A Systematic Review of the Associations Between Dose Regimens and Medication Compliance

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ABSTRACT

Background: Previous reviews of the literature on medication compliance have confirmed the inverse relationship between number of daily doses and rate of compliance. However, compliance in most of these studies was based on patient self-report, blood-level monitoring, prescription refills, or pill count data, none of which are as accurate as electronic monitoring (EM).

Objective: In this paper, we review studies in which compliance was measured with an EM device to determine the associations between dose frequency and medication compliance.

Methods: Articles included in this review were identified through literature searches of MEDLINE®, PsychInfo®, HealthStar, Health & Psychosocial Instruments, and the Cochrane Library using the search terms *patient compliance, patient adherence, electronic monitoring,* and *MEMS* (medication event monitoring systems). The review was limited to studies reporting compliance measured by EM devices, the most accurate compliance assessment method to date. Because EM was introduced only in 1986, the literature search was restricted to the years 1986 to 2000. In the identified studies, data were pooled to calculate mean compliance with once-daily, twice-daily, 3-times-daily, and 4-times-daily dosing regimens. Because of heterogeneity in definitions of compliance, 2 major categories of compliance rates were defined: dose-taking (taking the prescribed number of pills each day) and dose-timing (taking pills within the prescribed time frame).

Results: A total of 76 studies were identified. Mean dose-taking compliance was 71% ± 17% (range, 34%–97%) and declined as the number of daily doses increased: 1 dose = 79% ± 14%, 2 doses = 69% ± 15%, 3 doses = 65% ± 16%, 4 doses = 51% ± 20% ($P < 0.001$ among dose schedules). Compliance was significantly higher for once-daily versus

This report was presented in part at the European Congress of Clinical Psychopharmacology, London, England, September 1999.

Accepted for publication May 24, 2001.

0149-2918/01/$19.00

3-times-daily ($P = 0.008$), once-daily versus 4-times-daily ($P < 0.001$), and twice-daily versus 4-times-daily regimens ($P = 0.001$); however, there were no significant differences in compliance between once-daily and twice-daily regimens or between twice-daily and 3-times-daily regimens. In the subset of 14 studies that reported dose-timing results, mean dose-timing compliance was 59% ± 24%; more frequent dosing was associated with lower compliance rates.

Conclusions: A review of studies that measured compliance using EM confirmed that the prescribed number of doses per day is inversely related to compliance. Simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes.

Key words: compliance, adherence, electronic monitoring, MEMS, dosing regimen. (*Clin Ther.* 2001;23:1296–1310)

INTRODUCTION

Physicians are trained to diagnose a disorder and select an appropriate medication based on pharmacokinetic (eg, absorption, metabolism, elimination, and interaction) and pharmacodynamic (eg, adverse effects) properties. However, even the most carefully chosen and optimal medication cannot work if the patient does not take it appropriately. Medication compliance, an essential component of a successful health outcome, is largely in the domain of the patient. The responsibility for fulfillment of the prescribed regimen lies with the patient. Unfortunately, both clinical experience and the literature describe medication compliance as inadequate.

Patients can be classified into 1 of 3 general compliance categories: (1) full compliers, who take adequate amounts of medications to control the disorder; (2) partial compliers, who take many doses, but not regularly enough to control the disorder; or (3) noncompliers, who take few or no doses, and whose disorder is unaltered. These definitions cannot be described in terms of a specific proportion of doses because rarely is the threshold amount of medication known. One report noted that patients taking at least 80% of antihypertensive medication were more likely to achieve blood pressure control than patients taking <80%.[1] However, this cutoff point of 80% cannot be arbitrarily extrapolated to other disorders or other types of medications.

Although physicians have long been aware of partial compliance and noncompliance, the methods of ascertaining compliance have greatly improved over time. Standard measures of medication compliance include patient self-report, blood-level monitoring, prescription refills, pill count, and electronic monitoring (EM).

Compliance data based on patient self-report may be erroneous not because patients consciously falsify dosing reports, but because patients may forget about doses taken or missed. If a patient forgets to take a dose, he or she cannot then recall the dosing event in the patient report; in the memory of the patient, there is no record of planned or inadvertently missed doses.[2,3]

Blood-level monitoring can be misleading because most drugs are rapidly absorbed after dosing. Thus, even if numerous doses were omitted but a few doses were taken immediately before the blood test, the results would show the presence of a moderate amount of drug.[4] Metabolites and other pharmacokinetic parameters can be useful in assessing long-term compliance for some drugs.

Prescription refills are considered questionable for assessment of dosing compliance because they provide no information on timing or quantity of intake. For example, many patients request refills regularly when reminded, even if they have not run out of drug (and particularly if there is no cost), whereas others stockpile medications or have quantities of medications in several areas for convenience.[2]

Pill counts are often erroneous because patients do not always return bottles that have pills remaining. The accuracy of the pill count method is adequate when compliance is excellent because there is nothing to return; however, in cases of low compliance, the pill count is not accurate.[5,6]

EM is considered accurate because this relatively new technology records the time and date of actual dosing events. EM units commonly use microprocessors to record the precise time that a dose is removed from the EM unit. Medication events (ie, removal from the unit) can be tabulated into dose-taking compliance rates (the EM record matches the prescribed number of doses per day) and dose-timing compliance rates (the EM record demonstrates that doses were taken at the appropriate time interval).[4] Measurement of medication compliance was recognized as a factor in medical care and treatment outcome with the convening of a workshop on the topic in 1979[7] and a second international workshop in 1987.[2] Since that time, EM has become recognized as the gold standard for compliance assessment.[4] However, even EM is not entirely accurate because opening the EM unit to remove a tablet or release a spray does not necessarily mean that the dose was taken.

Prescribers often can select from a variety of formulations with 1 or multiple daily doses. If available, once-daily dosing is an intuitively appealing choice for increasing patient compliance. A review of the compliance literature in 1984 that described higher compliance with fewer daily doses was based on self-report, blood-level monitoring, prescription refills, and pill count data.[8] The pattern of decreased compliance with more complex regimens was also confirmed in an early EM study.[4]

In this paper, we review studies in which medication compliance was measured by EM devices to determine the associations between dosing frequency and rates of medication compliance among patients with a variety of medical disorders.

MATERIALS AND METHODS

Articles included in this review were identified through literature searches of MEDLINE®, PsychInfo®, HealthStar, Health & Psychosocial Instruments, and the Cochrane Library for the years 1986 to 2000 (EM devices became available in 1986). The search terms used were *patient compliance, patient adherence, electronic monitoring,* and *MEMS* (medication event monitoring systems). Additional reports were selected from the references in the articles identified in the search. Articles were included in this review if dosing was evaluated with any type of EM device and medication compliance rates were reported. The reports were highly variable in the amount of information provided about study design and methods for calculation of compliance. Few reports mentioned whether the patients took medications in addition to the one(s) studied, or had other medical disorders.

Definitions

Patient compliance can be defined as taking medication as prescribed. Dosing can be assessed by dose-taking and dose-timing measures. Dose-taking measures assess whether the appropriate number of doses were taken during each day. Dose-timing measures assess whether the doses were taken within the appropriate time interval during the day, usually within 25% of the dosing interval (eg, twice-daily doses should be taken 12 ± 3 hours apart). Partial compliance can thus be defined either as taking less than the prescribed amount of medication or taking the medication at inappropriate intervals (hours between doses). Total noncompliance can be defined as discontinuation of treatment. However, some of the studies reviewed used a specific cutoff point (eg, 70%, 80%, or 90%) below which patients were considered noncompliant with the regimen.

Electronic Monitoring Devices

EM units vary in design from standard pill containers with a microprocessor chip embedded in the cap to medication boxes with compartments for individual doses to metered-dose inhaler canisters that release puffs of medication. Most of the EM devices monitor medication dosing using special containers that store dosing information on a microprocessor inside the unit until the data are downloaded into specialized software. Patients are shown how to use the devices and instructed not to open the unit except when medication needs to be removed for dosing. On return to the clinic, the unit is inserted into a communicator apparatus that reads the electronic information and transmits it to the computer.

One of the earliest commercially available EM devices was the Medication Event Monitoring System (MEMS®, APREX, Union City, California). This has been succeeded by the Electronic Drug Exposure Monitor (eDEM®, AARDEX, Zurich, Switzerland, and Union City, California), a newer version with revised technology and software to calculate usage of medication in standard bottle packaging. The MDI Chronolog® (Medtrac Technologies, Lakewood, Colorado) measures use of inhaled medication prescribed for respiratory diseases. Other devices have additional features such as multiple compartments or packaging in blister cards for electronic measurement. Devices developed for research use only include the eyedrop monitor used by Kass et al,[9,10] the blister card device used by Eisen et al,[11,12] and an electronic box used by Cheung et al.[13]

Statistical Analyses

Given the heterogeneity of the data and sources, the mean compliance rates from each study were extracted or tabulated and then averaged. Variance was not consistently reported or derivable from the data presented, so adjustment for comparison of means was not possible. For a subset of studies, dose-taking and dose-timing compliance rates were compared using analysis of variance. Because of the simple nature of the analysis and the multiple comparisons made between dose regimens, the most conservative approach for declaring significance—the Bonferroni adjustment—was used. The Bonferroni adjustment divides the significance level by the number of comparisons made. In this case, differences were significant if $P < 0.0083$.

RESULTS

Seventy-six studies were identified in which EM was used to determine dose taking or dose timing.[4,9–83] EM bottle caps were the most widely used devices, with 59 of 76 reports describing studies performed with MEMS® or eDEM® units. Table I lists the types of devices used; some EM units are used only for specific types of medications (eg, liquid and nebulized drugs).

Combining all data that specified dose-taking compliance, the overall rate of compliance with prescribed regimens was 71% ± 17% (range, 34%–97%). Mean compliance rates by prescribed dose regimen are listed in Table II; increasing the number of daily doses was significantly related to a decline in compliance ($P < 0.001$ among dose schedules). Comparisons between dose regimens showed that compliance was significantly higher with once-daily regimens versus 3-times-daily ($P = 0.008$) or 4-times-daily regimens ($P < 0.001$). Similarly, compliance with twice-daily dosing was significantly higher than with 4-times-daily dosing ($P = 0.001$). There were no significant differences in compliance between once-daily and twice-

Table I. Types of electronic monitoring devices and studies.

Electronic Monitoring Device	Type of Medical Disorder Evaluated	No. of Published Articles
Bottle caps	Various disorders	60
Pill box	Various disorders	2
Metered-dose inhaler	Lung disorders	10
Blister card	Various disorders	2
Eyedrop dispenser	Ophthalmologic disorders	2

Table II. Rate of dose-taking compliance by frequency of regimen.

Frequency of Regimen	No. of Reports*	Mean Dose-Taking Compliance (%)	SD (%)	Range (%)
1 dose/d (QD)	29	79†‡§	14	35–97
2 doses/d (BID)	32	69‖	15	38–90
3 doses/d (TID)	13	65†	16	40–91
4 doses/d (QID)	11	51‖	20	33–81
All regimens	85*	71	17	34–97

*Some studies reported data for >1 dosing regimen.
†Differences between QD versus BID and BID versus TID regimens were not significant. Bonferroni comparisons are significant if $P < 0.0083$.
‡QD versus TID, $P = 0.008$.
§QD versus QID, $P < 0.001$.
‖BID versus QID, $P = 0.001$.

daily regimens or between twice-daily and 3-times-daily regimens.

A subset of 14 studies assessed the ability of patients to take doses within the prescribed time frame. The average overall dose-timing compliance rate was 59% ± 24% (Table III). Patients were better able to comply with once-daily regimens (mean 74% ± 31% of doses taken within 24-hour interval) than with regimens requiring multiple daily doses; 58% ± 23% of patients prescribed 2 doses per day took them within 12-hour intervals, and 46% ± 8% took 3 doses per day within 8-hour intervals. There were too few studies for statistical comparisons.

The majority of published reports were in cardiovascular disease (assessments of medications for hypertension) and respiratory disease (assessments of medications for asthma and chronic obstructive pulmonary disease), with several reports in areas of infectious disease, cancer, fertility, psychiatry, epilepsy, and general medical disorders (Table IV). Although the numbers of published articles across therapeutic fields differed, the mean dose-taking compliance rate ranged from 70% to 80% in all but respiratory disease, indicating the similarity of compliance rates across therapeutic areas. However, compliance rates for individual patients were as low as 34% across the range of therapeutic areas. In respiratory disease, the range was 51% to 55% for nasal inhaler (nebulizer) treatments ($P < 0.001$ vs all other therapeutic categories).

DISCUSSION

This review of published EM data clarifies our knowledge of the dosing behavior of patients with a variety of medical disorders and prescribed regimens. The data from studies using only gold-standard EM methodology suggest that patients are best able to follow less frequent dosing schedules and least able to follow more frequent dosing schedules. The complexity of the regimen is inversely related to compliance across the spectrum of therapeutic classes. Reviews of the literature before the development of EM suggested that at least 50% of patients unintentionally omit doses.[1,8,84–86] The present review of EM studies demonstrates overall compliance rates of 70% to 80% and a similar pattern of decreasing compliance with increasing complexity of the regimen.

Blackwell[85] noted that in recent years, ~850 papers per year listed patient compliance as a key word, resulting in >12,000 citations in a MEDLINE® literature search. However, most of these re-

Table III. Rate of dose-timing compliance by frequency of regimen.

Frequency of Regimen	No. of Reports	Mean Dose-Timing Compliance (%)	SD (%)	Range (%)
1 dose/24 h (QD)	4[19,28,31,35]	74	31	27–89
1 dose/12 h (BID)	6[18,28,29,35,36,62]	58	23	22–79
1 dose/8 h (TID)	3[39,62,75]	46	8	40–55
1 dose/6 h (QID)	1[78]	40	–	–
All regimens	14	59	24	22–89

Table IV. Compliance rates by therapeutic area.

Therapeutic Area	No. of Reports	Mean Compliance Rate (%)	Range (%)
Cancer[14–18]	5	80	35–97
Cardiovascular—all[19–43]	26	71	39–93
Hypertension only	17	73	39–93
Other cardiovascular	9	71	64–93
Epilepsy[4,44,45]	3	70	46–88
Fertility[46–50]	5	71	34–97
Glaucoma[9,10]	2	78	76–80
Infectious disease[13,51–57]	8	74	40–92
Medical, general—all[66–78]	14	75	51–85
Diabetes only	3	73	66–85
Thalassemia only	3	79	72–85
Other medical only	8	74	51–84
Medical education[83]	1	47	–
Psychiatry[79–82]	4	78	75–83
Respiratory—all[58–65]	10	54	37–92
Asthma only	7	55	37–92
Chronic obstructive pulmonary disease only	3	51	50–52

ports described compliance measured by patient self-reports, clinician estimates, blood levels, prescription refills, or counts of remaining pills, all of which have been demonstrated to be less accurate than EM.[5,6] Documentation of compliance takes many forms, but "simple measurements are not accurate and accurate measurements are not simple."[87] Now, >10 years after the introduction of EM, adequate data are available to assess compliance rates as documented by EM. EM methods have revealed that compliance rates in clinical trials are lower than previously assumed.[88] Although patients in EM studies are aware that their compliance is being monitored, the EM unit has not been demonstrated to influence compliance.[89] The results suggest that despite the positive milieu of a clinical trial, which probably enhances compliance because of the special attention given to the investigational medication, complex schedules remain difficult even among a motivated population.[45]

The most important limitation of this review is the lack of a single definition for compliance. Most studies defined compliance as the proportion of days in which the prescribed number of doses was taken or the number of medication events within a specified time span. Other studies used the proportion of patients taking 70%, 80%, or 90% of doses overall, or a similar a priori definition, to assess compliance. A few studies required a nearly perfect dosing record. The fact that 59 of 76 reports defined compliance as the proportion of days with the appropriate number of doses taken suggests that this is becoming the standard definition for dose-taking compliance. A second limitation of these findings is the lack of infor-

mation about dose timing. Additional research is needed in this area. A third limitation of the review is the overrepresentation of particular disorders (cardiovascular and respiratory) and multiple reports by several authors. Reports from a wider spectrum of medical disorders are being published each year using the new EM technology. To date, the only therapeutic area for which medication compliance was lower than average was respiratory disorders, most of which require inhaled medications.

The fact that compliance with once-daily regimens was significantly higher than with 3-times-daily and 4-times-daily regimens reinforces the principle of simplicity. However, even once-daily dosing does not result in perfect compliance. A previous review[86] of compliance with once-daily antihypertensive drugs found a compliance rate of 73%. Thus, even if all drugs could be prescribed once daily, additional resources are needed to ensure that dose timing is appropriate. Patients need to learn about the duration of action of drugs to understand why doses should be taken at approximately the same time of day and at equal time intervals during the day. This is particularly important for drugs with a duration of action ≤24 hours. Taking doses of once-daily drugs at different times on different days may result in periods during which drug levels are inadequate. For example, women who alternate taking a low-dose oral contraceptive in the morning and evening have a 36-hour interval between doses. Omission of a single dose during the ovulatory phase could result in pregnancy. For most drugs, taking doses too close together can cause transient adverse effects whereas long intervals between doses may result in decreased efficacy.[4,44] Recognizing that poor compliance can contribute to treatment failure, clinicians should counsel patients about the importance of taking doses within a time interval (dose timing) as well as taking the medication every day (dose taking). Few papers in this series explored the interdose interval as a measure of duration of therapeutic action.

The clinical importance of regular dose taking is exemplified in 2 studies of antihypertensive drug therapy demonstrating that blood pressure rises quickly when a dose is omitted.[28,90] In these studies of planned noncompliance, blood pressure did not increase when placebo was substituted for long-acting amlodipine[28] or long-acting betaxolol was substituted for short-acting atenolol,[90] whereas blood pressure rose among patients taking short-acting diltiazem.[28] In a similar design, abrupt interruption of 2 shorter-acting antidepressants, paroxetine and sertraline, was associated with the emergence of new somatic and psychologic symptoms, but no such effect was seen when longer-acting fluoxetine was interrupted.[91] These experiments in noncompliance suggest that missing a few doses of medication can result in rebound effects and can have a significant impact on treatment outcome.

The next step toward better therapeutic coverage is use of medications with a very long duration of action, which would alleviate the need for daily dosing. A number of medications meet this criterion, including phenobarbital, fluoxetine, and aspirin. Several medications are formulated for monthly depot injection, including the contraceptive medroxyprogesterone and the antipsychotic agent haloperidol decanoate. The major drawback to the use of depot formulations is the need for medical personnel to inject the medication. With formulations in which hormone is

implanted in muscle tissue, contraception can be achieved for 5 years, virtually eliminating the problem of compliance.

A few studies have evaluated the effectiveness of dosing intervals of >24 hours. Rindone et al[92] compared the lipid-lowering properties of fluvastatin 20 mg once daily versus 40 mg every other day. Both regimens were equally effective in reducing cholesterol, but actual compliance with the regimen was not described. Two studies have assessed the efficacy of daily versus weekly iron supplementation for pregnant women.[93,94] Compliance was 54% for daily dosing and 62% for weekly dosing.[93] The advantage of weekly dosing was decreased gastrointestinal irritation. De Klerk et al[68] described 100% compliance with weekly methotrexate dosing by patients with rheumatoid arthritis versus 73% compliance with twice-daily sulfasalazine. In a study of 82 patients taking once-weekly mefloquine for malaria prophylaxis, 72% took all doses; 55% of patients took their doses every 7 days.[95]

Health care personnel expend many resources caring for patients who do not respond to initial treatment with a new drug. However, treatment failures that are usually assumed to be medication failures may be a result of noncompliance rather than lack of response. Thus, extra efforts should be made to tailor prescriptions to suit the capacity of the individual.

Considering the variety of medical disorders evaluated in the present study, it is likely that these findings can be extrapolated to other medications, formulations, and medical disorders. Research has demonstrated that physicians are poor judges of patients' compliance, and that patients are poor judges of their own level of compliance with the prescribed regimen.[2,7] Level of education, IQ, social status, and other demographic variables have not been found to correlate with medication compliance rates.[4] The lack of effect of EM on compliance suggests that telling patients that their dosing will be monitored is not sufficient to change behavior.[89] The number of investigations of medication compliance has been increasing since 1986 when EM devices became commercially available. EM devices could be used in clinical practice to evaluate the reason for lack of expected treatment effect.

CONCLUSIONS

This review of 76 studies that used gold-standard EM devices demonstrated that patients take ~51% to 79% of doses daily as prescribed across a wide range of therapeutic areas. Compliance is inversely related to the number of doses per day. These data suggest that inadequate compliance with prescribed regimens may be one reason for poor control of many medical disorders. Further recognition of the influence of medication compliance on health outcomes by payers, clinicians, and the pharmaceutical industry will enhance research in this area.

ACKNOWLEDGMENT

Financial support for this work was provided by Eli Lilly and Company, Indianapolis, Indiana. The authors thank Dr. Erik de Klerk for his helpful comments and his assistance in the literature search.

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