

Physician Alerts to Increase Antidepressant Adherence

Fax or Fiction?

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Background: Many managed care organizations use feedback based on electronically maintained claims data to alert physicians to potential treatment problems, including patient medication nonadherence. However, the efficacy of such interventions for improving adherence among patients treated for depression is unknown.

Methods: We examined an antidepressant compliance program consisting of faxed alerts to physicians beginning May 2003 using interrupted time series analysis to evaluate its impact on rates of antidepressant adherence between May 2002 and May 2004 among members of the managed care plan of Harvard Pilgrim Health Care, which is a health plan operating in 3 states in New England, with corporate headquarters in Wellesley, Mass. The program alerted prescribing physicians to patients with gaps of more than 10 days in refilling antidepressant prescriptions during the first 180 days of treatment. Our outcome measures were rates of nonadherence among patients with refill gaps of more than 10 days ("delayed refill") and proportion of days without treatment within the first 180 days of treatment.

Results: A total of 13 128 patients (≥ 18 years of age) who were starting treatment with antidepressants met the study criteria. Rates of nonadherence among patients with delayed refills remained constant ($P = .22$) over the 2-year study period, averaging 75% (95% confidence interval, 72.7%-77.3%). Rates of antidepressant nonadherence significantly increased over time ($P = .04$), with an average of 40% (95% confidence interval, 38.4%-41.6%) of days without dispensed antidepressants available during treatment episodes.

Conclusions: Using real-time pharmacy information to alert physicians regarding patient adherence was not successful in increasing antidepressant adherence rates among members of the managed care plan. Effectiveness of electronically triggered, patient-specific, faxed feedback should be carefully evaluated before widespread implementation, because faxes are insufficient as a stand-alone policy tool.

Arch Intern Med. 2006;166:498-504

DEPRESSION IS A MAJOR source of morbidity,¹ lost productivity,² and health care costs.³⁻⁵ Antidepressants are most effective in reducing symptoms, relapse, and recurrence when taken in accordance with guidelines.^{6,7} Yet, rates of adherence to a 6-month regimen of antidepressants, which is the recommended minimum duration of therapy, are low.⁷⁻¹⁴

See also pages 486 and 507

Several studies have identified effective methods for increasing adherence to antidepressant therapy in the primary care setting.^{7,15,16} Unfortunately, these strategies, which often involve intensive one-on-one interventions with clinicians and

patients, can be time-consuming, complex, and prohibitively expensive for many health care providers.^{17,18} Effective, feasible, and inexpensive approaches to improving antidepressant adherence are needed.

There are a growing number of interventions conducted by managed care organizations (MCOs) that involve the use of electronic medical or pharmaceutical claims to try to influence behavior change at a lower cost.¹⁹ For example, electronic information or feedback may be given to providers or patients regarding patient adherence to drug therapy. However, the evidence of the effectiveness of these approaches is mixed at best.¹⁹

Harvard Pilgrim Health Care (HPHC), a large nonprofit MCO that operates in 3 states in New England, with corporate headquarters in Wellesley, Mass, has engaged in several approaches to improve an-

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Date:

Transaction ID:

Dear Dr. :

Harvard Pilgrim Health Care (Harvard Pilgrim) is deeply committed to partnering with practitioners to deliver the highest quality care to our members. In order to assist you in caring for patients with Major Depression and related disorders, Harvard Pilgrim developed this clinical reminder to assist you in facilitating member compliance with antidepressant medication use as well as appropriate follow-up.

Using guidelines developed by the Agency for Healthcare Research and Quality (AHRQ),¹ and the National Committee for Quality Assurance (NCQA)² Harvard Pilgrim seeks to improve member compliance with:

- At least three follow-up visits within 12-weeks of initiating treatment, at least one of these visits with a practitioner with prescribing authority.
- Adherence with antidepressant medication for 3 months after initiating treatment.
- Adherence with antidepressant medication for at least 6 months after initiating treatment.

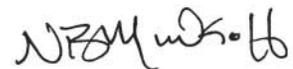
As you know, while acute depression symptoms may resolve within 4-6 weeks, full therapeutic doses of antidepressant medication should continue at least 6 months to assure full remission. It is reported that only 40% of individuals started on medication therapy adhere to treatment, therefore follow-up visits are essential to a member's understanding of the illness and compliance with medication.

, has gone 10 days or more beyond the expected timeframe for refilling his/her medication, quantity of for days supply.

Harvard Pilgrim provides you and your patients with access to the latest member education tools and clinical guidelines. You can locate these tools and guidelines at www.harvardpilgrim.org. If you need additional prescription history for your patient or any other Harvard Pilgrim member in active treatment with you, please call (858)790-7466.

We appreciate your continuing efforts to provide the highest quality of care to Harvard Pilgrim members.

Sincerely,



Neil Minkoff, M.D.
Medical Director for Pharmacy

Figure 1. Sample of faxed alert sent to physicians.

antidepressant adherence among its members. Such efforts have included providing print and Internet-accessible educational materials that are designed to enforce medication compliance and an opt-in comprehensive depression management program. In 2003, HPHC instituted an antidepressant adherence program that alerted physicians regarding early nonadherence to antidepressant therapy via fax during the first 6 months of treatment. The purpose of this article is to evaluate the impact of a faxed alert intervention at HPHC on antidepressant medication adherence.

Using 3 years of pharmacy claims data (November 2001-November 2004) obtained from HPHC and MedImpact (the pharmacy benefits manager for HPHC), we examined responses to the pilot antidepressant compli-

ance program (ACP), which began in May 2003. The ACP identified patients who were beginning treatment with antidepressants (no use in the previous 100 days) and followed them up for 6 months. If eligible patients did not refill their antidepressant prescription for at least 10 days beyond the expected date when the previously dispensed prescription should have been completed ("delayed refill"), a letter was faxed to the prescribing physicians alerting them to the situation. **Figure 1** depicts a sample of the faxed alert that was sent to physicians. If the targeted patients refilled their antidepressant prescription within a 30-day time frame (ie, within 20 days after the initial 10-day gap that triggered the alert), they were considered adherent and continued to be monitored by the program; a subsequent gap of 10 days in the

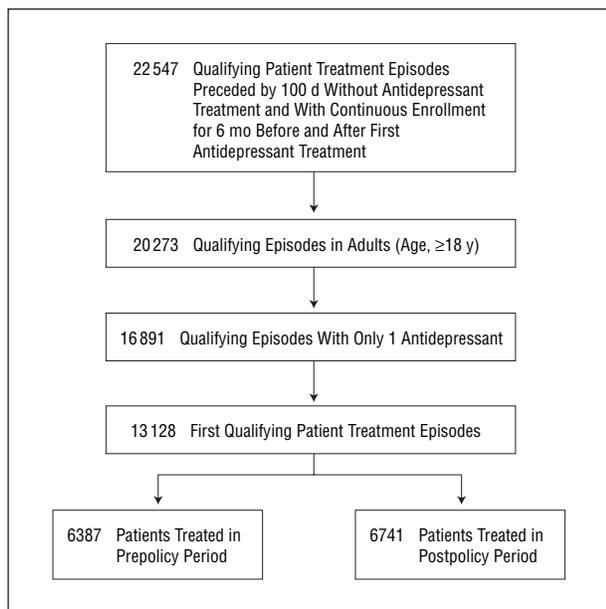


Figure 2. Derivation of the study cohort. The episodes were initiated between May 15, 2002, and February 14, 2003, and between May 15, 2003, and May 14, 2004.

same 6-month treatment episode could trigger another faxed alert. If the patients did not refill their antidepressant prescription within 30 days, they were considered nonadherent for the treatment episode and were no longer tracked, but could reenter the program if they restarted treatment with antidepressants after a gap of 100 days. We investigated whether the ACP would decrease the rate of nonadherence after controlling for the preprogram trend. This study addresses an important question regarding the efficacy of salient, faxed, patient-specific alerts to physicians about potential patient noncompliance with an essential treatment regimen.

METHODS

OVERALL DESIGN

We used interrupted time-series analysis, a strong quasi-experimental design,^{20,21} to examine a rolling cohort of HPHC patients who were enrolled for at least 6 months before and after initiating a new episode of antidepressant treatment between May 15, 2002, and May 14, 2004. The use of longitudinal methods allows us to control for any pre-ACP trends in rates of antidepressant adherence. This study was approved by the institutional review board at HPHC and Harvard Medical School, Boston, Mass.

SETTING AND SOURCES OF DATA

Harvard Pilgrim Health Care is the one of the largest non-profit MCOs in New England, currently serving approximately 800 000 members in Massachusetts, New Hampshire, and Maine in a variety of organizational settings, including medical groups, community health centers, independent physician practices, and a preferred provider network. MedImpact provided pharmacy refill data on study patients, including age, sex, prescribing provider, classes of prescriptions that may identify key comorbid health conditions, prescription refill date and

dosage, and number of days' supply of antidepressant pills dispensed. From HPHC enrollment files, we also identified the duration and continuity of enrollment for all patients who began antidepressant therapy.

COHORT IDENTIFICATION

We identified patients who used any of the following antidepressants included in the fax alert program between May 15, 2002, and May 14, 2004: amoxapine, citalopram, escitalopram, fluoxetine, fluvoxamine, isocarboxazid, maprotiline, mirtazepine, nefazodone, paroxetine, phenelzine, sertraline, tricyclopromine, or venlafaxine. Study inclusion criteria required patients to be continuously enrolled in an HPHC insurance plan (0 days out of plan) for at least 6 months before and after first antidepressant use, defined as having gone 100 days without previous antidepressant treatment. Patients younger than 18 years were excluded because psychiatric prescribing patterns and recommendations for therapy may be different for children than for adults. Patients who used more than 1 type of antidepressant during an episode of therapy (17% of episodes) were excluded because of the difficulty of using claims data to define adherence for more than 1 medication concurrently. Only the first instance of new use (ie, first qualifying episode of care) was selected for each eligible cohort member. Patients could have been treated by any type of HPHC provider, not just psychiatrists or primary care physicians.

MEASURES OF ANTIDEPRESSANT ADHERENCE

We examined rates of medication adherence before and after the implementation of the ACP. Patients were considered adherent if they never experienced a gap of more than 10 days between refills during the first 6 months of antidepressant therapy. Patients with delayed refills (gaps >10 days) were considered nonadherent if their gaps exceeded 30 days before their prescription was refilled. These definitions of adherence were defined by the ACP and were intended to be consistent with current guideline-based recommendations for therapy.

STATISTICAL ANALYSIS

We used interrupted time-series analysis to evaluate the impact of the ACP on rates of adherence. Interrupted time-series is the strongest quasi-experimental design for studying changes due to a policy,^{20,22} especially when study outcomes are stable over time. Such designs produce more valid evidence of policy effects than simple pre-post research designs because they control for prepolicy trends in study outcomes.²³⁻²⁵ We determined whether there were changes in the level and trend in adherence before and after the ACP was implemented. Patients whose episodes began between February 15, 2003, and May 14, 2003, were excluded from the analysis because their treatments were initiated before the ACP was implemented, but the initiation phase of therapy (first 90 days during which patients are most at risk for nonadherence) extended into the post-ACP period.

RESULTS

A diagram illustrating the cohort selection process is shown in **Figure 2**. A total of 13 128 patients met the study criteria. Basic demographic characteristics of the study participants are presented in the **Table**. Among these patients, 6387 (49%) of the episodes began during the pre-ACP period, and 6741 (51%) of the episodes took

Table. Baseline Characteristics of 13 128 Study Participants*

Characteristic	Pre-ACP Patients (n = 6387)	Post-ACP Patients (n = 6741)
Age, mean (SD), y	42 (11)	42 (11)
Sex		
Female	4401 (69)	4678 (69)
Male	1986 (31)	2063 (31)
ACP variables		
Adherent (no gap >10 d)	1159 (18)	1171 (17)
Delayed refill (gap >10 d but ≤30 d)	1822 (29)	1928 (29)
Nonadherent (refill gap >30 d)	3406 (53)	3642 (54)

Abbreviation: ACP, antidepressant compliance program.

*All values other than age are expressed as number (percentage).

place during the post-ACP period. Overall, 69% of the patients were female, and the mean (SD) age of patients in both the pre-ACP and the post-ACP periods was 42 (11) years.

Figure 3 shows the estimated effect of the ACP on the proportion of patients with delayed refills (ie, with gaps >10 days) who proceeded to become nonadherent. After baseline level and trend were controlled for, there was an immediate but nonsignificant decrease of 2% in rates of treatment nonadherence among patients with delayed refills ($P = .15$) and a nonsignificant increase of 0.3% in rates of treatment nonadherence among patients with delayed refills ($P = .22$) each month after the intervention. Therefore, over the 2-year study period, the proportion of nonadherent patients among those with delayed refills remained relatively constant, averaging 75% (95% confidence interval, 72.7%-77.3%).

In the time series presented in **Figure 4**, we examined how many days antidepressant medication was dispensed to patients during the initial 180 days of treatment. In general, instead of the number of days without treatment decreasing as expected, there was an immediate but nonsignificant decrease of 2% in the rates of antidepressant nonadherence ($P = .15$) and a significant increase of 0.4% ($P = .04$) each month after the intervention, with an average of 40% (95% confidence interval, 38.4%-41.6%) of days without antidepressant treatment available within each treatment episode.

To examine whether there may have been an intervention effect by provider specialty, we repeated the analyses described herein using groups of patients treated by psychiatrists vs internal medicine physicians (data not shown). In both instances, the rates of nonadherence did not improve.

COMMENT

Faxed alerts to physicians based on real-time pharmacy information about patients with delayed refills did not increase the antidepressant adherence rates among HPHC members. The steady rate of delayed refills that proceed to treatment nonadherence indicates that faxing physicians to alert them about delayed refills does not appear to achieve a measurable impact as a free-standing inter-

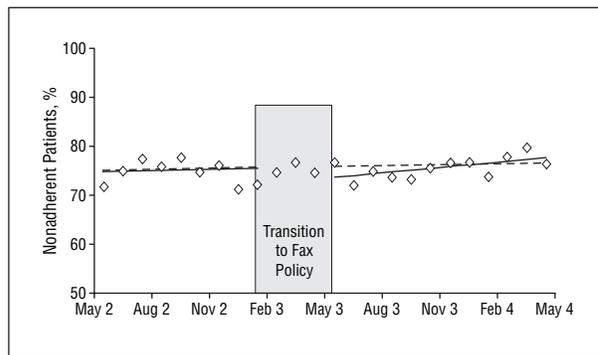


Figure 3. The estimated effect of the antidepressant compliance program (ACP) on the proportion of patients with delayed refills. Diamonds indicate the mean monthly percentage of patients starting treatment who proceeded to treatment nonadherence; solid lines, estimated pre-ACP and post-ACP values based on time series model; and dotted lines, expected post-ACP values based on pre-ACP trends.

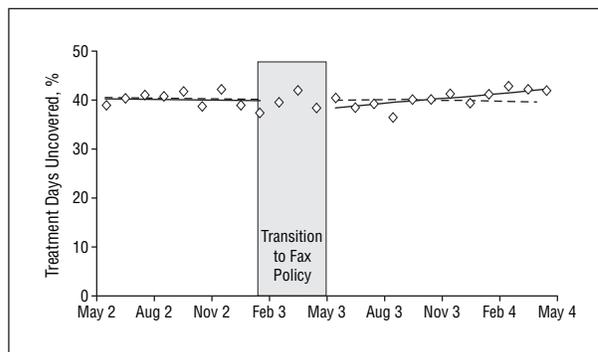


Figure 4. The number of days that antidepressant medication was dispensed to patients during the initial 180 days of treatment. Diamonds indicate the mean percentage of treatment days not covered; solid lines, estimated pre-antidepressant compliance program (ACP) and post-ACP values based on time series model; and dotted lines, expected post-ACP values based on pre-ACP trends.

vention. Furthermore, the rate of patients with delayed refills who proceed to nonadherence is quite high, indicating that a 10-day delay in refilling antidepressant prescriptions may be a useful identifier of the patients who are most likely to remain nonadherent.

To our knowledge, this is the first study to examine the effect of a faxed alert system to physicians regarding medication nonadherence. Our findings are in agreement with those of several recent studies in which it was found that an approach that is targeted to improve medication adherence rates using electronic data in the absence of a larger, coordinated effort is unlikely to be successful²⁶⁻³⁰ and that multifaceted approaches are frequently necessary.³¹⁻³³ When simpler approaches are used, they are more successful when they are repeated, such as multiple mailings or telephone calls to patients³⁴ or multiple patient visits with physicians.³⁵ Unfortunately, comprehensive reviews of interventions that are designed to improve patient adherence to drug therapy have not found convincing evidence of the superiority of any intervention strategy.^{27,36} Our findings confirm that patient-specific alerts using faxes to physicians are not effective at improving patient adherence to antidepressant therapy in the absence of other complementary, coordinated interventions.

During the study period (May 2002-May 2004), HPHC engaged in other efforts (in addition to the ACP) targeting physicians to improve antidepressant adherence. These efforts included providing financial incentives beginning in January 2004 for physicians who increased the rate of contacts with patients who were under treatment for depression. Also, nonfinancial "honor roll" rewards for physicians who improved rates of patient contact and antidepressant adherence among depressed patients began in January 2003. In independent analyses (not shown), we found that neither of these interventions, alone or combined with the antidepressant fax program, improved the rates of antidepressant adherence.

Patient nonadherence to drug therapy is a complex phenomenon, and reasons for nonadherence to recommended therapy may vary depending on where patients are in the treatment process.¹⁰ Patients who are starting a medication regimen may have needs that are different from those of patients who have been taking the medication for some time or who have taken the medication (either successfully or unsuccessfully) in the past. Particular attention is required by physicians who are treating patients with antidepressants, as patients may be ambivalent about treatment and concerned about adverse effects^{14,37} or stigma associated with the use of psychoactive medications. It may also be helpful for physicians to have information about suspected patient nonadherence during patient visits,³⁸ so that physicians may address adherence concerns. Finally, interventions that make use of pharmacists, nurses, or depression care managers may be more effective^{16,39,40} because they involve repeated direct personal contact with patients.

Another drawback to an automated fax intervention is that physicians could become desensitized over time if there is a high rate of false-positives. If physicians receive faxes on multiple patients who are actually adherent (eg, they fill prescription on day 11, or there is a lag in recording dispensing data from the pharmacy) or who have discontinued taking medication because of adverse effects, the physicians could become increasingly frustrated and ignore the faxed reminders. However, HPHC sought to maximize the identification of patient nonadherence despite the occurrence of potential false-positive alerts. Our findings confirm those of recent studies indicating that physician reminder systems had no effect on process or quality of care, including patient nonadherence to antidepressant treatment.^{41,42} Therefore, the disappointing results from this intervention are not surprising.

Although automated electronic reminder and alert systems have become popular in recent years, they may not improve patient adherence. Nevertheless, programs using this type of intervention are being conducted in the absence of data supporting their efficacy.¹⁹ The likelihood of success of such interventions is increased if the following conditions are met: the prescribing physician, rather than an office staff member or a colleague, actually receives the faxed message about patient nonadherence; the physician (or staff member) makes contact with the patient; and a clinician-patient conversation occurs that effectively deals with the reasons for patient nonadherence in a timely fashion. It is possible

that 1 or more of these steps did not occur in the intervention that we studied. Adherence is a complex phenomenon, and by using electronic records, we are unable to determine what type of communication takes place between the physician and the patient. However, our study provides evidence that this type of intervention is not effective as a stand-alone approach to improving patient adherence.

In this study, the prescribing physician was the target of the intervention, and it was expected that physicians would be motivated to communicate with patients to promote better adherence. While the results from this and similar physician-oriented interventions have been suboptimal, a mail intervention targeted directly at patients was recently shown to be effective at improving rates of adherence to antidepressant therapy.⁴³ Perhaps it is the target, rather than the intensity and complexity of this type of intervention, that is problematic.

The strengths of the present study lie in its use of longitudinal pharmacy claims. Furthermore, we would have had more than 80% power to detect either a 6% immediate decrease in rates of treatment nonadherence among patients with delayed refills, or a decrease of 1.5% per month after the intervention, based on an overall variance of 0.0005, which was estimated based on data from the prepolicy period. The power analysis provides confirmation that our findings of little or no effect of the intervention are real and not a consequence of inadequate sample size.

However, our study was quasi-experimental, with a number of potential methodological problems that merit discussion. Our measure of antidepressant adherence was based on pharmacy claims data, and we did not have any information about patient diagnosis or about actual daily adherence to treatment. Furthermore, we excluded patients who took more than 1 type of antidepressant or who switched to a different type of antidepressant during the study. It is possible that patients are using antidepressants for reasons other than depression treatment (and in fact bupropion was excluded as a study medication because of its widespread use for smoking cessation). The ACP specifically targeted newer antidepressants to avoid focusing on antidepressants that were used for other treatment indications. Furthermore, a study from the National Center for Quality Assurance to develop the current Health Plan Employer Data and Information Set antidepressant quality indicator demonstrated that more than 95% of HPHC patients who receive a prescription for an antidepressant medication are, in fact, being treated for depression.^{44,45} Because our data were limited to dispensing records, we did not have data available on how many contacts patients had with providers, which is another indicator of quality of care for depression. Finally, because of the nature of our data, we were unable to determine whether treatment was given to appropriate patients and whether the antidepressants were prescribed at the correct dosage.

Pharmacy dispensing records alone may not be able to capture adherence behavior. Previous studies with HPHC data have demonstrated that pharmacy dispensing records provided a useful and convenient means of measuring cumulative exposure to and gaps in medica-

tion supply.⁴⁶ Furthermore, the data are likely to be reliable and complete because most (>90%) HPHC members have a prescription drug benefit that provides a strong incentive for them to fill prescriptions at HPHC-affiliated pharmacies.⁴⁷ Other research studies demonstrate that drug claims data can be used effectively in studies of medication adherence among persons with mental disorders.⁴⁸ It is possible that pharmacy claims-based reminders can promote better adherence, especially if they are directed at patients or are a part of a more complex intervention directed at physicians. It remains important to try to achieve intervention strategies that are clinically salient, feasible, and efficient.

Finally, this study allows us to draw conclusions about adherence behavior among patients receiving antidepressant treatment in a managed care setting. It is uncertain to what extent the results from this analysis are generalizable to other patient populations, managed care plans, or other chronic diseases treated with medications. Given the high rates of nonadherence to long-term drug therapy in general^{8,14,49} and to the use of antidepressants in particular,^{7,9,50} inexpensive interventions to improve adherence are needed. However, based on the results of this study, MCOs should be cautious about using this form of faxed reminder system as a singular approach for physicians to improve patient medication adherence.

Accepted for Publication: October 4, 2005.

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Financial Disclosure: None.

Funding/Support: This work was funded by a faculty grant from the HPHC Foundation. Dr Soumerai is an investigator in the HMO Research Network Center for Education and Research in Therapeutics, supported by the Agency for Healthcare Research and Quality, Rockville, Md.

Role of the Sponsor: The HPHC had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript; only the authors occupied these roles.

Previous Presentation: This study was presented in abstract form at the AcademyHealth Meeting; June 28, 2005; Boston, Mass.

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