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Adherence to Osteoporosis Medications After Patient and Physician Brief Education: Post Hoc Analysis of a Randomized Controlled Trial

Aimee Der-Huey Shu, MD, **Margaret R. Stedman, MPH**, **Jennifer M. Polinski, MPH, MS**, **Saira A. Jan, MS, PharmD**, **Minal Patel, MD, MPH**, **Colleen Truppo, RN, MBA**, **Laura Breiner, RN, BSN**, **Ya-ting Chen, PhD**, **Thomas W. Weiss, DrPH**, and **Daniel H. Solomon, MD, MPH**
Division of Pharmacoepidemiology (AD-HS, MRS, JMP, DHS) and Division of Rheumatology (DHS), Brigham and Women's Hospital, Boston, MA; Division of Endocrinology (AD-HS), Columbia Presbyterian Hospital, New York, NY; Horizon Blue Cross Blue Shield (SAJ, MP, CT, LB), Newark, NJ; and Outcomes Research Group (Y-TC, TWW), Merck & Co, Inc, West Point, PA

Abstract

Objective—To examine whether adherence to osteoporosis medications can be improved by educational interventions targeted at primary care physicians (PCPs) and patients.

Study Design—Post hoc analysis of data collected as part of a prospective randomized controlled trial to improve initiation of osteoporosis management such as bone mineral density testing or osteoporosis drug initiation.

Methods—The trial was conducted among patients at risk for osteoporosis enrolled in Horizon Blue Cross Blue Shield of New Jersey. For a 3-month period, randomly selected PCPs and their patients received education about osteoporosis diagnosis and treatment. The PCPs received face-to-face education by trained pharmacists, while patients received letters and automated telephone calls. The control group received no education. We assessed medication adherence during 10 months following the start of the intervention using the medication possession ratio (MPR), the ratio of available medication to the total number of days studied.

Results—These analyses included 1867 patients (972 randomized to the intervention group and 875 to the control group) and their 436 PCPs. During 10 months following the intervention, the median MPRs were 74% (interquartile range [IQR], 19%–93%) for the intervention group and 73% (IQR, 0%–93%) for the control group (P =.18). The median times until medication discontinuation after the intervention were 85 days (IQR, 58–174 days) for the intervention group and 79 days (IQR, 31–158 days) for the control group.

Address correspondence to: Daniel H. Solomon, MD, MPH, Division of Pharmacoepidemiology, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. dhsolomon@partners.org.
Ms Truppo is now with Care Management International, Hoboken, NJ.
Ms Breiner is now with NYC Department of Health, New York, NY

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Conclusion—The educational intervention did not significantly improve medication compliance or persistence with osteoporosis drugs.

Improving patient adherence with osteoporosis medications is an important challenge. Higher levels of adherence may be associated with reduced fracture rates[1]; however, studies[2,3] demonstrate suboptimal adherence among patients in the community. Oft-cited barriers to achieving adequate adherence include insufficient patient education, specific patient health beliefs, complex medication regimens, polypharmacy, poor provider-patient relations, patient forgetfulness, and medication costs.[4–6] Strategies targeting these barriers, as well as patient monitoring systems and feedback based on clinical markers, have been proposed to improve medication adherence for osteoporosis treatments.[6–9]

Successful medication adherence interventions for other chronic diseases such as hypertension and asthma have been multifactorial and focused on the patient.[5] A small randomized trial attempted to enhance adherence to raloxifene hydrochloride among 75 women with osteopenia; a nurse-run patient monitoring program with clinic appointments every 12 weeks improved adherence to raloxifene at 1 year.[10] Another population-based study[11] of patients with osteoporosis who sustained distal forearm fractures showed that timely provision of educational brochures, primary care provider appointments, and bone mineral density testing appointments improved adherence over 6 months of follow-up. However, many of the most adherent patients had the best bone mineral density.

While medication adherence may be primarily a patient behavior, it is unclear whether physician-directed interventions can influence this behavior. To our knowledge, no prior intervention for osteoporosis medication adherence has focused on the physician. In this study, we performed a post hoc analysis of data from a randomized controlled trial for improving osteoporosis management to determine whether a brief physician-oriented intervention improved compliance or persistence with osteoporosis medications.

METHODS

Design

These analyses are based on a cluster randomized controlled trial conducted in Horizon Blue Cross Blue Shield of New Jersey (HBCBSNJ) that has been described in detail elsewhere.[12] Briefly, we randomly assigned primary care physicians (PCPs) and their patients at risk for osteoporosis (defined herein) to receive a multifaceted intervention or usual care. Randomization was clustered so that all patients of a particular physician were assigned to the same arm, either intervention or usual care. Patients were randomized with their PCP to reduce any contamination within a given physician's practice. The trial was aimed at improving the management of osteoporosis among at-risk patients, including initiation of bone mineral density testing and pharmacotherapy for osteoporosis. The brief intervention proved effective for the primary outcome: initiation of osteoporosis management was enhanced by 45% (95% confidence interval [CI], 9%–93%) in the intervention group compared with the control group.[12]

While initiation of testing and treatment are the necessary first steps for osteoporosis management, we pursued the present analyses to determine whether this intervention also enhanced adherence with medications used for osteoporosis. We examined 2 aspects of adherence, compliance and persistence. These analyses are post hoc and should be considered in light of all the known limitations of such analyses.[13]

We ascertained baseline patient and physician characteristics during the period from July 1, 2002, through August 31, 2004. The intervention occurred during a 3-month interval between

September 1, 2004, and December 1, 2004. Adherence was assessed by prescription filling data from September 1, 2004, through June 24, 2005. All aspects of the study were approved by the Partners Healthcare Institutional Review Board.

Study Population

Eligible participants for the parent trial were insured by HBCBSNJ and were at risk for osteoporosis. At-risk status was defined as the following: (1) women 65 years or older, (2) men or women 45 years or older with a prior fragility fracture (including hip, wrist, humerus, or spine), or (3) men or women 45 years or older who took oral glucocorticoids for at least 90 days during the baseline period.

All subjects who filled at least 1 prescription during the baseline or follow-up period for a medication used for osteoporosis were included. Osteoporosis medications were alendronate sodium, calcitonin, estrogen, raloxifene hydrochloride, risedronate sodium, and teriparatide (there was no use of ibandronate sodium in the study population). Estrogen therapy was included, although we cannot determine the indication for use in the study database. Subjects were further classified into the following 3 groups: new users of osteoporosis medications during the intervention period, current users at the time the intervention started, and past users based on prescription filling during the baseline period. New users had never filled a prescription for an osteoporosis medication during the baseline period. Current users filled at least 1 prescription for an osteoporosis medication during the baseline period and filled at least 1 prescription in the 90 days before the start of the study period. Ninety days represents the longest prescription duration allowed. This definition intended to capture those patients who were filling prescriptions for osteoporosis medications on a somewhat regular basis immediately before the intervention. Past users filled at least 1 prescription for an osteoporosis medication during the baseline period but did not fill in the 90 days before the start of the study period. We assumed that these patients used osteoporosis medications in the past but stopped before the intervention.

Intervention

The intervention consisted of education about osteoporosis diagnosis and appropriate treatment. This information was delivered to physicians in a single one-on-one educational encounter during a 3-month intervention period. Physician education was accomplished with a visit from a pharmacist-educator. These pharmacists had participated in a 1-day training session and several follow-up teleconferences about osteoporosis and the principles of one-on-one physician education ("academic detailing").[14–16] They learned specific teaching techniques and included the continuing medical education curriculum during their visits with the physicians. At the visits, they provided the physicians with the following educational material: a list of the physician's patients who were deemed at risk for osteoporosis; written summaries of osteoporosis epidemiology, diagnosis, and treatment; an algorithm for diagnosis and treatment of osteoporosis that was laminated as a card to fit in a coat pocket; a guide to osteoporosis pharmacotherapy; "tear sheets" resembling prescription pads with check boxes for fall prevention, calcium and vitamin D use, bone mineral density testing, and treatment; and patient pamphlets on fall prevention (available from the author on request). Finally, the study paid for physicians to apply for continuing medical education credit on completion of a postvisit test.

In addition to the physician-directed education, patients in the intervention group received an introductory letter outlining the importance of osteoporosis, its diagnosis, and appropriate treatment. This letter was followed by an automated telephone call inviting them to undergo bone mineral density testing. This call used interactive voice response technology that has been used for other screening tests but which was ineffective in that trial.[17]

Outcomes

This study measured medication compliance as the primary end point and persistence as a secondary end point. Compliance was expressed as the medication possession ratio (MPR), defined as number of days for which medication is available divided by number of days in the follow-up period.[18–21] A patient who consistently fills prescriptions and has medication available for each day is 100% adherent. For new and past users (who did not have osteoporosis medications available in the 90 days before the intervention), the follow-up period started on the date of the first filled prescription for an osteoporosis medication on or after September 1, 2004 (the first day of the study period). For current users, the follow-up period started on September 1, 2004, with "rollover" of available osteoporosis medications from previously filled prescriptions. The end of follow-up occurred at the first of the following: death, loss of HBCBSNJ eligibility, or the end of the study period.

As a secondary end point, we examined persistence. Persistence measures complement the MPR in that they provide insight into a patient's medication use over time.[7,21] Persistence was expressed as days until discontinuation, where discontinuation was defined as at least 30 days without any medication available. Prior analyses found that 30 days without any medication available strongly correlated with permanent discontinuation.[3] For new, current, and past users, the follow-up period started on the date of the first filled prescription for osteoporosis medications on or after September 1, 2004. As already defined, the end of follow-up occurred at the first of the following: death, loss of HBCBSNJ eligibility, or the end of the study period.

Two different patients could have the same MPR but different persistence values. For example, a patient who has medication available for the first 150 days of a 300-day study period has an MPR of 50%. Likewise, a patient who takes osteoporosis medications every other day for all 300 days also has an MPR of 50%. The first patient was persistent for 150 days, whereas the second patient was persistent for 300 days.

Data Source

We used insurance claims as our source of outcomes and baseline patient data. Patient baseline data included demographics, comorbidities associated with increased risk of osteoporosis and fractures, health-seeking behaviors such as immunizations and cancer screening, and types of preintervention osteoporosis medications. We also collected data regarding filling of prescriptions for osteoporosis medications, including types of medication, dates filled, and amount of medication dispensed. This source of data does not contain indications for medication use; thus, some of the estrogen therapy was likely used for nonosteoporosis indications.

Statistical Analysis

We compared the characteristics of patients randomized to intervention versus control groups. The outcome analyses considered new users of osteoporosis medications separately from current or past users. All analyses used an intent-to-treat approach, including physicians and patients in whom the educational interventions were not successfully completed. The median MPR and days until discontinuation were calculated and compared for intervention and control groups. We modeled MPRs using Poisson distribution regression analysis adjusting for the correlation with generalized estimating equations. Time until discontinuation or persistence was modeled with Cox proportional hazards regression analysis using sandwich estimators to adjust for the clustering within physician practice. For both adjusted models, we included all variables using the inverse probability treatment weighting method.[22] Analyses were performed using SAS version 8.02 (SAS Institute, Cary, NC).

RESULTS

A total of 1867 patients and 436 PCPs were randomized and included in this study. There were 126 new osteoporosis medication users, 1157 current users, and 584 past users. Demographic characteristics, medical history, risk factors for osteoporosis, and health behavior were not notably different between the intervention and control groups (Table 1). Most patients were between 65 and 74 years old, and almost all were female. Few patients had documented osteoporosis by diagnosis codes during the baseline period, and approximately 1 in 10 had sustained a fracture. Baseline osteoporosis treatments included all of the major categories, with bisphosphonates predominating (Table 2).

Across all patients studied, new and prevalent users, the median MPRs were 74% (interquartile range [IQR], 19%–93%) for the intervention group and 73% (IQR, 0%–93%) for the control group (P =.18). The median times until first refill after the intervention were 57 days (IQR, 22–298 days) for the intervention group and 61 days (IQR, 23–298 days) for the control group (P =.11).

Among new users, the unadjusted median MPR was 88.6% for the intervention group compared with 76.4% for the control group (P = .28) (Table 3). After adjusting for baseline characteristics listed in Table 1, there was no difference in MPRs (relative risk [RR], 1.05; 95% CI, 0.89–1.23). Before adjustment, persistence (measured as the median days until discontinuation) was 85 days for the intervention group compared with 79 days for the control group (P = .16) (Table 4). The intervention group exhibited a trend toward higher number of days until discontinuation; however, this increase was not statistically significant in the adjusted model (RR, 0.85; 95% CI, 0.48–1.49).

As with new users, the median MPR and median persistence were similar between current users in the intervention and control groups. The median MPRs were 87.6% for the intervention group and 88.8% for the control group (P = .60) (Table 3). The median persistence durations were 227 days for the intervention group and 229 days for the control group (P = .31) (Table 4). Among current users, only 0.84% in the intervention group and 0.53% in the control group did not fill any osteoporosis medication prescriptions during the study period. Adjusted analyses showed no difference in the MPR or persistence.

Past users in both groups did not frequently begin to fill prescriptions for osteoporosis medications again during the study follow-up. The median MPR for the intervention group was 0.0 (IQR, 0.0–36.0), while the median for the control group was also 0.0 but with a much narrower IQR of 0.0 to 10.4 (Table 3). The adjusted analysis showed an increase in the MPR for the intervention group (RR, 1.35; 95% CI, 1.00–1.81). The median times until medication discontinuation (for those who filled ≥1 prescription) were 130 days for the intervention group and 104 days for the control group (P = .21). The adjusted analysis suggested a trend toward a reduced risk of discontinuation among the intervention group (RR, 0.81; 95% CI, 0.56–1.18). Among past users, 62.7% of the intervention group and 73.7% of the control group never filled osteoporosis medication prescriptions during the study period.

DISCUSSION

A randomized brief educational intervention targeting initiation of testing and treatment for osteoporosis did not improve compliance or persistence with osteoporosis medications over a 10-month follow-up period. There was a suggestion for some improvement among patients who had used osteoporosis medications in the past, but there was no demonstrable improvement among current or new users of these medications. The intervention was successful at improving the frequency of initiating of bone mineral density testing and osteoporosis medication prescription.[12] Our ability to observe a difference in compliance or persistence may have been

affected by our 10-month follow-up and a high rate of baseline adherence in the control group. In general, an MPR of 80% or higher is regarded as adequate. Furthermore, results of some studies[1,23,24] suggest that an MPR of 80% or higher is associated with reduced rates of fracture.

The analyses we present are secondary analyses of a trial designed to improve initiation of osteoporosis management. We pursued these post hoc analyses because the intervention produced a positive effect on initiation of medication use, suggesting that there might have been benefits to adherence. However, the intervention (focused more on PCPs than on patients) did not produce substantial gains in medication adherence. This implies that medication adherence is a specific behavior that likely requires potent interventions designed specifically for adherence.

Several limitations of this intervention need mention. Our source of data for this study was a large healthcare utilization database that does not contain information on the reasons for prescribing a given medication. Some of the estrogen therapy users were likely using this treatment for other indications. We followed up patients for 10 months to determine their compliance. This limits our ability to detect clinical outcomes such as fractures. The compliance level of the control arm was high, limiting our ability to detect an incremental effect due to the intervention. Finally, our intervention was brief; a more sustained intervention might have been more effective at enhancing adherence.

Strengths of this study include its randomized nature and the use of a typical community population versus a clinical trial population, where volunteers may be different from usual patients. Much of the literature on medication adherence is based on observational findings[3] rather than randomized findings and suggests that adherent patients have improved outcomes such as reduced fractures.[1,23,24] It is critical to recognize that adherence is not a random behavior; adherent patients may have improved outcomes for many reasons, only one of them being consuming more osteoporosis medication. In fact, randomized trials in other areas have found that adherent patients receiving placebo often fare better than non-adherent patients in the intervention arm.[25]

Our negative results, using a brief intervention focused on physicians, suggest that adherence interventions for osteoporosis might be more effective when focused on patients. A recent successful intervention for other chronic medications targeted patients with education and the use of medication blister packs.[26] Prior interventions to improve osteoporosis medication adherence have examined the effects of simpler regimens, patient monitoring, and education. Several studies[18,19,26] demonstrate that oral bisphosphonates dosed weekly versus daily may improve adherence. An observational study[18] of 2741 postmenopausal American women starting bisphosphonate therapy showed a significantly higher mean MPR for weekly dosing (69.2%) compared with 57.6% for daily dosing. Over 365 days, the median persistence was significantly increased for weekly dosing versus daily dosing (269 vs 134 days). Another observational study[26] involving 2124 post-menopausal Dutch women starting bisphosphonate therapy also demonstrated better persistence at the end of 1 year for weekly versus daily dosing. Despite these encouraging results, all study authors pointed out that, even for the patients taking bisphosphonates dosed weekly, adherence and persistence were suboptimal. Although it is possible that a less frequently dosed bisphosphonate might further improve adherence,[9] the literature suggests that enhancing medication adherence is much more complicated than implementing less frequent dosing.[4–7]

Clowes and colleagues[10] conducted a randomized controlled trial using a monitoring intervention. In that study, 75 postmenopausal women with osteopenia were newly prescribed raloxifene and assigned to nurse monitoring or usual care (no monitoring). Those patients who were randomized to the monitoring group attended 3 appointments (spaced 12 weeks apart)

with nursing staff, during which they were asked 6 questions related to well-being, problems with medication, and adverse events. No information about osteoporosis per se was offered, unless patients happened to ask about it. Monitored patients demonstrated a statistically significant increase in rates of adherence: 65% were adherent (defined as taking >75% of prescribed raloxifene tablets) at 1 year compared with 42% in the nonmonitored group. These study findings suggest that a patient-directed program of ongoing intensive counseling improves adherence.

The intervention by Clowes et al[10] suggests that patient education is an important strategy for improving adherence. Additional studies[5,27] of patients with chronic diseases such as rheumatoid arthritis and asthma show that face-to-face counseling from healthcare providers can improve adherence. Other than our study, there are few studies investigating the effect of education on adherence with osteoporosis medications. Cuddihy and colleagues[11] describe a prospective non-randomized population-based study involving women with osteoporosis having recent distal forearm fractures. Soon after the fracture, patients were provided educational pamphlets, a PCP appointment, and a bone mineral density testing appointment. For 38 women advised to begin therapy for osteoporosis, the intervention improved self-reported medication adherence at 6 months (36% were adherent compared with 9% in a historical cohort). Nielsen and colleagues[28] describe preliminary results from a prospective randomized study of 280 patients with osteoporosis undergoing an educational intervention consisting of “school” comprising 16 days of classes over 4 weeks. Self-reported persistence with pharmacotherapy was higher in the school group compared with the control group. However, the high persistence rates (93%–99%) for the 61 patients who reached 24 months of follow-up suggest that this extraordinarily motivated study population may not be representative of the wider community.

The brief intervention we tested that targeted PCPs to improve their initiation of management of osteoporosis did not enhance medication adherence, primarily a patient behavior. We have since conducted several focus groups with patients that suggest the following: it is critical to convince patients of the importance of treating a largely asymptomatic condition at the outset of treatment; most patients would rather not take medications chronically, and thus any adverse experience or concern is often enough to interfere with adherence; and persistent use of treatments requires reminder systems that are often idiosyncratic to a given patient. These observations and recent review articles [29,30] have helped us to design new adherence interventions for osteoporosis that we anticipate will be more effective than what we describe herein. We will not realize the full potential of our new treatments for osteoporosis without better adherence.

Take-Away Points

Medication adherence for osteoporosis is poor, and there are few proven effective interventions.

- In a post hoc analysis of a randomized controlled trial of brief education, medication adherence was no better in the intervention group compared with the control group.
- Interventions focused on initiation of chronic disease management may not enhance medication adherence.
- Adherence interventions should focus on patients, not physicians.

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Table 1

Baseline Patient Characteristics[a]

	New Users		Current Users		Past Users	
Characteristic	**Intervention (n = 80)**	**Control (n = 46)**	**Intervention (n = 593)**	**Control (n = 564)**	**Intervention (n = 299)**	**Control (n = 285)**
Demographics						
Age, y, %						
45–54	5.0	0.0	4.2	4.1	5.4	5.3
55–64	7.5	6.5	4.9	4.3	9.0	7.7
65–74	68.8	70.0	75.7	72.0	71.6	73.7
75–84	17.5	23.9	14.3	18.3	14.1	12.6
≥85	1.3	0.0	0.8	1.4	0.0	0.7
Female sex, %	96.3	97.8	98.0	99.1	98.0	97.9
No. of comorbid conditions, mean	1.6	1.8	1.2	1.1	1.3	1.5
No. of medications	13.4	15.2	14.7	15.6	15.5	17.4
Diagnosed osteoporosis, %	3.8	13.0	15.7	11.4	9.0	7.0
Depression, %	2.5	0	4.4	4.1	3.7	4.2
Follow-up period, mean, d	152.5	156.2	291.0	292.0	289.0	290.4
Osteoporosis Related, %						
Fracture	8.8	6.5	8.6	9.6	9.4	11.2
Glucocorticoid use	31.3	37.0	24.6	21.5	27.4	27.2
Bone mineral density test	26.3	26.1	64.1	63.1	54.5	49.1
Hyperthyroidism	0.0	0.0	1.5	0.4	0.0	0.4
Hyperparathyroidism	0.0	2.2	0.2	0.5	0.7	0.4
Crohn disease or ulcerative colitis	2.5	2.2	1.2	1.8	1.0	0.7
Anorexia nervosa	0.0	0.0	0.0	0.0	0.0	0.0
Alcoholism and alcohol dependence	0.0	0.0	0.0	0.4	0.0	0.4
Health-Seeking Behaviors						
No. of physician visits, mean	20.0	21.8	17.9	18.3	17.8	19.4
No. of hospitalizations, mean	0.5	0.6	0.3	0.3	0.5	0.6
Influenza vaccination, %	41.3	26.1	38.5	39.0	42.1	45.3

Characteristic	New Users		Current Users		Past Users	
	Intervention (n = 80)	Control (n = 46)	Intervention (n = 593)	Control (n = 564)	Intervention (n = 299)	Control (n = 285)
Pneumonia vaccination, %	15.0	8.7	10.6	10.3	12.4	9.5
Mammogram, %	61.3	58.7	71.0	74.3	70.2	68.4
Pap smear, %	8.8	8.7	8.4	8.7	8.7	8.4
Prostate-specific antigen test, %	1.3	0.0	0.5	0.7	0.0	0.7
Cholesterol panel, %	0.0	0.0	1.5	1.8	1.7	1.8
Colonoscopy, %	21.3	23.9	26.3	28.0	21.7	26.3

Due to rounding, percentanges do not add up to 100.

[a]Patient characteristics were calculated based on data from the 2 years before the intervention (September 1, 2002, through September 1, 2004).

Table 2

Baseline Osteoporosis Therapy[a]

	Current Users		Past Users	
Variable	**Intervention**	**Control**	**Intervention**	**Control**
Osteoporosis medication started, %				
Alendronate sodium	53.6	59.6	33.1	36.5
Calcitonin	12.7	11.5	9.7	8.4
Estrogen preparations	18.2	18.3	37.5	38.6
Raloxifene hydrochloride	21.9	18.6	15.1	11.9
Risedronate sodium	23.1	22.7	19.4	18.3
Teriparatide	0.0	0.7	0.0	0.7
No. of osteoporosis prescriptions filled, mean	11.1	11.5	4.7	4.8

[a]New users are not included because by definition they had no use of osteoporosis therapy during the baseline period.

Table 3

Medication Possession Ratio[a]

Variable	No. of Patients	Medication Possession Ratio		
		Median (IQR)	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
New users				
Intervention	80	88.6 (70.1–100)	1.09 (0.93–1.28)	1.05 (0.89–1.23)
Control	46	76.4 (58.4–100)	1 [Reference]	1 [Reference]
Current users				
Intervention	593	87.6 (68.5–96.0)	1.01 (0.97–1.05)	1.01 (0.98–1.05)
Control	564	88.8 (68.1–96.0)	1 [Reference]	1 [Reference]
Past users				
Intervention	299	0.0 (0.0–36.0)	1.40 (1.05–1.88)	1.35 (1.00–1.81)
Control	285	0.0 (0.0–10.4)	1 [Reference]	1 [Reference]

CI indicates confidence interval; IQR, interquartile range.

[a]The relative risks compare intervention with control patients and were calculated in models that accounted for the clustering of patients within a physician's practice. The adjusted relative risk was calculated in models that included all of the covariates listed in Table 1.

Table 4

Relative Risk of Persistence (Days Until Discontinuing Medication)[a]

		Days Until Discontinuation		
Variable	**No. of Patients**	**Median (IQR)**	**Unadjusted Relative Risk (95% CI)**	**Adjusted Relative Risk (95% CI)**
New users				
Intervention	80	85 (58–174)	0.68 (0.39–1.17)	0.85 (0.48–1.49)
Control	46	79 (31–158)	1 [Reference]	1 [Reference]
Current users				
Intervention	593	227 (91–269)	1.10 (0.91–1.34)	1.10 (0.91–1.34)
Control	564	229 (121–225)	1 [Reference]	1 [Reference]
Past users				
Intervention	299	130 (85–225)	0.79 (0.54–1.15)	0.81 (0.56–1.18)
Control	285	104 (79–200)	1 [Reference]	1 [Reference]

CI indicates confidence interval; IQR, interquartile range.

[a]The relative risks were calculated in Cox proportional hazards models. The adjusted models include all the covariates listed in Table 1.