow-up was not statistically significant ($P = .60$ for interaction). The percentages above the pairs of bars represent the difference in the medication possession ratios between the intervention and control arms.

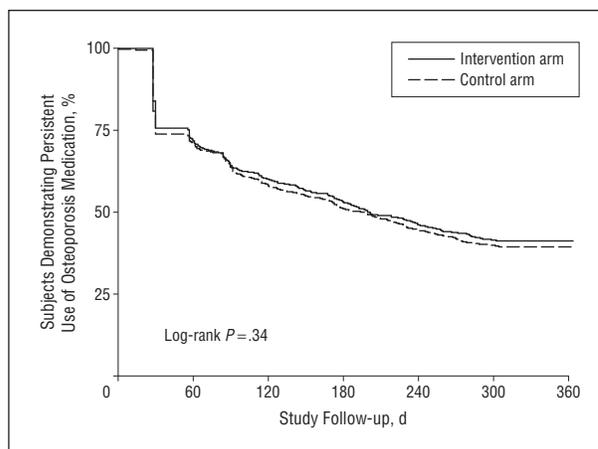


Figure 4. Persistence over time in use of medications for osteoporosis.

ence to recommended regimens. We used health care and pharmacy insurance claims data to identify people starting medication therapy for osteoporosis, segment them for analyses, and collect outcomes data. Since the expansion of Medicare to include drug benefits, the Centers for Medicare and Medicaid Services has the most extensive database of longitudinal health care utilization on a large portion of the US population. These data should facilitate case finding and follow-up in care improvement programs as demonstrated in our intervention trial. Similar capabilities are in place in most large managed-care programs and for most health insurers that cover prescription benefits. This trial also demonstrates the power of health care and pharmacy insurance claims data to conduct a large pragmatic trial. We recruited more than 2000 subjects, followed them up for a year, and conducted extensive analyses on a budget of less than \$1 million (direct costs for 5 years). This economy of scale could only be achieved through relying on administrative data collected as part of routine health care delivery.

The use of routinely collected data presents important methodologic challenges. We relied on pharmacy

claims data to identify recent initiators of an osteoporosis medication regimen. These data needed to be processed, and then we allowed potential subjects to opt out of recruitment. This meant that, by the time subjects were recruited and received their first intervention call, a median of 113 days had passed since they filled their first prescription. Although data shown in Figure 3 suggest that the intervention's effect increased during the study, the lag period may have limited the benefit of our intervention because many subjects had already discontinued use of their osteoporosis medication at the time of their first telephone call (see Figure 4). If a health care delivery system were to provide the intervention itself, data would be more immediately available and lag times would be reduced. In addition, by relying on pharmacy claims data, we do not know that patients actually took the medicine, only that they filled prescriptions. Finally, we were able to enroll only a fraction of those who were potentially eligible. The groups were similar with respect to age, sex, race, and number of prescription medications (see the eTable).

CONCLUSIONS

We conducted a randomized controlled trial of more than 2000 patients that did not demonstrate a statistically significant improvement in adherence to a medication regimen associated with a telephone-based motivational interviewing counseling intervention. Subgroup analyses suggest that the intervention may be more effective in specific populations, including patients 75 years or older compared with those aged 65 to 74 years. Further research is necessary to determine how to best target this intervention. The study also demonstrated the potential utility of routinely collected prescription data to identify new users of a particular medication class and follow them up for outcomes. Given the widespread nature of nonadherence to medication regimens, this work may provide useful information for further studies to improve the appropriateness of prescription drug use.

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Author Contributions: Dr Solomon had access to all the data and takes full responsibility for the accuracy and completeness of the data and the data analysis. *Study concept and design:* Solomon, Iversen, Avorn, Patrick, Shrank, Losina, and Katz. *Acquisition of data:* Solomon, Avorn, Gleeson, and Rekedal. *Analysis and interpretation of data:* Solomon, Iversen, Avorn, Gleeson, Brookhart, Patrick, Shrank, Lii, Losina, and Katz. *Drafting of the manuscript:* Solomon, Iversen, Brookhart, and Lii. *Critical revision of the manuscript for important intellectual content:* Solomon, Iversen, Avorn, Gleeson, Patrick, Rekedal, Shrank, Losina, and Katz. *Statistical analysis:* Solomon, Brookhart, Patrick, Shrank, Lii, and Losina. *Obtained funding:* Drs

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Images From Our Readers



Autumn leaves.

Courtesy of: Tine Vindenes, MD, Internal Medicine, Danbury Hospital, Danbury, Connecticut.