The Effect of Prescribed Daily Dose Frequency on Patient Medication Compliance

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• **The objective of this study was to determine the relationship between prescribed daily dose frequency and patient medication compliance. The medication compliance of 105 patients receiving antihypertensive medications was monitored by analyzing data obtained from special pill containers that electronically record the date and time of medication removal. Inaccurate compliance estimates derived using the simple pill count method were thereby avoided. Compliance was defined as the percent of days during which the prescribed number of doses were removed. Compliance improved from 59.0% on a three-time daily regimen to 83.6% on a once-daily regimen. Thus, compliance improves dramatically as prescribed dose frequency decreases. Probably the single most important action that health care providers can take to improve compliance is to select medications that permit the lowest daily prescribed dose frequency.**

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Numerous studies have demonstrated that poor medication compliance poses a significant impediment to the effective treatment of a wide variety of illnesses.[1] One suggested method for improving compliance is to decrease the number of prescribed daily doses. However, the relationship between daily dose frequency and compliance is uncertain, with many[2-10] but not all[11-17] studies indicating that compliance progressively improves as daily dose frequency decreases. Defining the relationship between compliance and dose frequency is further complicated because almost all published studies use the pill count method for quantitating compliance. Pill counts must be interpreted with caution, since they provide no information about the day or time of dose removal.[18]

Medications that are effective when administered once or twice daily have become increasingly available and promotion of these drugs has focused on their alleged compliance-enhancing characteristics. An evaluation of the validity of these claims and an assessment of the expected degree of compliance improvement for these typically more expensive long-acting dose formulations is warranted.

The purpose of this study was to investigate the relationship between the prescribed daily dose frequency for antihypertensive medications and patient medication compliance by analyzing medication compliance data obtained from unique pill containers that electronically record the date and time of medication removal.

SUBJECTS AND METHODS

Subjects

Data were collected as part of a broader research effort to evaluate the effect of feedback of compliance information to health care providers on the medication compliance of their patients. Participation was solicited from 756 consecutive patients who fulfilled the following criteria: history of hypertension (controlled or not controlled while receiving medication), attending the St Louis (Mo) Veterans Affairs Medical Center in a continuity of care clinic environment, being treated with a once, twice, or three times a day dose frequency medication regimen, and all medications (excluding those prescribed on an "as needed" basis, most commonly antacid and acetaminophen tablets) able to fit into the compliance monitors.

One hundred ninety-two patients agreed to participate and were randomly allocated to a pill count monitored (60 patients) or compliance device monitored without feedback (67 patients) or with feedback (65 patients). Reasons given for not wishing to participate included "not interested" (48%), unable to keep the required monthly appointments (34%), and miscellaneous explanations (18%). Compliance data were obtained from 112 patients in the two compliance monitored groups. Data were lost from 20 patients who withdrew from the study before receiving the first monitoring device or after accepting one monitor. In addition, the initially prescribed dose frequency for seven patients was changed by the health care provider during the course of the study. Compliance data collected on these patients were excluded from this study, although their inclusion had no effect on the results. This study therefore analyzes data obtained from 105 compliance device monitored patients.

Protocol

At the time of recruitment, all subjects were informed that the research project was being performed to study "methods of helping patients remember to take their blood pressure pills," that the con-

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tainer in which they would receive their medication would electronically record the time at which medication doses were removed, and that the compliance information might be given to their health care provider.

The goal was to collect six consecutive months of compliance monitor data from each patient for a total of 630 months. The final data, however, included 516 months (an average of 5 months per patient). Data were lost because of patients resigning from the project (13 patients, 47 months), death (2 patients, 7 months), and compliance monitor malfunction (51 patients, 60 months).

Compliance Monitor

A detailed description of the compliance monitor has been published.[19] The following is a brief overview. Two clear plastic blister sheets, each containing 21 blisters, were filled with the patient's medications. A self-adhering paper, with loops of conductive "wires" in the same pattern as the blisters, was then placed over the open face of each of the sheets of blisters to form blister packs. The packs were connected to electronic components and were placed inside an easily opened plastic case. Every 15 minutes, the battery-operated electronic memory sent an impulse through each loop of conductive material. If a dose of medication has been removed (that is, if the paper covering a blister was torn), the electrical impulse failed to return to the electronic memory and the 15-minute interval during which this occurred was recorded. After the patient returned the compliance monitor, the data were collected with a microcomputer.

Questionnaires

A questionnaire that solicited the following information was administered at the time of recruitment and at the conclusion of compliance monitor data collection: perceived problems taking medications (memory for taking pills, self-reported compliance, and attitude toward pill taking, side effects, and medication efficacy), satisfaction with care, health locus of control, and health habits (coffee, alcohol, and cigarette use). In addition, during each monthly appointment, a questionnaire was administered that solicited the following information about events in the preceding month: health status (nine questions addressing perceived psychological and physical health), interim outpatient visits and hospitalizations, perceived number of omitted or late medication doses, and medication side effects. All questions except those relating to perceived problems taking medications were modified from previously defined scales.[20-23] Blood pressure was also recorded at each visit.

Medication Compliance Definitions

Many alternative definitions of compliance, using compliance monitor data, can be developed to investigate the relationship between compliance and the prescribed daily dose frequency. To address the current problem, two definitions were selected.

Definition 1 = (No. of doses removed/No. of doses prescribed) × 100

Definition 1 represents the percentage of prescribed doses that the patient removed during the interval of observation (ie, the standard pill count). This definition can be calculated without using data from the compliance monitor and is independent of information about *timing* of dose removal. For example, definition 1 indicates perfect compliance even if the patient forgets doses and subsequently removes all remaining doses on the day of the return clinic visit.

Definition 2 equals percent of days during which less than the prescribed number, the prescribed number, and greater than the prescribed number of doses were removed.

Definition 2 quantitates daily compliance without necessarily penalizing patients for removing more than one dose simultaneously (eg, to take a midday dose to work for later ingestion), but does penalize patients who do not remove the prescribed number of doses each day. A day was defined as the time interval between 3 AM and 2:45 AM the following day because inspection of compliance data demonstrated that all patients began their medication day after 3 AM.

Table 1.—Selected Characteristics in the Total Patient Sample and in Each Prescribed Dose Frequency Category

Characteristic	Total Sample, No. (%)	3 Times Daily, No. (%)	2 Times Daily, No. (%)	1 Time Daily, No. (%)
Age, y				
<50	11 (10.5)	3 (15.0)	4 (10.0)	4 (8.9)
51-65	62 (59.0)	12 (60.0)	21 (52.5)	29 (64.4)
>65	31 (29.5)	5 (25.0)	15 (37.5)	11 (24.4)
No data	1 (1.0)	...	...	1 (2.2)
Race				
White	18 (17.1)	2 (10.0)	9 (22.2)	7 (15.6)
Black	87 (82.9)	18 (90.0)	31 (77.5)	38 (84.4)
Education				
<High school	50 (47.6)	10 (50.0)	17 (42.5)	23 (51.1)
High school graduate	29 (27.6)	4 (20.0)	11 (27.5)	14 (31.1)
Some college	25 (23.8)	6 (30.0)	12 (30.0)	7 (15.6)
No data	1 (1.0)	...	...	1 (2.2)
Marital status				
Never married	11 (10.5)	1 (5.0)	5 (12.5)	5 (11.1)
Married	62 (59.0)	11 (55.0)	27 (67.5)	24 (53.3)
Divorced, separated	21 (20.0)	5 (25.0)	5 (12.5)	11 (24.4)
Widowed	10 (9.5)	3 (15.0)	3 (7.5)	4 (8.9)
No data	1 (1.0)	...	...	1 (2.2)
Employment				
Employed	34 (32.4)	3 (15.0)	12 (30.0)	19 (42.2)
Retired	54 (51.4)	14 (70.0)	23 (57.5)	17 (37.8)
Unemployed	16 (15.2)	3 (15.0)	5 (12.5)	8 (17.8)
No data	1 (1.0)	...	...	1 (2.2)
Annual income				
<$5000	26 (24.8)	6 (30.0)	10 (25.0)	10 (22.2)
$5000-$14 999	45 (42.9)	8 (40.0)	18 (45.0)	19 (42.2)
>$15 000	29 (27.6)	6 (30.0)	11 (27.5)	12 (26.7)
No data	5 (4.8)	...	1 (2.5)	4 (8.9)
Feedback				
Yes	52 (49.5)	10 (50.0)	20 (50.0)	22 (48.9)
No	53 (50.5)	10 (50.0)	20 (50.0)	23 (51.1)

Statistical Analyses

Significant differences in average compliance (defined by two measures) among the three dose frequencies were detected with Bonferroni t tests and Scheffe's tests. Similar bivariate tests were performed for the relationship between compliance (definition 2) and demographic, health status, and attitudinal variables. A stepwise regression was used to assess the multivariate relationship between compliance (dependent variable, definition 2) and prescribed daily dose frequency, sociodemographic characteristics, and scale scores derived from the questionnaire.

RESULTS

The study population was male, the median age was 61 years, 83% were black, half had graduated from high school, most were married or widowed, half were retired and one third were employed, and median income was less than $15 000 annually (Table 1). No significant differences in sociodemographic attributes or the proportion of patients whose health care providers received feedback about their compliance were found among the three-dose frequency groups.

Mean patient compliance (definition 1) was higher on a once- (96.0%) or twice- (93.0%) daily dose regimen compared with a three (83.8%) times a day dose regimen ($P<.05$) (Table 2). Once- and twice-daily regimens were not significantly different from each other.

More detailed insight into compliance was obtained by examining mean daily compliance (definition 2) (Table 3). The percent of days on which the prescribed number of doses were removed increased dramatically with decreasing dose fre-

Table 2.—Mean Percent of Prescribed Doses Removed From Compliance Monitors (Definition 1) as a Function of Prescribed Daily Dose Frequency

Prescribed Daily Dose Frequency	No. of Patients	Mean Compliance in Percent (SD)
One	45	96.0 (6.9)
Two	40	93.0 (11.9)
Three	20	83.8 (15.3)*

*Three times daily is significantly different from both once and twice daily ($P<.05$). Once- and twice-daily groups are not significantly different from each other.

Table 3.—Mean Percent of Medication Days During Which the Indicated Proportion of Prescribed Doses Were Removed From Compliance Monitors (Definition 2) as a Function of Prescribed Daily Dose Frequency

Prescribed Daily Dose Frequency	No. of Patients	Percent (SD) of Days With Compliance		
		<100	100	>100
One	45	13.0 (18.4)	83.6 (19.9)	3.3 (2.7)
Two	40	19.2 (18.0)	74.9 (20.2)	5.7 (5.6)*
Three	20	36.1 (29.1)†	59.0 (30.2)†	4.8 (3.9)

*Twice daily is significantly different from once daily ($P<.05$).

†Three times daily is significantly different from both once and twice daily ($P<.05$). Once- and twice-daily groups are not significantly different from each other.

quency. Thus, for patients on a thrice, twice, or once daily antihypertensive medication dose regimen, the prescribed number of doses were removed on 59.0%, 74.9%, and 83.6% of days, respectively. Contrariwise, the percent of days on which less than the prescribed number of doses were removed decreased with decreasing dose frequency (from 36.1% to 19.2% to 13.0%). The three-times daily regimen was significantly different from the once- and twice-daily regimens ($P<.05$) for both compliance estimates.

One explanation for the inverse relationship between daily dose frequency and compliance is that patients in the three-dose frequency groups may have had different sociodemographic or health attitudes or different responses to feedback from their health care providers. Using a stepwise regression procedure, 28 sociodemographic and health attitude variables (see 'Subjects and Methods' section) and feedback group were examined to determine their relationship to compliance. The following factors predicted better compliance: once- ($P<.0001$) and twice- ($P<.0001$) daily medication regimens, higher income ($P<.0002$), education greater than elementary school ($P<.007$), living alone ($P<.005$), and being employed ($P<.004$).

Thus, while patient attributes other than dose regimen do contribute to the observed differences in compliance, they do not negate the large effect of dose regimen.

COMMENT

This study demonstrates that in a group of older, male patients receiving long-term treatment for hypertension in a continuity of care environment, once or twice daily dose regimens are associated with moderately improved monthly pill counts (definition 1, 95.2% and 93.0%, respectively) by comparison with a three-times daily regimen (83.8%). When compliance is defined as the percent of total medication days on which the prescribed number of doses are removed (definition 2), patients on a once-daily dose regimen were found to remove the prescribed number of doses on 83.6% of days, while patients on two- or three-times daily dose regimens removed the prescribed number of doses on only 74.9% and 59.0% of days, respectively. The difference in compliance when measured with the pill count and daily methods dramatically demonstrates the degree to which poor compliance is underestimated with the simple pill count method.

Two caveats should be noted in the interpretation of this study. A large proportion of eligible patients (76%) declined to participate and 13% of patients who initially agreed to participate subsequently withdrew. This suggests that selection bias may be present. Indeed, patients who volunteer to participate in research projects are probably more compliant than those who refuse.[24] The relationship between prescribed dose frequency and compliance in the ostensibly less compliant nonparticipants cannot reliably be predicted.

Because of the organization and treatment protocol of the hypertension clinic in which our research was performed, the stronger experimental design afforded by a randomized controlled trial was not possible. Instead, subjects who were already under treatment were recruited and known or alleged covariates of noncompliance (in addition to prescribed medication frequency) were compared with dose frequency groups. The analysis supports the conclusion that improved compliance is a true effect of decreased dose frequency.

Only one other study has used an electronic monitor to examine the relationship between prescribed dose frequency and compliance. Cramer et al,[10] measuring compliance with data derived from pill containers that recorded the time and date of bottle cap removal and replacement, found that compliance (defined using definition 2) for medications prescribed once, twice, three, or four times daily was 87%, 81%, 77%, and 39%, respectively. Statistically significant differences were identified only for the daily vs four times daily and twice daily vs three times daily regimens, perhaps because of their small sample size (24 patients).

In conclusion, our study demonstrated that as the daily prescribed dose frequency decreased from three times to once daily, medication compliance (defined as the proportion of days on which the prescribed number of doses were removed from the compliance monitor) improved by 42%. A large number of medications are currently available that are effective when administered once or twice daily. Therefore, probably the simplest and single most important action that health care providers can take to improve compliance is to select medications that permit the lowest daily dose frequency possible.

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