Gaps in Cardiovascular Medication Taking:

The Tip of the Iceberg

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Objective: To search for major gaps in medication-taking behavior predisposing patients to cardiovascular morbidity and mortality.
Design: Convenience sample; cohort prospectively followed for ≤5 months.
Setting: General internal medicine and cardiology clinics in a university medical center.
Patients: From among 893 patients, the authors identified 132 eligible individuals and entered 33 subjects (25%) with chronic cardiovascular conditions, 1–3 chronic oral medications for these conditions, overall regimen of ≤6 drugs, regular visits at 1–3-month intervals, literacy in English, willingness to use electronic monitors, and physician permission to participate.
Outcome measures: Medication compliance rates and patterns by patient self-report, physician estimates, pill count, and electronic monitoring of pill vial opening.
Results: Despite moderately complex regimens (5.4 ± 0.5 pills daily; range 1–11), most subjects took most medications according to the prescription: median intervals between pill vial openings were 1.00, 0.50, and 0.43 days for once, twice, and three times daily dosing, respectively. Medication-taking gaps of ≥2 times the prescribed interdosing interval occurred for 48% of the patients. Patients' dosing patterns often produced "uncovered" intervals (mean duration 3.7 days, range 0–25) with doubtful pharmacologic effectiveness. These lapses were underestimated by patients and poorly perceived by their treating physicians, despite familiarity with their care. Baseline sociodemographic, psychosocial, medical system, or clinical characteristics did not predict the patterns or degrees of medication noncompliance.
Conclusions: Major treatment gaps occur frequently, even in carefully selected ambulatory populations, and generally escape detection. The compliance patterns and gaps may contribute to reported excesses of cardiovascular morbidity and mortality.
Key words: medication compliance; drug therapy; cardiovascular disease; electronic monitoring; predictors; compliance measures; morbidity; mortality.
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THE PRESCRIPTION and consumption of oral medication are fundamental to much of outpatient clinical practice, yet we know surprisingly little about medication-taking behavior. Despite considerable data to the contrary,[1-4] many clinicians believe that they can successfully recognize and interpret deviations from the prescription. More critically, most clinicians identify few consequences from suboptimal compliance and conclude that any decreased therapeutic benefit is the patient's own fault.

Several investigators have recently confirmed that 1) medication taking is frequently imperfect,[5-11] 2) partial compliance with prescribed regimens is difficult to diagnose from self-report or pill counts.[11, 12] and 3) suboptimal medication taking may lead to additional hospitalizations[13] and increased rates of coronary events.[14] Coronary events were especially prevalent among patients prescribed nadolol or propranolol for uncomplicated hypertension but displaying <80% compliance by prescription refill rates.[14] Major gaps in taking cardiovascular drugs might predispose patients to fluctuating drug concentrations and to withdrawal phenomena. To assess whether such treatment gaps actually occur, we used electronic monitors to evaluate medication-taking patterns among outpatients receiving cardiovascular medications.

METHODS

We carried out a descriptive study of ambulatory patients at the Stanford University Medical Center.

Subjects

Over two months, we reviewed the medial records of all patients scheduled for appointments in primary care and cardiology clinics. We sought individuals with 1) chronic conditions, 2) one to three chronic oral cardiovascular medications and six or fewer different drugs in their regimens, 3) regular return visits to the index clinic at one- to three-month intervals, 4) ability to read and write English, and 5) willingness to use a specialized medication dispenser and to return it at study completion. All participating subjects gave informed consent. All prescribing physicians permitted us to approach the patients, understanding that the study would not interfere with the physicians' usual prescribing practices. We deliberately selected a population whose self-reported medication-taking behavior would likely be near-optimal, whose socioeconomic characteristics removed most external constraints on high compliance (e.g., poor comprehension of English, inability to pay for prescribed medications, or prolonged intervals between visits), and whose clinical status was stable. We hoped to demonstrate that potentially serious gaps in medication taking still occurred.

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TABLE 1
Subject Characteristics

	Whole Group ($n = 33$)	Full Data ($n = 25$)	Partial Data ($n = 8$)	Significance—Full vs Partial
Age—mean ± SEM (range)	56.0 ± 2.4 (32–80) years	54.2 ± 2.7 (33–76) years	60.7 ± 4.8 (32–80) years	t = −1.21 (df 31) p = 0.24
Gender—male	64%	68%	50%	Chi-square (df 1)* = 0.25 p = 0.62
Marital status		($n = 24$)		
Single	12%	13%	13%	
Married	52%	46%	62%	Chi-square (df 3)* = 4.33
Divorced	24%	33%	0%	p = 0.31
Widowed	12%	8%	25%	
Number in household—mean ± SEM (range)	2.2 ± 0.2 (1–5)	2.1 ± 0.2 (1–4)	2.2 ± 0.3 (1–4)	t = −0.267 (df 31) p = 0.79
Highest level of education completed				
≤12th grade	6%	5%	14%	
1–3 years of college	45%	42%	57%	Chi-square (df 3)* = 3.41
Completed college	16%	17%	14%	p = 0.49
Some graduate school	32%	38%	14%	
Household income (annually)	($n = 30$)	($n = 23$)	($n = 7$)	
<$10,000	17%	13%	29%	
$10,000–29,999	30%	29%	29%	Chi-square (df 3)* = 2.40
$30,000–49,000	17%	21%	0%	p = 0.67
≥ $50,000	37%	38%	42%	
Principal health insurance				
Private indemnity insurance	24%	20%	38%	
Prepaid capitation	27%	32%	12%	Chi-square (df 4)* = 5.41
Medicaid (Medi-Cal)	21%	20%	25%	p = 0.25
Medicare	24%	28%	12%	
Other	2%	0%	12%	
Insurance for prescription drugs	($n = 31$)	($n = 24$)	($n = 7$)	
Pays no drug costs	13%	13%	14%	
Pays some costs after deductible	45%	42%	29%	Chi-square (df 4)* = 2.79 p = 0.59
Pays all drug costs	19%	8%	43%	
Pays for only some drugs	16%	25%	14%	
Principal cardiovascular diagnoses				
Hypertension	46%	56%	12%	
Angina	15%	8%	36%	Chi-square (df 4)* = 6.68
Arrhythmia	15%	12%	24%	p = 0.15
Congestive heart failure	12%	12%	12%	
≥ 2 diagnoses	12%	12%	12%	

*All categorical comparisons were not statistically significant by Fisher's exact test as well.

Medication Monitor

We employed the MEMS-3 (Aprex Corporation, Fremont, CA), a plastic pill vial with a microcircuitry concealed in its cap. The device recorded the precise time of each vial opening and closing for subsequent retrieval. We dispensed one MEMS vial with each cardiovascular medication for each patient (maximum three per patient) and verbally reminded them to dispense each pill just before consumption. No information from the monitor was fed back to either the patient or the prescribing physician.

We defined compliance differently by pill count and by electronic monitor. By monitor, compliance was the number of observed vial openings by intervisit interval as a percentage of the prescribed openings. We used the monitor output to generate tables and graphs of intervals between openings and scanned the data to

confirm opening for direct consumption rather than predispensing of pills for delayed consumption. Finally, we performed pill counts on the remaining medications to validate the vial openings. By pill count, compliance was defined as the number of missing pills as a percentage of the prescribed pills for the intervisit interval.

To identify patterns of medication-taking behavior, we took liberties with the pharmacokinetic dissimilarities among the drugs. We calculated the proportion of days during which the patient would likely be "uncovered," given the duration of drug effect and the observed interopening interval, or time between openings of the pill vial. We selected two reasonable but arbitrary compliance criteria, based on the duration of drug effect: 1.25 and 2.00 times the prescribed interdosing interval. For example, by the "1.25 × dosing" criterion, a regimen of atenolol once every 24 hours would generate "uncovered days" if the interopening interval were ≥30 hours, and by the "2.00 × dosing" criterion if the interopening interval were ≥48 hours. Exceeding the 1.25 × dosing criterion would reflect moderate deviation with intermediate likelihood of producing important variation in blood concentrations. Such variability would be important to avoid for some drugs such as antiarrhythmic medications. Exceeding the 2.00 × dosing criterion would yield a high likelihood of important variation in blood concentrations for most drugs. For ease of comparison we converted the number of uncovered intervals (hours) into the corresponding number of uncovered days by dividing the uncovered period by 24 hours per day.

Study Sequence

Participating subjects completed a five-minute self-administered questionnaire at the initial clinical visit and repeated the process at the final clinic visit one to five months later. The instrument explored patients' 1) sociodemographic characteristics, 2) understanding of the current regimen (drug name, purpose, dosing), and 3) self-reports of medication-taking behavior. Prescribing physicians completed a one-page self-administered questionnaire after each patient's final study visit, estimating 1) the patient's average compliance since the prior visit, 2) the physician's confidence in the estimate, and 3) the degree to which the patient had achieved all therapeutic goals.

Data Analysis

We employed proprietary Apex Corporation software for downloading and summarizing data from the electronic medication monitors and the Stata statistical program for descriptive statistics, correlation coefficients, Student's t-test, chi-square, and Fisher's exact tests, analysis of variance, and simple, multiple, and stepwise linear regression analyses in search of predictors. We reported most central tendencies as the mean ± 1 SEM and used $p = 0.05$ as the upper limit of statistical significance, except where otherwise noted. When data deviated markedly from symmetrical, unimodal patterns, we used the median and range to summarize distributions.

RESULTS

Subject Characteristics

Our original review of 893 medical records from clinic appointment lists identified 132 patients who potentially met our entry criteria. Follow-up by contacting the primary physicians and patients reduced the study group for a variety of reasons: 1) primary physicians did not give explicit permission (19 patients, 14%); 2) patients declined participation (48, 36%), 3) patients were unable to speak or read English (11, 8%); and 4) patients insisted on their own alternative pill dispensers (21, 16%).

A total of 33 subjects (25% of the originally eligible cohort) actually entered the study, and 25 individuals provided a complete patient data set, including full electronic monitoring and questionnaires before and after the monitoring. Among the eight subjects with an incomplete data set, five declined to complete the second questionnaire, two discontinued participation after less than one week, and one failed to return the electronic monitor despite reminders. Table 1 summarizes the subjects' characteristics. There was no significant sociodemographic, psychosocial, or clinical difference between those subjects with and those without a full data set. In essence, we studied a group of predominantly middle-aged, relatively affluent, and well-educated patients with relatively stable disease and few obvious constraints on obtaining and taking their cardiovascular medications as prescribed.

Initial Regimen Characteristics

At the initial visit, the study subjects reported a mean of 3.6 ± 0.3 different medications each day (range 1–6), totaling an average of 5.4 ± 0.5 pills daily (range 1–11). Prescriptions called for drug administration a mean of 2.3 ± 0.2 times each day (range 1–6). In decreasing order of monitored frequency, the most common regimens included enalapril (8 patients), diltiazem (7), digoxin (5), nifedipine (4), Dyazide (3), and atenolol (3).

Self-reported Compliance

By self-report, the 33 respondents claimed near-perfect compliance for the preceding 48 hours, consuming 98% of the pills prescribed for the two-day interval. The timing of particular prescribed doses was less ideal: only 82% were taken "on schedule." Only two of the 33 individuals acknowledged *any deviation*

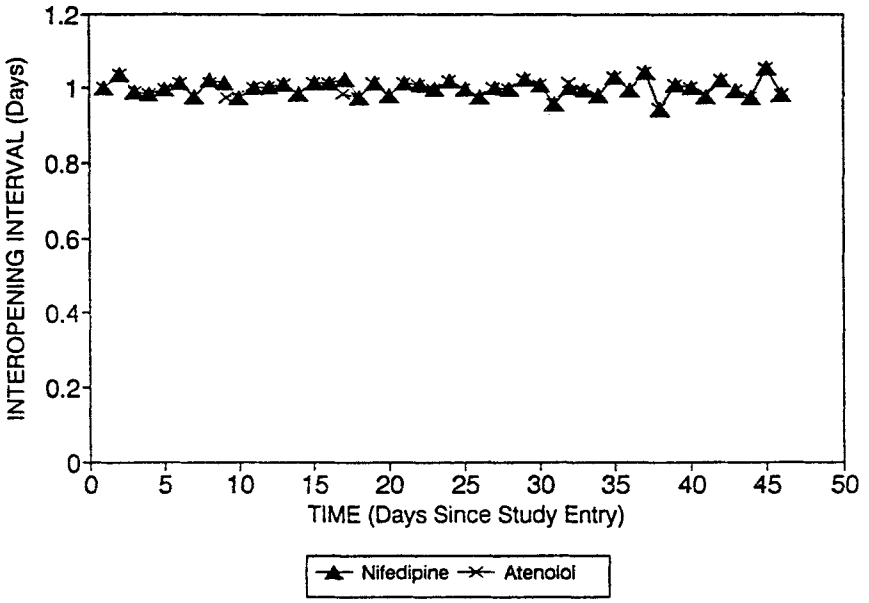

FIGURE 1. Optimal medication taking over time for a 76-year-old man receiving nifedipine and atenolol therapy, one tablet of each once daily. Interopening intervals by medication monitor: mean 0.98 ± 0.15 days; median 1.00 day (range 0.94–1.25).

from the prescription, both in the direction of omitted doses.

Self-reported Attitudes and Barriers

The majority of respondents had favorable *attitudes* despite legitimate barriers for medication compliance. They agreed that 1) the treated condition was serious (86% of the respondents), 2) they were personally at high risk of complications without treatment (86%), 3) the prescribed treatment was effective (86%), 4) they understood their regimen satisfactorily (100%), and 5) they felt themselves capable of following all regimen-related instructions (95%). Among perceived *barriers* to optimal medication taking, the respondents reported interference with daily schedule

TABLE 2

Regimens and Compliance Rates

	1 Time per Day	2 Times per Day	3 Times per Day	All Regimens
Number of patients	20	8	2	25
Number of monitored regimens	30	8	2	40
Monitoring duration				
Median	55 days	90 days	56 days	84 days
(95% CI)	*(49–92 days)*	*(49–131 days)*	*(56 days)*	*(54–99 days)*
Range	35–141 days	49–131 days	56 days	35–141 days
Compliance rates				
Pill count—mean ± SEM	87.8 ± 4.6%	94.1 ± 2.5%	87.6 ± 5.6%	88.7 ± 3.8%
(95% CI)	*(37.1–138.5%)*	*(77.4–110.8%)*	*(16.5–158.8%)*	*(51.6–125.8%)*
Medication monitor—mean ± SEM	81.8 ± 5.3%	75.9 ± 12.7%	72.4 ± 19.8%	78.3 ± 6.0%
(95% CI)	*(23.2–140.3%)*	*(−9.1–160.9%)*	*(−179.2—324.0%)*	*(1.5–155.1%)*
Interopening intervals				
Mean ± SEM	1.01 ± 0.03 days	0.58 ± 0.05 days	1.04 ± 0.42 days	0.94 ± 0.07 days
(95% CI)	*(0.68–1.34 days)*	*(0.25–0.91 days)*	*(−4.3–6.4 days)*	*(0.41–1.47 days)*
Median	1.00 day	0.50 days	0.43 days	0.85 days
(95% CI)	*(0.99–1.00 day)*	*(0.48–0.96 days)*	*(0.34–0.52 days)*	*(0.95–1.00 day)*
Range	0.08–21.0 days	0.09–9.11 days	0.34–25.0 days	0.08–25.0 days
"Uncovered" days (1.25 × dosing)				
Median	2.4%	11.1%	42.5%	5.5%
(95% CI)	*(0–10.9%)*	*(1.0–70.8%)*	*(20.6–64.4%)*	*(2.0–11.0%)*
Range	0–59.7%	1.0–70.8%	20.6–64.4%	0–70.8%
"Uncovered" days (2.00 × dosing)				
Median	0.02%	1.7%	35.2%	0.05%
(95% CI)	*(0–3.0%)*	*(0–10.7%)*	*(16.7–53.6%)*	*(0.0–3.1%)*
Range	0–47.9%	0–10.7%	16.7–53.6%	0.0–53.6%

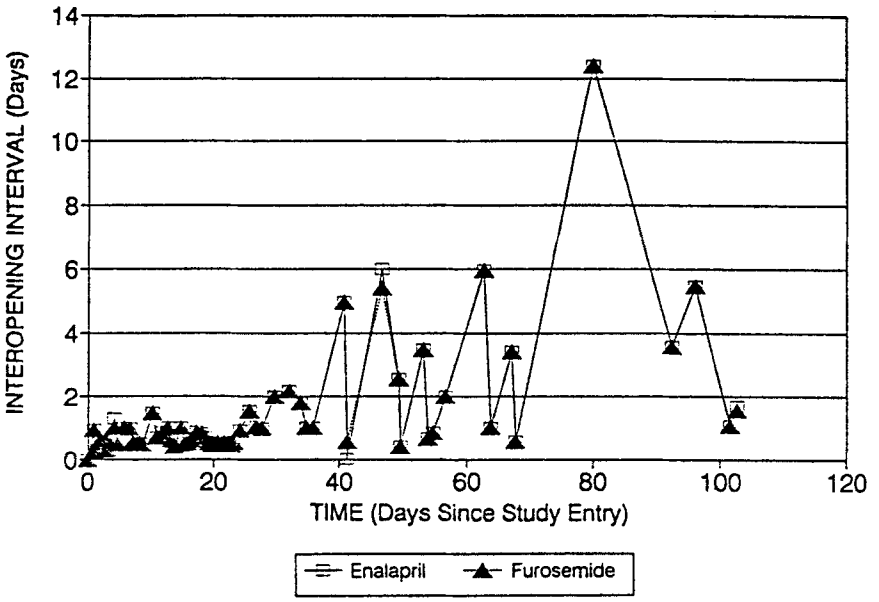

FIGURE 2. Suboptimal medication taking over time for a 35-year-old woman receiving enalapril and furosemide therapy, one table of each twice daily. Interopening intervals by medication monitor: mean 1.51 ± 1.96 days; median 0.87 days (range 0.3–12.4); "uncovered" days [see text] at "2.00 × dosing" = 44%.

(38%), inability to remember their pills (37%), and drug-related side effects (23%) more prominently than prohibitive cost (19%), uncertainty about the drug's value (12%), difficulty swallowing the pills (8%), or personal embarrassment at taking medication (4%).

Medication Taking by Pill Count and Monitor

Table 2 summarizes the data describing medication-taking behavior by pill count and electronic monitor. The period of observation by electronic monitor covered a median of 84 days (range 35–141), corresponding to the interval between two scheduled appointments. For both once-daily and twice-daily regimens, the median intervals between medication vial openings closely approximated the prescription. The small number of subjects ($n = 2$) requiring three daily doses limits generalizability. Most subjects took most doses of most medications quite well. Assessments by pill counts and medication monitors showed high intermeasure correlation by subject ($r = 0.588$; 95% CI = 0.252–0.797) and similar pill count versus monitor compliance rates (mean paired sample difference 4.9%; 95% CI = −17.9–27.9%; $t_{21} = 1.23$; $p = 0.231$).

In contrast, some patients experienced important gaps in the timing of doses. The relatively small numbers of patients (≤8) for any one drug precluded strong statements about inter-regimen differences. The median number of medication-taking gaps exceeding 2.00 × dosing per subject was 1 (range 0–14) with an average duration of 3.7 days (range 0–25). All but four patients (84%) had at least one dosing interval that exceeded 25% of the prescribed interval between dosings. Fully 14 of 25 subjects (56%) had at least one dosing interval that exceeded twice the prescribed interval between dosings.

Figures 1 and 2 illustrate the extremes of the medication-taking patterns we observed. They summarize the vial opening-to-opening intervals for two subjects, each prescribed two different cardiotropic medications. Figure 1 shows a near-perfect pattern with no uncovered days and almost precisely 24 hours between openings. Figure 2 shows episodic and progressive lengthening of the interopening interval from the prescribed 0.5 days to 1–2 weeks between openings. The pharmacologic coverage was suboptimal on 44% of the days by the 2.00 × dosing criterion, falling short of steady-state conditions at the return visit.

Using the criterion of 2.00 × dosing, we generated the distribution in Figure 3, which summarizes the average number of uncovered days for the 25 subjects with full monitoring. Because several patients produced monitor patterns for more than one drug, we used the average percentage of uncovered days per subject to generate the figure. The distribution readily falls into three subgroups: 1) *near-optimal compliers* (52% of the group) at ≥80% of the prescription for both the number and the timing of their medications; 2) *partial compliers* (40% of the group) at 40–79% of the prescription; and 3) *noncompliers* (8% of the group) at <40% of the prescription.

Correlation of Compliance with Baseline and Process Predictors

Few baseline *sociodemographic* characteristics significantly predicted subsequent compliance rates or patterns by pill count or by medication monitor. Male gender was associated with higher pill count compliance rates than was female gender ($t_{20} = 3.39$; $p = 0.003$), but medication monitor rates did not correlate significantly with gender. There were also trends ($0.10 > p > 0.05$) for lower educational level and

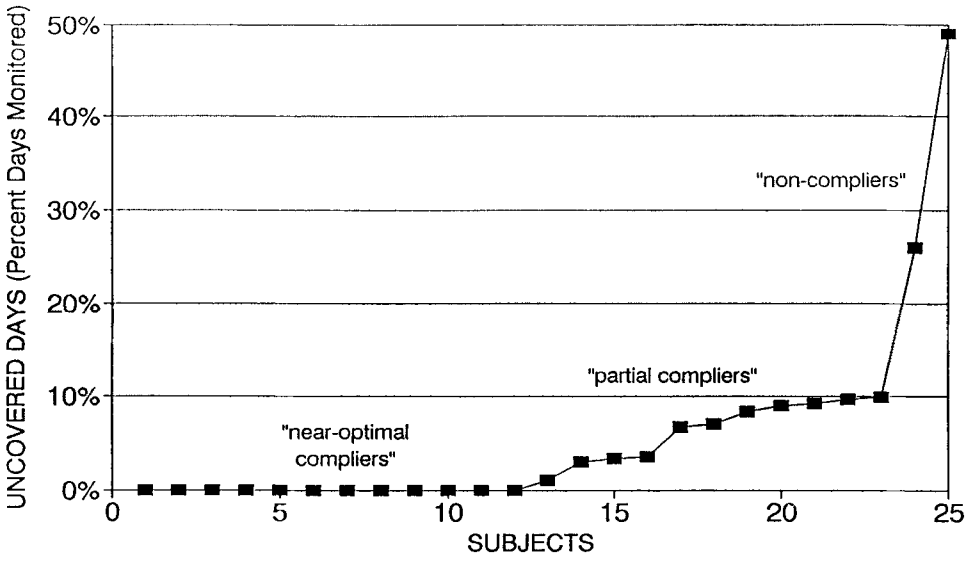

FIGURE 3. "Uncovered" days from gaps in medication taking: distribution, by subject, of the percentage of study days in which interopening intervals of at least twice the prescribed interdosing interval passed without drug dispensing, forming three patient clusters: near-optimal compliers, partial compliers, and noncompliers.

lower household income to be associated with lower compliance rates by pill count but not by medication monitor.

Among the *self-reported barriers*, there were trends ($0.20 > p > 0.10$) for difficulty remembering and high cost of medications to impair compliance but no correlation with perceived seriousness or susceptibility for the medical condition nor with self-efficacy in the treatment. The small sample size precludes formal testing of the health belief model.[15, 16] When examined by multiple and stepwise regression, none of the baseline predictors exhibited significant predictive ability, in part because of small sample size.

The predictive value of *regimen* parameters was limited. The total number of medication-taking gaps correlated closely with their mean duration ($r = 0.858$; 95% CI = 0.399–0.995; $p = 0.000$) but with neither the number of medications nor the total of pills. The mean interopening interval for the five doses before the scheduled visit, equivalent to steady-state conditions, predicted both the number ($F_{2,19} = 19.93$; $p = 0.000$; $R^2 = 0.677$) and the duration ($F_{2,19} = 47.77$; $p = 0.000$; $R^2 = 0.834$) of treatment gaps between scheduled visits.

None of the *medical system* variables such as medical insurance or drug coverage by insurance served as predictors of compliance rates.

Physicians' Judgment of Their Patients' Compliance

Despite numerous requests, we obtained completed physician questionnaires for only 14 of the 25 patients (56%) with an otherwise full data set. These 14 patients did not differ significantly from those without such estimates. Eleven of the physician respondents (79%) were faculty, the remainder housestaff. The individual physicians were familiar with the studied patients: 29% had seen the same patients for three to six previous clinic visits, and 57% had treated them for more than six visits or more than one year. All the physician respondents agreed that their patients understood "perfectly" what they were supposed to do in taking the prescribed medication. The respondents concluded that the patients had achieved all (29%) or most (57%) of the therapeutic goals for the visit. The responding physicians estimated their patients' compliance rates for prescribed number and timing of medications at an average of 91.6 ± 1.7% (range 80–100%). Moreover, all respondents were extremely (>80%; 79% of the respondents) or moderately (50–80%; 21% of the respondents) confident of this estimate. Higher estimates of compliance were associated with higher confidence in the estimate ($r = 0.698$; $p = 0.006$).

On average, physicians' estimated compliance rates approximated global assessments by patients themselves (mean difference 0.21 ± 3.7%; range −20 to +30%; $t_{13} = 0.06$; $r = 0.220$, NS). These favorable estimates showed poor correlation with compliance rates by pill count or by medication monitor ($r = -0.100$, NS).

DISCUSSION

The current study arose in response to several issues raised by the report of Psaty and coworkers.[14] They noted that partial compliance with antihypertensive medications was associated with nearly a fivefold increase in coronary heart disease events compared with near-perfect compliance, even among low-risk hypertensive patients. This striking finding was one of the first demonstrations of concrete, negative consequences from failing to take medications as prescribed. They ascribed much of the consequences to using β-blockers, which are prone to rebound phenomena or to heightened β-receptor sensitivity upon brusque cessation of medication.[17-19]

Our data confirm that a subset of patients have

important gaps in their medication-taking behavior, which might produce major swings in drug concentrations, blood pressure control, and myocardial workload. Such events might occur among few patients and still account for a disproportionate share of cardiovascular morbidity and mortality. They might even explain some coronary deaths among patients with moderate rather than mild reductions in blood pressure after treatment.,[20] the so-called "J-curve phenomenon."[21-23]

We confirmed previous reports of three important subgroupings of outpatients by their degree of adhering to the prescribed regimen. Reported patterns are similar among outpatients receiving antiglaucoma eyedrops[4, 24, 25] or antiseizure pills.[6, 8, 26] The largest single group consists of *near-optimal compliers*, accounting for 50–60% of the total. Such individuals appear convinced about the value of treatment and are effective in maintaining dosing frequency within acceptable limits. The second group, totaling 30–40% of ambulatory patients, are *partial compliers*. These individuals accept the principle of treatment but fail to adhere with sufficient consistency to avoid clinical problems.[6] Their most common deviation is dose omission. Prolonged dosing gaps carry risks of submaximal clinical benefit, withdrawal or rebound phenomena, and clinicians' unnecessarily and inappropriately escalating the regimen. The final group, comprising up to 10% in most series,[4, 6, 8, 24-26] are *noncompliers*. Even if their intentions are excellent, their execution remains poor. Some patients may take their medications especially well just before seeing their physicians, confounding the clinical assessment.[8]

Our data confirm the relative insensitivity of physicians, even when familiar with their patients, to identify major deviations in medication-taking behavior,[1-4] The insensitivity is greatest for dose omissions, particularly before a scheduled visit.[11] Finally, we confirm that some patients deviate markedly from the prescription, even with important cardiovascular disease. Similar deviations emerged among patients taking digoxin up to three months posthospitalization,[27] taking antiarrhythmic agents prescribed for potentially life-threatening, mostly ventricular arrhythmias,[28] and on admission to an acute care hospital for apparent noncompliance.[29] Many patients with symptomatic cardiovascular disease keep appointments while failing to take medications as prescribed.[30] Comparable patterns with poor clinical outcomes may occur among patients with hematologic malignancies[31, 32] and organ transplantation.[33-35] Abrupt withdrawal from β-blockers coupled with catecholamine surges on first arising or with exercise thus represents just another example of the same phenomenon.[36-38]

Our study population is not representative of all clinical populations or all treatment settings. The study's generalizability is further limited by small sample size, highly self-selected patients, and lack of outcome data. Our data likely represent an underestimate of the prevalence and degree of partial compliance. Simplifying the pharmacology allowed us to monitor dissimilar compounds for underlying patterns rather than seeking more atypical subjects on standardized regimens. More extensive studies will be needed to examine predictors of medication-taking behavior and resultant clinical outcomes.

Satisfactory adherence to the regimen should never be assumed, since some potentially important gaps may occur in up to 40% of outpatients. Regular inquiries about obstacles to full compliance should occur at each visit in nonconfrontational ways, seeking solutions rather than fault finding. Whenever reasonable, longer-acting preparations should be preferred to blunt the impact of gaps in medication taking.[39, 40] Electronic monitoring may prove useful for selected patients when therapeutic goals remain elusive despite apparent compliance.[11]

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