Analyzing Variations in Medication Compliance Related to Individual Drug, Drug Class, and Prescribing Physician

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OBJECTIVE: To evaluate the effects of individual drugs, drug classes, and prescribing physicians on a patient's medication compliance.

DESIGN: A retrospective review of prescription claims submitted between January 1, 1994, and September 30, 1995, by members of a preferred provider organization. The unit of compliance used was the medication possession ratio (MPR), defined as the days supply of medication divided by the days between refills, of 20 selected medications used as maintenance therapy (three or more refills). Three separate analyses were performed to assess differences in compliance by medication, therapeutic class, and prescribing physician.

SETTING: A 275,000-member preferred provider organization in the Mid-Atlantic Region.

PATIENTS: 1,776 patients, 639 males and 1,137 females, identified as having filed three or more claims for at least one of the selected medications. The average age of the patients was 55.3 years.

MAIN OUTCOME MEASURES: Medication possession ratio (MPR)

RESULTS: The average MPR of this sample was 0.905, weighted with regard to the frequency of each medication within the database. Medication-specific MPRs ranged from 0.79 for conjugated estrogens to 0.99 for simvastatin. Differences in individual drug compliance were found in 14 of 190 possible comparisons.

CONCLUSION: Prescription claims can be a useful probe for detecting differences in patient compliance related to individual drug, therapeutic class, and prescribing physician. Efforts to improve patient compliance should focus more of the type of medications the patient is receiving and also on helping the physician identify non-compliant patients.

KEYWORDS: Medication possession ratio, Compliance, Prescription claims, Adherence

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Patients with chronic medical conditions usually require long-term treatment with medications to control symptoms or prevent complications. However, these patients often misunderstand, forget, or ignore the proper instructions for taking medications. The result is a high prevalence of patient noncompliance (or nonadherence). It has been estimated that prescriptions fail to yield desired results 30%–50% of the time.¹ Several studies have linked noncompliance with increased morbidity and mortality in several disease states, including congestive heart failure,² hypertension,^{3,4} and hypercholesterolemia.⁵ Estimates of the cost of noncompliance in the United States, including hospital and nursing home admissions, lost productivity, premature deaths, and excessive treatments surpass \$100 billion per year.⁶

Although medication compliance has received more attention in recent years, it is not a new problem. Hippocrates is reputed to have said, "Keep watch also on the fault of patients which often makes them lie about taking of things prescribed." A patient's ability to take things as prescribed seems to be influenced by several factors.¹ Some patients do not put a premium on health or may believe the treatment is unnecessary if they feel well. This often is the case in hypertensive patients, who normally do not exhibit any symptoms of illness. Patients also may believe the medication will not work or do not allow enough time for it to take effect, as is typical in patients with depression, where medications may take as long as four weeks or more to exert their effect. Medications associated with

Table 1. Individual Medications and Therapeutic Classes

Therapeutic Class	Drug Name
ACE inhibitors	enalapril
	lisinopril
Anticonvulsants	phenytoin sodium
Antidepressants	fluoxetine
	sertraline
Beta blockers	atenolol
	metoprolol
Calcium-channel blockers	amlodipine
	nifedipine core-coated
	nifedipine GITS
	verapamil
HMG CoA reductase inhibitors	pravastatin
	simvastatin
Thyroid replacement	levothyroxine
No assigned class	allopurinol
	conjugated estrogens
	digoxin
	glyburide
	terazosin
	transdermal nitroglycerin

unpleasant side effects or a complex dosing regimen also may contribute to noncompliance.^{7,8} Inadequate physician-patient communication may lead to unresolved patient concerns about diagnosis, disease, or prescribed therapy, which may cause the patient to misperceive the value of the medications prescribed. The extent to which physicians help patients understand their diagnosis, disease, and therapy affects a patient's ability to comply with instructions.⁹⁻¹³ Additionally, physicians often are unable to identify patients who are noncompliant: Mushlin and Appel found that physicians predicted 35% of actual noncompliers and half their predictions of noncompliance were inaccurate.

As a pharmacy benefit management company (PBM), we have access to pharmacy claims for large groups of patients. This provided us with the opportunity to measure compliance using a method called the medication possession ratio (MPR), first reported by Sclar and coworkers in 1991.⁴ Our goal was to assess variations in medication compliance by comparing calculated MPRs specifically related to individual drug, therapeutic class, and prescribing physician. By using such a large perspective to identify areas in which patients tend to be less compliant, we can design population-wide programs addressing these areas to improve compliance. While others have previously used prescription claims databases to determine differences in compliance for individual medications^{4,7,15,16} and therapeutic classes,^{7,16} this is the first attempt we know of to use this method to detect differences among prescribing physicians.

METHODS

This study analyzed the prescription claims submitted between January 1, 1994, and September 30, 1995, by a 275,000-member Mid-Atlantic preferred provider organization. The members of this organization are mainly employees and their dependents. Only those members who were eligible for pharmacy benefits throughout the study period were included in the analysis. Eligibility was assumed if the member had received a prescription within the first three months and the last three months of the study period. The unit of compliance was the MPR, defined as the days supply of medication divided by the days between fills of the medication—information readily available in pharmacy claims data. Due to its dependence upon at least two fill dates, this method is useful only for medications used chronically for maintenance therapy. We defined maintenance therapy to include only those medications for which a patient submitted at least three prescription claims.

The pharmacy claims data were loaded into an Access database in table format. Three separate analyses were performed to assess differences in compliance by individual medication, therapeutic class, and prescribing physician. Twenty individual medications were selected first for analysis based on their high

Table 2. Medication Possession Ratios for Individual Medications

Drug Name	Medication Possession Ratios*
simvastatin	0.99
lisinopril	0.97
glyburide	0.96
amlodipine	0.96
nifedipine GITS	0.96
levothyroxine	0.96
digoxin	0.95
terazosin	0.93
enalapril	0.93
atenolol	0.92
verapamil	0.90
phenytoin sodium	0.88
transdermal nitroglycerin	0.87
pravastatin	0.87
fluoxetine	0.87
allopurinol	0.86
nifedipine core-coated	0.84
metoprolol	0.84
sertraline	0.83
conjugated estrogens	0.79

*Days supply of medication ÷ days between refills.

Table 3. Medication Possession Ratios for Therapeutic Classes

Drug Class	Medication Possession Ratio
Thyroid replacement	0.96
ACE Inhibitors	0.94
Calcium channel blockers	0.93
HMG CoA reductase inhibitors	0.93
Beta blockers	0.90
Anticonvulsants	0.88
Antidepressants	0.85

frequency of use and likelihood of use as maintenance therapy for chronic diseases (see Table 1). For the second analysis, the selected medications were grouped into therapeutic drug classes (see Table 1). The third analysis involved identifying the top 25 physicians, selected by overall prescribing frequency of the selected medications, and their patients' compliance with the selected medications. An MPR was calculated for each medication, therapeutic class, and selected physician.

The physician's effect on patient compliance was determined by averaging the MPRs of the patients for whom they ordered prescriptions. A patient was assigned to a physician if at least 50% of the patient's prescription claims were attributable to a particular physician's DEA number. Physicians' MPRs were calculated by averaging the MPRs of their assigned patients.

The three MPR groupings (individual drug, therapeutic class, and prescribing physician) were analyzed using one-way and two-way ANOVA tests. Multiple comparisons were made to determine differences between MPRs within each model using Tukey's Studentized tests. A p value of <0.05 was considered to be a statistically significant difference.

RESULTS

Individual Medications

A total of 1,776 patients—639 males and 1,137 females—were identified as having filed three or more claims for at least one of the selected medications.⁶ The overall average age was 55.3 years. For those patients who received more than one of the selected medications, an MPR was calculated for each medication, resulting in 2,810 instances in which an MPR could be calculated. The average MPR of this sample was 0.905, which was weighted with regard to the frequency of each medication within the database. Medication-specific MPRs ranged from 0.79 for conjugated estrogens to 0.99 for simvastatin (see Table 2). The overall analysis was found to contain statistically significant differences between the MPRs of individual drugs ($p=0.0001$). Differences in individual drug compliance were found in 14 of 190 possible comparisons ($p<0.05$). Eleven of these comparisons involved conjugated estrogens, the medication with the lowest MPR.

Drug Classes

As shown in Table 3, an MPR was assigned to each drug class by averaging the MPRs of the individual medications within each class, except for anticonvulsants and thyroid replacement medications, which were assigned the MPR of the single medication composing that class (phenytoin sodium and levothyroxine, respectively). A one-way ANOVA yielded statistically significant differences ($p=0.004$) in MPRs of the drug classes. The lowest MPR was associated with antidepressants (0.85), while thyroid replacement represented the highest compliance (0.96). The difference between these two was found to be statistically significant ($p<0.05$), as were pairwise comparisons between antidepressants and both ACE inhibitors and calcium channel blockers.

Prescribing Physician

Of the 1,776 members using the selected medications, 711 members were assigned to only one physician each. These patients accounted for 1,016 instances in which an MPR could

Table 4. Composite Medication Possession Ratios for the Top 25 Prescribing Physicians

Physician	Medication Possession Ratios
T	1.02
I	1.00
E	0.98
F	0.96
Q	0.96
R	0.96
W	0.96
G	0.95
K	0.95
C	0.94
A	0.93
X	0.93
Y	0.93
O	0.92
U	0.92
P	0.90
L	0.89
M	0.88
V	0.86
H	0.85
D	0.82
S	0.82
B	0.80
J	0.77
N	0.76

be generated. The top 25 prescribing physicians were identified based on number of prescription claims. The unadjusted average MPR for each physician ranged from 0.76 to 1.02, with an overall average of 0.91 (see Table 4). A two-way ANOVA model resulted in statistically significant differences in average MPRs by physician ($p=0.0015$), after adjusting for medication mix. Adjusted differences among physicians were found to be statistically significant ($p<0.05$) in 52 out of 300 possible comparisons (17%).

DISCUSSION

The average compliance rate of 91% reported here is much higher than previously reported. We believe this was a result of several factors unique to the method of compliance measurement that we chose. By analyzing prescription claims only, patients not filling a prescription from their physician cannot be identified, although clearly they are noncompliers. Also, those patients who do not submit their prescription to the health plan could not be identified in this analysis. As stated above, we chose to include only those patients who had at least three claims for one of the selected medications during the study period. This eliminated those patients who obtained only one or two prescription fills, so that certain initial compliers may have become noncompliant. Because of these exclusions, we were left with a small subset of the population and, therefore, the findings cannot be generalized to the entire study population. However, patients who have received at least three fills of a particular medication are more likely to be stabilized on the medication and should continue its use. Consequently, though the three analyses (individual drug, drug class, and prescribing physician) may not accurately measure compliance rates, they may actually serve as a better method of measuring variations in compliance, which was the goal of our study.

The medication with the lowest compliance rate was conjugated estrogens at 0.79. This result may indicate a unique aspect of the use of prescription claims as a measure of compliance. Clinically, conjugated estrogens often are prescribed in a cycle of 21 days on and seven days off, mimicking the natural release of estrogen in premenopausal women. The directions on a prescription for this regimen are often stated as "once daily, dispense #21." Most pharmacy computers will automatically calculate a days supply based on the directions and number of units. In this instance, the days supply would be calculated at 21, when it is actually a 28-day supply. Although the days supply value can be overridden at the pharmacy level, it may go unnoticed by a busy pharmacist. The lower days supply decreases the numerator in the MPR, thereby decreasing the MPR itself. The effect of this anomaly on our measurements is impossible to determine. However, it is important to note this result, because it illustrates the dependence of the MPR method on the accuracy of the pharmacist processing the claim. Other medications, such as inhalers and insulin, could

be expected to present similar results, a fact which precludes the use of this measurement instrument for all medications. The fact that 11 of the 14 significant differences found between medications involved conjugated estrogens leads us to conclude that while the analysis was found to contain significant differences, few pairwise comparisons were found to be statistically significant.

Although not statistically significant, several other interesting findings are worthy of note. The MPRs for different medications within the same classes appeared quite different, specifically simvastatin (0.99) and pravastatin (0.87). Even medications with the same ingredient, nifedipine core-coated (0.84) and nifedipine GITS (0.96), appeared to have differing compliances. No pairwise comparisons found any significant differences in the compliance of medications with different routes (transdermal nitroglycerin—0.87) or higher frequencies of administration (verapamil HCl—0.90, phenytoin sodium—0.88).

When the medications were grouped into therapeutic classes, some interesting findings resulted. The highest compliance was for thyroid replacement (0.96), a once-daily medication used to treat a symptomatic condition. When dosed appropriately, this drug relieves symptoms and rarely causes adverse events. These are the characteristics of an ideal drug. The lowest compliance was for antidepressants (0.85). The medications in this class are usually administered once daily; however, it may take up to four weeks or more for these drugs to result in beneficial effects for a condition that may be very subjective in its diagnosis and assessment. While more tolerable than previous therapies, these medications have the potential to cause several side effects. The difference between these two classes of medications was found to be statistically significant ($p<0.05$).

Although the differences are very small and not statistically significant, an interesting trend resulted among the medication classes often used to treat hypertension. ACE inhibitors had the highest compliance (0.94), followed closely by the calcium channel blockers at (0.93). Beta-blockers ranked the lowest among the three at 0.90. This coincides with the consensus opinion that beta-blockers cause more side effects than ACE inhibitors or calcium channel blockers.

In the absence of a designated primary care physician, we chose to determine a physician's MPR by assigning patients who received at least 50% of their submitted prescriptions from these physicians. Clearly, this is an arbitrary definition. We recognize that physician-affected patient compliance behavior may not be a function of the percentage of prescriptions received from a particular physician. However, in light of the importance of the physician-patient relationship, patients who receive at least the majority of their prescriptions from an individual physician are likely to be influenced by that particular physician.

Physicians' MPRs varied widely, resulting in numerous statistically significant differences between physicians, even after adjusting for the medication mix of each physician. The highest adjusted MPR was 1.02. An MPR greater than 1.0 is

possible due to early refills, vacation supplies, and noncompliant behavior expressed as overutilization, among other reasons.

Another confounder in determining the physician MPR is the reliance on the DEA number associated with the prescription claim as a means of identifying the physician. DEA numbers submitted with a prescription claim may not accurately represent the prescribing physician. A preliminary analysis showed that out of the top 10 most frequent DEA numbers, only three were associated with physicians. The remaining were numbers assigned to hospitals, pharmacies, or no entity, or they were "dummy" numbers, often used to adjudicate nonnarcotics prescription claims if the physician's DEA number is not known. Although these factors limit the implications of our results, we still feel confident that important differences exist among physicians with regard to patient compliance. Whether this is due to the type of population physicians serve, the types of diseases they treat, or their ability to communicate with patients is beyond the scope of this study.

Other limitations of the study involve the use of prescription claims as the sole source of information to measure compliance with therapy. Assuming a prescription claim is submitted each time a patient receives a refill, this method actually measures compliance in obtaining medication. Although we cannot assume that patients will take medication as prescribed once they receive it, timely refilling of prescriptions suggests that they do.

Prescription claims also are unable to adjust for dosage titration, drug samples, vacation supplies, or nonsubmitted medication fills. Also, members included in the study actually may have had a break in enrollment outside of the first and last three months of the study. Prescriptions could have been filled during this time that would not have been submitted to this organization and consequently not captured in our analysis.

CONCLUSION

Despite these limitations, we feel that prescription claims can be a useful probe for detecting differences in patient compliance related to individual drugs, therapeutic classes, and prescribing physicians. Efforts to improve patient compliance should focus on the types of medications the patient is receiving

and also on helping the physician identify noncompliant patients. Studies examining the specific reasons for these differences, especially relating to physician-patient communication, can enhance our understanding of factors that affect compliance. Specific interventions can then be developed to improve medication compliance and enhance patient outcomes.

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