

# Impact of an Antidepressant Management Program on Medication Adherence

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**Objective:** To evaluate the impact of mail-based physician and member educational interventions on patient adherence to antidepressant medications.

**Study Design:** The randomized controlled prospective design included patients followed for 6 months after filling a new prescription for an antidepressant. A pharmacy claims database was used to identify patients and track medication adherence.

**Patients and Methods:** Patients receiving a new prescription for an antidepressant and their prescribers were included. Prescribers were randomly assigned to the intervention and control groups. Patient assignment was linked to their physician's assignment. The control group received no intervention. The educational intervention consisted of monthly letters to patients and prescribers regarding the Health Plan Employer Data and Information Set (HEDIS) standards or educational information regarding the importance of medication adherence. The primary outcome was adherence as measured by the medication possession ratio and measurement as specified by HEDIS. The Student's *t* test, the  $\chi^2$  test, and a logistic regression model were used to compare groups and the variables that affect adherence. Other secondary measurements of adherence were performed.

**Results:** A total of 9564 patients were included. Patients in the intervention group demonstrated greater adherence compared with the control group at 90 and 180 days ( $P < .05$ ). After adjusting for variables, the intervention variable stood alone in its significant impact on adherence ( $P < .01$ ; confidence interval, 1.003-1.197). Adherence in the total population was significantly higher for selective serotonin reuptake inhibitors than for other agents ( $P < .001$ ).

**Conclusion:** A monthly mail-based educational intervention program regarding antidepressant medications can positively influence patient adherence to therapy.

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Depressive disorders have a high prevalence in the general population and are associated with significant morbidity. One in 8 persons may require treatment for depression during their

lifetime.<sup>1</sup> The Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality) Executive Summary on Depression in Primary Care reports that the point prevalence of major depressive disorder ranges from 4.8% to 8.6%.<sup>1</sup> Persons diagnosed as having depression are known to use more healthcare services than those without this diagnosis. One study<sup>2</sup> found that the mean annual healthcare cost per patient with depression was nearly double that for patients without depression. Indirect costs can be high in this population as well owing to the potential adverse impact on job productivity, performance, and interpersonal relationships.<sup>3</sup> The Health Plan Employer Data and Information Set (HEDIS) Effectiveness of Care Standard for Antidepressant Medication Management contains 2 measures regarding the successful pharmacologic management of depression for patients diagnosed as having a new episode of depression and prescribed an antidepressant medication<sup>4</sup>:

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Eli Lilly Corporation, Indianapolis, Ind, provided a grant to offset postage costs for the educational interventions performed in this study and also supplied the patient education pads and treatment of depression Agency for Healthcare Research and Quality guidelines that were included in initial physician educational letters.

A portion of these data regarding the impact of the intervention on the measurement as specified by the Health Plan Employer Data and Information Set (HEDIS) was included in a 20-minute presentation as part of an Exhibitors Theater continuing education meeting at the American Society of Health-System Pharmacists clinical midyear meeting, New Orleans, LA, December 2-6, 2001. In addition, a subset of the HEDIS portion of the data was shared in a 10-minute presentation to the Blue Cross Association, Chicago, IL, October 23, 2001.

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- The percentage of eligible members who continued taking an antidepressant drug during the entire 84-day (12-week) acute treatment phase
- The percentage of those who continued taking an antidepressant drug for at least 180 days (6 months) (continuation phase)

Considering the substantial economic burden associated with depression and the standards set by regulating agencies, quality improvement programs are increasingly being used by managed care organizations to target management and recognition of the disease.

The mainstay of depression management is drug therapy. Pharmacotherapy of depression is often considered in 3 phases: acute, continuation, and maintenance. The goal of acute therapy is to treat the signs and symptoms of a current episode and restore functioning. It is recommended that acute therapy be continued at therapeutic dosage levels for 4 to 9 months after diagnosis of depression to prevent relapse (worsening of symptoms after improvement or return of initial symptoms).<sup>1</sup> A vital factor in the prevention of relapse is patient adherence to antidepressant drug therapy.<sup>5,6</sup> Despite the importance of medication adherence in the management of depression, adherence rates for antidepressant therapy are poor. One study<sup>7</sup> found that only 25% of patients remain adherent to therapy in the initial 30 days. Other studies<sup>6</sup> have suggested that approximately 40% to 70% of patients adhere to their antidepressant drug regimen during the acute phase of therapy, whereas only 15% to 50% comply with therapy during the continuation phase.

Programs geared toward improving patient adherence to medication therapy have had variable success.<sup>8</sup> Antidepressant drug adherence has been demonstrated to improve with patient counseling, but informational leaflets had no effect on adherence.<sup>9</sup> One study<sup>10</sup> evaluated the impact of an educational intervention on antidepressant medication adherence in a group-model HMO of 350 000 members. The study included 155 patients aged  $\geq 18$  years who were newly prescribed an antidepressant medication. Patients were interviewed monthly by telephone to assess medication adherence and the process of patient education regarding their medical condition and medication. The results indicated that the best adherence to medication occurred in patients who were provided educational messages concerning their medication and discussions of behavioral strategies from their physicians. Discontinuation rates were 25% in the first 3 months of therapy and 44% after 3 months. The specific educational compo-

nents proven to improve medication adherence were (1) asking patients about previous antidepressant drug use; (2) telling patients it would take 2 to 4 weeks before a noticeable effect would be seen; (3) telling patients to continue therapy even if they are feeling better; (4) telling patients to check with their physician before stopping medication use; (5) telling patients to take medication daily as prescribed; and (6) reminding patients to call the office if they have any questions.<sup>10</sup>

Measurement of medication adherence has been reported using various methods. Use of prescription claims data as a source for measurement of adherence has been described as a fairly reliable source of information regarding patient adherence to chronic medication regimens. The HEDIS standards for antidepressant medication management define adherence as a total of 30 gap days during the initial 84-day period and 51 gap days during the 180-day continuation phase. A recent evaluation of medication adherence measurement techniques using prescription claims data suggested examination of all measures (length of therapy, persistence, days of coverage, gaps, and medication possession ratio [MPR]) in assessment of a medication adherence program.<sup>11</sup>

Many types of managed care organizations, such as independent practice association (IPA)- and network-model HMOs, are in a challenging position to improve patient adherence to antidepressant therapy because of their limited role in direct patient care. Although IPA- or network-model HMOs have implemented a variety of educational programs intended to influence patient and provider behaviors, no published studies exist, to our knowledge, that describe the effectiveness of their attempts to influence antidepressant drug therapy adherence through mail interventions. The primary objective of this study was to evaluate the impact of monthly mail-based physician and member educational interventions on patient adherence to antidepressant medication.

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DESIGN

A randomized controlled prospective study was conducted of patients who were newly prescribed an antidepressant drug. The study was implemented from a large IPA-model HMO covering approximately 900 000 individuals in Florida. Pharmacy database claims were used to identify newly prescribed antidepressant therapies and subsequent patient and physician enrollment for targeted interventions.

Patients identified as nonadherent in the initial month of the study were followed for 6 months and were included in this analysis.

### **Patient Enrollment**

Inclusion criteria consisted of patients aged  $\geq 18$  years who were newly prescribed antidepressant drug therapy. Newly prescribed was defined as a prescription claim for an antidepressant medication within the most recent 30 days, with no record of claims for an antidepressant for the 6 months previous to that time. All members of commercial and Medicare lines of business were included (except for 2 employer groups because of contractual agreements), representing a population of 900 000 members. Patients were excluded if they were prescribed combination antidepressant and anxiolytic-type medications, such as chlorthalidone/amitriptyline and amitriptyline/perphenazine, because of the lack of a well-defined indication for major depressive disorder. Patients taking clomipramine or fluvoxamine were excluded because of use predominantly for obsessive-compulsive disorder. Patients were also excluded if they received one of the following concomitant medications within 120 days before the antidepressant prescription: valproic acid, carbamazepine, lithium, or lamotrigine. Such patients were excluded because these medications were suggestive of bipolar disorder, a diagnosis excluded from HEDIS 2000 specifications. Patients were required to have continuous enrollment during the pretreatment period (6 months before) and for at least 12 months after the initial prescription identification.

### **Prescriber Enrollment and Assignment**

All prescribers of antidepressants for 1 or more eligible patients in the previous 6 months were identified for initial recruitment. A random selection of ZIP codes for physician practices was performed to assign prescribers and their eligible patients to either the intervention or the control group. Randomization by physician ZIP codes was used to eliminate bias introduced from physician group practices and specialty physicians collaborating with a primary care physician. Physician office ZIP codes were listed in numerical order, and every other ZIP code was designated as a control group ZIP code. Physician ZIP codes were used instead of member ZIP codes to prevent discrepancies in physicians receiving an intervention letter for select patients (intervention patients) and not for others (control patients). Patients and physicians assigned to the control group received no interventions during the

study duration. Patient assignment to either the intervention or the control group was linked to their physician's group assignment.

### **Interventions**

*Initial Program Description.* All prescribers assigned to the intervention group received an intervention launch letter that included an outline description of the program along with regional HEDIS rates for that physician practice area, an Agency for Healthcare Research and Quality guidelines schematic, a patient information pad, and copies of patient letters. On initial identification, intervention patients also received a launch letter with a brief description of the program and an outline of the 5 key educational points illustrated in the study by Lin et al<sup>10</sup> to improve medication adherence.

*Physician Intervention Letter.* After the initial launch letter, 20 to 25 days after the end of each month, prescribers for patients in the intervention group were mailed a list of patients taking antidepressant drugs who were identified as nonadherent, as defined by HEDIS specifications (see the "Outcome Measures" section for specification of study measures). The intervention letter explained that a claims evaluation had identified patients who seemed to have missed  $>10$  days of antidepressant therapy according to prescription refill records. The letter also contained the list of identified nonadherent patients each month. The first intervention letter identified patients in the most recent 90-day period who seemed potentially nonadherent. Subsequent monthly letters identified potentially nonadherent patients in the most recent 30 days.

*Patient Intervention Letter.* Twenty to 25 days after the end of each month, patients identified as nonadherent who were assigned to the intervention group received an intervention letter reminding them of the importance of adhering to their medication regimen. The letters were personalized in that they contained the patient's name and address and the medication identified in the evaluation. The outside envelopes and letters were marked clearly as personal and confidential. The letters contained general information regarding the importance of adhering to any medication regimen prescribed by a physician. Important points regarding contact with a healthcare professional if adverse events occurred were noted. The letter also contained a bulleted list of the following 5 reminders regarding medication compliance: (1) it may take 2 to 4 weeks before a noticeable effect is seen; (2) continue therapy even

if feeling better; (3) check with the physician before stopping medication use; (4) take medication daily as prescribed; and (5) maintain regular visits with their healthcare professional and call their physician if they have any questions. Patients were identified as nonadherent by a retrospective evaluation of prescription claims in the previous 30 days. Patients who were defined as nonadherent and who seemed to have missed 114 days of continuous therapy were not sent further patient mailings. A threshold of 114 days was chosen in accordance with HEDIS specifications for antidepressant therapy. Patients who received the intervention also had the option of being removed from the mailing list by indicating this on the letter. Only patients who disenrolled from the health plan during the evaluation were excluded from the analysis; patients asking to be removed from mailings were not removed from the analysis.

### Outcome Measures

The primary outcome measure used in this evaluation was medication adherence. During baseline and first observation, adherence was defined as <10 gap days in a 30-day period. Gap days were measured by the number of open days between the assumed depletion date calculated from the days supply of the prescription and the fill date of the next refill.

Adherence during the second and third observations was measured using the MPR and the HEDIS definition of adherence at 1 to 84 and 1 to 180 days (as described by the HEDIS standards). Adherence was also evaluated in the intervention and control groups using the measures of days of coverage, median gap, and persistence.

The MPR was measured by calculating the sum of the days supply for all claims during the defined period divided by the number of days elapsed for the same period. Adherence was defined as <10 gap days per 30-day period. The HEDIS measure at 1 to 84 and 1 to 180 days was measured by summing the number of treatment days for a maximum of 114 days (second observation) or 231 (third observation) as defined by the HEDIS specifications; patients whose gap days exceeded 30 or 51, respectively, were counted as nonadherent.

Days of coverage were calculated using the total days supply of the medication for the 6 months as evidenced from the pharmacy claims. Median gap was measured by calculating the gap days measured (as described earlier) for the specific period (90 or 180 days) for each patient and then calculating the

median for the group. Persistence was defined as the time span a patient continued taking the antidepressant prescription during the study. If the date of the last prescription filled plus the days supply was  $\leq 10$  days from the end of the study, the patient was considered to be persistent.

Adherence was evaluated according to drug category (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], and atypical antidepressants) and product line (commercial vs Medicare patients). At the end of the 6-month study duration, medical claims data were reviewed retrospectively to identify patients who may have a medical claim on file for an *International Classification of Diseases, Ninth Revision, Clinical Modification* code of 296.2 to 296.9, 298.0, 300.4, 309.0, 309.1, 309.28, or 311, indicating a diagnosis of depression. All medical claims on file were reviewed for the period of the evaluation (3 months before study commencement and 6 months of the study duration). Claims for bipolar disorder and psychotic disorders were not included. No other diagnostic codes were evaluated. Subsequent adherence measures were also conducted for this subgroup of patients with depression.

### Statistical Analysis

All data were analyzed using statistical software (SAS 8.1 for Windows NT; SAS Institute Inc, Cary, NC). Univariate analysis was used to describe and examine the distribution and variability in study measures. Characteristics of the intervention and control groups at 3 time points were compared using *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. The 3 time points were the first observation (1 month after enrollment into the study), the second observation (84- or 90-day adherence measure), and the third observation (180-day adherence measure). A 1-way analysis of variance test was used to compare the differences among the 3 drug classes (SSRIs, TCAs, and atypical agents) in the entire study population. A multivariate logistic regression analysis was conducted to estimate the associations of adherence at the last 2 measurement periods and intervention, while adjusting for age, sex, line of business, type of therapy, and diagnosis in addition to 2-level interactions among them. Residual score statistics and the Hosmer and Lemeshow goodness-of-fit test (value of 13.626;  $P = .092$ ) were used to check the model's adequacy. All statistical significance was evaluated with .05-level 2-sided tests when appropriate.

**Table 1.** Descriptive Statistics for 9564 Study Patients

Variable	Patients, No. (%)
Sex	
Female	6502 (67.98)
Male	3062 (32.02)
Line of business	
Commercial	7003 (73.22)
Medicare	2561 (26.78)
Type of antidepressant drug	
Selective serotonin reuptake inhibitors	5426 (56.73)
Tricyclic antidepressants	1709 (17.87)
Atypical agents	2429 (25.40)
Diagnosis	
Depression	1982 (20.72)
Unknown (no depression claims)	7582 (79.28)
Study group	
Intervention	4899 (51.22)
Control	4665 (48.78)
Adherence	
HEDIS—84 d	5561 (58.15)
HEDIS—180 d	2916 (30.49)

HEDIS indicates Health Plan Employer Data and Information Set.

RESULTS

**Participants**

A total of 9564 patients and 7021 physicians were included in the cohort. The intention-to-treat analysis included the intervention arm (4899 patients and 3474 physicians) and the control group (4665 patients and 3547 physicians). Patient characteristics are given in **Table 1**. The group as a whole was predominantly female (67.98%) and was in the commercial line of business (73.22%). Most patients were being treated with an SSRI. Although medical claims were unavailable until 4 months into the evaluation, in retrospect, 20.72% of patients had a diagnosis of depression on file; there was no behavioral health diagnosis available for the remaining patients at the time of study analysis. Adherence, as measured by the HEDIS specifications, for all study participants was 58.15% at the second observation and 30.49% at the third observation. The sociodemographic characteristics were similar between the 2 study groups (**Table 2**).

**Overall Adherence Measures**

Adherence was measured during the first month of therapy (first observation) and 3 months (second observation) and 6 months (third observation) after program initiation. Overall, adherence rates were similar between the 2 groups at the first observation (58.9% for intervention patients and 57.4% for controls) (**Table 3**). However, a larger percentage of the control group was adherent to SSRI therapy, and intervention patients were more adherent to TCA therapy than were controls ( $P < .05$  for both). At subsequent observations, greater differences were seen when comparing the study groups.

**Adherence Measured Using the MPR**

Results of the MPR measure demonstrated a significantly higher adherence rate for intervention patients at the second observation (66.9% vs

**Table 2.** Baseline Sociodemographic Characteristics of 9564 Patients

Characteristic	Intervention Group (n = 4899)	Control Group (n = 4665)	P
Age, mean ± SD, y	51.9 ± 16.7	51.2 ± 16.5	.056, $\chi^2$ , <i>df</i> = 1
Sex, male/female, %	32.1/67.9	32.4/67.6	.768, $\chi^2$ , <i>df</i> = 1
Drug category, %			
SSRIs	57.1	56.2	.381, $\chi^2$ , <i>df</i> = 1
TCAs	17.5	18.2	.367, $\chi^2$ , <i>df</i> = 1
Atypical agents	25.2	25.4	.839, $\chi^2$ , <i>df</i> = 1
Line of business, No. (%)			
Commercial	3556 (72.6)	3447 (73.9)	.150, $\chi^2$ , <i>df</i> = 1
Medicare	1343 (27.4)	1218 (26.1)	.150, $\chi^2$ , <i>df</i> = 1
Diagnosis of depression, No. (%)	1007 (20.6)	974 (20.9)	.695, $\chi^2$ , <i>df</i> = 1

NS indicates not significant; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

65.5%;  $P < .01$ ) (Table 4) and the third observation (52.3% vs 50.2%,  $P < .001$ ) (Table 5). Across lines of business, no significant differences were observed between the Medicare groups. However, intervention patients in the commercial line of business demonstrated significantly higher adherence rates at both observations than the control group. At the second observation, similar to the first observation, a significantly greater proportion of intervention patients complied with TCA use (62.2% vs 57.8%;  $P < .01$ ). No difference was found between the other drug categories in the first and second observations. At the third observation, however, adherence rates were significantly greater for intervention patients treated with SSRIs and TCAs. A comparison between the subgroups of patients with a definitive diagnosis of depression showed a slightly higher adherence rate in the intervention group; however, no significant differences were realized at either observation.

**Adherence Measured Using the HEDIS Specifications**

The HEDIS specifications included measures of adherence at 1 to 84 days, allowing for 30 gap days (second observation), and again at 1 to 180 days, allowing for 51 gap days (third observation). At the

**Table 3.** Adherence Rates: First Observation (Patients With <10 Gap Days in the Initial Month of Therapy)

Adherence Variable	Adherence Rate, % Intervention Group (n = 4899)	Control Group (n = 4665)	P
All patients	58.9	57.4	.136, $\chi^2$ , $df = 1$
By drug category			
SSRIs (n = 5427)	60.7	64.0	<.05, $\chi^2$ , $df = 1$
TCAs (n = 1709)	52.4	45.4	<.05, $\chi^2$ , $df = 1$
Atypical agents (n = 2428)	52.1	51.1	.608, $\chi^2$ , $df = 1$
By product line of business			
Commercial (n = 7003)	58.2	56.5	.151, $\chi^2$ , $df = 1$
Medicare (n = 2561)	60.9	59.7	.528, $\chi^2$ , $df = 1$
Depression diagnosis (n = 1981)	65.4	65.4	.985, $\chi^2$ , $df = 1$

NS indicates not significant; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants;  $df$ , degrees of freedom.

**Table 4.** Adherence Rates: Second Observation (90 Days)

	Medication Possession Ratio, %			HEDIS, %		
	Intervention Group (n = 4899)	Control Group (n = 4665)	P (2-Sample t Test)	Intervention Group (n = 4899)	Control Group (n = 4665)	P ( $\chi^2$ )
All patients	66.9	65.5	<.01, $df = 9562$	59.6	56.6	<.01, $df = 1$
Line of business						
Medicare	68.7	67.4	.24, $df = 2559$	61.9	58.7	.101, $df = 1$
Commercial	66.3	64.8	<.05, $df = 7001$	58.7	55.9	<.05, $df = 1$
Drug category						
SSRIs	70.3	69.7	.35, $df = 5425$	65.4	64.1	.324, $df = 1$
TCAs	62.2	57.8	<.01, $df = 1707$	51.0	42.2	<.001, $df = 1$
Atypical agents	62.7	62.0	.52, $df = 2426$	52.4	50.5	.356, $df = 1$
Depression diagnosis	71.3	70.2	.33, $df = 1979$	67.1	65.5	.525, $df = 1$

HEDIS indicates Health Plan Employer Data and Information Set; NS, not significant;  $df$ , degrees of freedom; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

**Table 5.** Adherence Rates: Third Observation (180 Days)

	Medication Possession Ratio, %			HEDIS, %		
	Intervention Group (n = 4899)	Control Group (n = 4665)	P (2-Sample t Test)	Intervention Group (n = 4899)	Control Group (n = 4665)	P ( $\chi^2$ )
All patients	52.3	50.2	<.001, <i>df</i> = 9562	31.5	29.4	<.05, <i>df</i> = 1
Line of business						
Medicare	53.7	52.3	.23, <i>df</i> = 2559	32.8	32.2	.725, <i>df</i> = 1
Commercial	51.8	49.5	<.001, <i>df</i> = 7001	31.0	28.4	<.05, <i>df</i> = 1
Drug category						
SSRIs	56.1	54.6	<.05, <i>df</i> = 5425	35.4	33.8	.215, <i>df</i> = 1
TCAs	46.2	42.8	<.05, <i>df</i> = 1707	25.4	23.2	.282, <i>df</i> = 1
Atypical agents	48.1	46.0	.072, <i>df</i> = 2426	26.9	24.2	.126, <i>df</i> = 1
Depression diagnosis	57.7	55.4	.06, <i>df</i> = 1979	36.8	34.7	.321, <i>df</i> = 1

HEDIS indicates Health Plan Employer Data and Information Set; NS, not significant; *df*, degrees of freedom; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

**Table 6.** Logistic Regression Examining Adherence as Measured Using the HEDIS Specifications While Adjusting for the Relevant Covariates: Second Observation

Parameter	Odds Ratio	95% Confidence Interval
Intervention group	1.123	1.034-1.220
Age	1.020	1.015-1.026
SSRI	3.675	2.709-4.987
Atypical agent	1.230	1.078-1.404
Medicare	2.558	1.392-4.700
Depression	2.087	1.730-2.516
Age x SSRI	0.991	0.985-0.996
Age x Medicare	0.985	0.976-0.994
SSRI x depression	0.673	0.540-0.840
Medicare x depression	0.643	0.506-0.817

HEDIS indicates Health Plan Employer Data and Information Set; SSRI, selective serotonin reuptake inhibitor.

second and third observations, the intervention group displayed greater adherence than the control group ( $P < .01$  and  $P < .05$ , respectively) (Tables 4 and 5). The improved adherence in the intervention group was significant at the second observation for

those prescribed TCAs (51.0% vs 42.2%;  $P < .0001$ ) and at both observations for the commercial line of business (58.7% vs 55.9%;  $P < .05$  and 31% vs 28.4%;  $P < .05$ ).

**Predictors of Adherence as Measured Using the HEDIS Specifications**

Logistic regression was performed to examine adherence as measured using the HEDIS specifications while adjusting for the relevant covariates of age, sex, type of diagnosis, and line of business (Tables 6 and 7). Using this model, interaction terms were analyzed. At the second and third observations, the analysis showed the existence of interactions among age, SSRI use, the Medicare line of business, and a diagnosis of depression. Once adjusted for all variables, only the intervention and use of atypical antidepressants were significantly related to adherence at the second observation (Table 6). At the third observation, the intervention and male sex were significantly related to adherence (Table 7).

**Adherence Measured Using Alternative Approaches**

In addition to evaluation of the impact of medication category on adherence rates measured by the MPR and the HEDIS specifications as described in the previous sections, measurement was performed by combining all patients in each medication cate-

gory to determine potential differences (Table 8). Adherence rates were significantly higher for individuals receiving SSRIs at all observations compared with those receiving TCAs and atypical agents. The difference varied between 7.6 and 18.2 percentage points higher for the SSRIs depending on the observation point and the measure used.

Changes in adherence were evaluated in patients with a confirmed diagnosis of depression compared with each group without a diagnosis of depression (Table 9). As expected, adherence rates decreased over time in patients with a confirmed diagnosis of depression. Using the measures of MPR and HEDIS, medication adherence was consistently higher in patients with a diagnosis of depression vs populations without a claim on file for depression.

Last, days of coverage, median gap, and persistency were examined to compare the intervention and control groups (Table 10). The intervention group continued to display improved medication therapy adherence compared with the control group using these measures. During the 180-day study, the intervention group averaged nearly 6 additional days of coverage compared with controls. Similarly, the median gap measure showed that the intervention group experienced significantly fewer gap days than the control group at both observations (27.8 vs 29.0;  $P < .01$  and 85.8 vs 89.6;  $P < .001$ ). At the second and third observations, persistency was higher in the intervention group than in the control group. The greatest reduction in adherence as measured by persistency occurred between months 2 and 3 of therapy (Table 11).

DISCUSSION

Evaluating adherence to antidepressant medication provided insight into the impact of a program that included monthly mail interventions to patients and physician providers in an IPA-model HMO setting. The study findings gener-

ally support the usefulness of mail-based monthly interventions to improve adherence to antidepressant medication therapy. Although the impact of the intervention was modest, it demonstrated that mail-based interventions can improve adherence rates. Several studies have been performed to evaluate interventions designed to positively impact medica-

**Table 7.** Logistic Regression Examining Adherence as Measured Using the HEDIS Specifications While Adjusting for the Relevant Covariates: Third Observation

Parameter	Odds Ratio	95% Confidence Interval
Intervention group	1.096	1.003-1.197
Male sex	0.904	0.821-0.994
Age	1.020	1.015-1.024
SSRI	1.884	1.674-2.122
Medicare	3.666	1.936-2.516
Depression	1.796	1.496-2.154
Age x Medicare	0.980	0.970-0.989
SSRI x Medicare	0.710	0.581-0.867
SSRI x depression	0.645	0.516-0.807

HEDIS indicates Health Plan Employer Data and Information Set; SSRI, selective serotonin reuptake inhibitor.

**Table 8.** Adherence Rates in All Patients by Medication Category

Observation and Measure	Adherence Rate, %			P
	SSRI Group (n = 5427)	TCA Group (n = 1709)	Atypical Agent Group (n = 2428)	
First				
Gap <10 d	63.9	48.9	51.6	<.001, ANOVA, <i>df</i> = 2, 9563
Second				
MPR	69.9	60	62.3	<.001, ANOVA, <i>df</i> = 2, 9563
HEDIS	64.8	46.6	51.4	<.001, $\chi^2$ , <i>df</i> = 2
Third				
MPR	55.4	44.5	47.0	<.001, ANOVA, <i>df</i> = 2, 9563
HEDIS	34.6	24.3	25.6	<.001, $\chi^2$ , <i>df</i> = 2

SSRI indicates selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; ANOVA, 1-way analysis of variance; *df*, degrees of freedom; MPR, medication possession ratio; HEDIS, Health Plan Employer Data and Information Set.

**Table 9.** Adherence Rate by Diagnosis

Observation and Measure	Intervention Group, %		P	Control Group, % P		P
	Without Depression (n=3892)	With Depression (n=1007)		Without Depression (n = 3691)	With Depression (n = 974)	
First						
Gap >10 d	57.2	65.4	<.001, 2-sample t test, df = 4897	55.2	65.4	<.001, 2-sample t test, df = 4663
Second						
MPR	65.8	71.3	<.0001, 2-sample t test, df = 4897	64.3	70.2	<.001, 2-sample t test, df = 4663
HEDIS	57.6%	67%	<.001, $\chi^2$ , df = 1	54.3	65.5	<.001, $\chi^2$ , df = 1
Third						
MPR	51.0	57.7	<.0001, 2-sample t test, df = 4897	48.9	55.4	<.0001, 2-sample t test, df = 4663
HEDIS	30.1	36.8	<.000, $\chi^2$ , df = 1	28	34.7	<.0001, $\chi^2$ , df = 1

df indicates degrees of freedom; MPR, medication possession ratio; HEDIS, Health Plan Employer Data and Information Set.

**Table 10.** Other Adherence Measures

	Intervention Group (n = 4899)	Control Group (n = 4665)	P
Days of coverage, mean $\pm$ SD, 1-180 d	126.1 $\pm$ 89.7	120.2 $\pm$ 90.8	<.01, 2-sample t test, df = 9562
Median gap days			
1-84 d	27.8	29.0	<.01, 2-sample t test, df = 9562
1-180 d	85.8	89.6	<.001, 2-sample t test, df = 9562
Persistency, mean $\pm$ SD, %			
1-90 d	36.8 $\pm$ 24.3	35.3 $\pm$ 12.4	.127, $\chi^2$ , df = 1
1-180 d	24.9 $\pm$ 51.9	23.3 $\pm$ 51.9	.067, $\chi^2$ , df = 1

df indicates degrees of freedom; NS, not significant.

tion adherence. Pa-tient education and behavioral discussion after diagnosis of depression was reported to improve medication adherence in a group health cooperative setting.<sup>10</sup> How-ever, other attempts to improve patient adherence with 1-time educational interventions of educational leaflets distributed in the physician office setting or drug- and disease-specific videotapes in an HMO setting have proven unsuccessful.<sup>8,9</sup> This study was performed in an IPA setting and is one of the first to find value in frequent (monthly) educational interventions to patients and physicians by mail.

Antidepressant drug adherence in the first month of therapy was 58.9% and 57.4% in the

intervention and control groups, respectively. These adherence rates are consistent with those in reports in the medical and pharmacy literature that discuss poor antidepressant drug adherence rates. In fact, most studies<sup>7,12-14</sup> have shown that <50% of outpatients who receive an initial prescription for an antidepressant drug continue their therapy after the first month. The percentage of patients who may have received a prescription from their provider but did not get it filled at the pharmacy was not measured in this evaluation.

The monthly mail intervention initiative was commenced in an effort to positively impact antidepres-

sant drug compliance and potentially improve the HEDIS rate measurements that address antidepressant medication management with respect to medication adherence.<sup>4</sup> The HEDIS allowance of a 10-day grace period within 1 month as a measure of medication adherence was one of the adherence measures used in this evaluation. Using this measure, the intervention group displayed higher medication adherence consistently compared with the control group. The difference was significant during the second and third observations. The implications of this evaluation on future measurement of the HEDIS standards at the health plan are unknown owing to the short duration of this intervention initiative.

Although, it has been suggested that medication adherence may be improved with newer antidepressant categories of drugs, some have found the drug class prescribed to have little effect on adherence management.<sup>15</sup> This study found that the intervention group displayed greater adherence compared with the control group in the SSRI and TCA categories as measured by the MPR (Table 5). All patients prescribed SSRIs displayed significantly greater therapy adherence compared with those taking the alternative agents. This difference has been referred to in the medical and pharmacy literature. Prescriptions for the indications of sleep disorder and smoking cessation, as well as others, may have had an impact on the measured adherence rate in any of the groups. Interestingly, at the second observation, after controlling for all variables, atypical agent therapy had a significant main effect on adherence. This may have been because atypical agents are not as commonly used for alternative diagnoses; therefore, possibly the contribution to adherence was not clouded by their use for other medical conditions (premenstrual syndrome, hot flashes, etc).

Although the HEDIS specifications include only patients with a diagnosis of depression; this evaluation was not designed to include only those with this diagnosis. Owing to a lag in medical claims data of 3 to 4 months, an impact of the intervention on adherence at the first and second observation would be lost waiting for medical claims confirmation of depression. In addition, internal barrier analysis results provided the health plan with information on the frequent noncoding of patients for depression when the condition was in fact suspected or confirmed. Therefore, the potential impact of diagnosis of depression was reviewed in retrospect by an evaluation of medical claims that were on file at the end

**Table 11.** Persistency by Month

Group	Persistency, %				
	2 mo	3 mo	4 mo	5 mo	6 mo
Intervention	45.9	36.8	30.2	28.8	24.9
Control	44.3	35.3	28.9	27.3	23.4

of the 6-month study. No other diagnoses were evaluated; the medical claims data were reviewed merely to search for patients with a depression diagnosis who were part of this evaluation only. Interesting results were found when evaluating adherence in patients known to have a diagnosis of depression. Patients with a diagnosis of depression displayed a higher adherence rate than the population with no record of a diagnosis of depression. Furthermore, improved adherence in the intervention group was positively associated with the diagnosis of depression at the second and third observations.

Using the 5 different measures of adherence provided consistent findings concerning the impact of the educational letter to patients prescribed antidepressant medications. In general, the intervention program kept approximately 2% more of the population prescribed antidepressant therapy adherent to medication. The clinical significance of this difference is unknown as clinical outcomes were not part of this evaluation. It could be surmised, however, that if a hospitalization or a suicide due to depression were prevented in even one patient of the 2% who experienced greater adherence to therapy, then the intervention would have been deemed clinically significant. Although this evaluation was not designed to measure economic outcomes, \$30,000 was spent in development and mailing costs in the 6-month period. The benefits of an improvement in adherence on utilization of medical services, improved productivity, reduced absenteeism, and quality of life were not part of this evaluation. Considering productivity loss estimates of \$182 to \$395 per depressed employee per month,<sup>16</sup> however, the cost effectiveness of this type of intervention to improve medication adherence in patients with depression was assumed to be favorable.

The study has several limitations. One limitation was the difficulty in extrapolating the impact of the intervention to patients with a diagnosis specific for depression. The HEDIS standards require evaluation of medication adherence at 84 and 180 days for all newly diagnosed and initially treated patients with a diagnosis of depression. Only pharmacy

claims data were used to identify patients in this evaluation. Thus, the study included all patients who were newly prescribed an antidepressant drug, regardless of diagnosis. During the evaluation, a retrospective analysis was performed to identify patients with a diagnosis of depression. Twenty percent of the study population had a diagnosis of depression. Calculation of adherence rates for this population subset demonstrated a higher rate of adherence in the intervention group compared with the control group. The findings suggest that despite the program limitation of including all patients taking antidepressants, improvements in adherence rates occurred in the subset of intervention patients with a diagnosis of depression compared with all patients taking an antidepressant.

Because our study included 2 initiatives for the single intervention group (ie, a patient-directed educational intervention and a physician-directed [patient-specific] intervention), we are unable to determine which one of these activities had the greatest overall impact on patient adherence to drug therapy. It may be possible that the 2 activities together are necessary to achieve program success or perhaps that only 1 of the 2 activities is needed to achieve success.

The 6-month evaluation of the intervention was most likely too short in duration to evaluate health outcomes or a change in health plan HEDIS measurements as a result of improved medication adherence. Further consideration is being given at this time to determining the value of continuing the intervention and including a future assessment of depression recurrence rates, relapse rates, hospitalizations, emergency department visits, and office visits.

Last, the clinical and economic significance of an improvement of 2% in antidepressant medication adherence is not known. Neither clinical nor economic outcome measures were examined in this study.

CONCLUSION

This study supported the positive impact of educational messages directed at patients and their physicians through mail interventions in an IPA-model HMO setting.<sup>10</sup> In addition to patient-directed education, the intervention in this evaluation also included provider education, which consisted of Agency for Healthcare Research and Quality guidelines, HEDIS measurements, and specific data on potentially nonadherent patients. The results of this study suggest that although patient education is

important in enhancing adherence, the benefits of patient identification for provider scrutiny could also potentially be a key component of adherence management.

Some managed care organizations are disadvantaged by lacking a direct patient care influence; however, programs that include monthly physician and patient mail interventions can positively influence antidepressant adherence rates. Further investigation is needed to determine the impact of this type of intervention initiative on HEDIS rates and clinical outcomes.

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