# Adherence to Single Daily Dose of Aspirin in a Chemoprevention Trial

## *An Evaluation of Self-report and Microelectronic Monitoring*

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A consecutive sample of 64 healthy adults (33 female and 31 male) were recruited at the University of Michigan Medical Center, Ann Arbor. Data were available for analysis on 57 subjects. The participants were asked to take a single daily dose of aspirin ranging from 0 to 640 mg. Adherence to the daily aspirin ingestion was measured by self-report and the Medication Event Monitoring System (MEMS, Aprex Corp, Fremont, Calif); adherence rate for the study population was 35%. The adherence rates for all dosing errors between self-report and Medication Event Monitoring System were significantly different ($P$=.002). There was no significant gender difference in adherence rates. Adherence to regular aspirin ingestion was poor in healthy, paid subjects despite explicit, written and verbal instructions. Patient self-report alone is not a reliable measure of adherence. *(Arch Fam Med. 1996;5:297-300)*

**Editor's Note:** Only 35% compliance by the monitoring system and self-report! I agree with the author. If an educated group of individuals, who volunteer to take a once-a-day medicine, agreed to undergo sigmoidoscopic biopsies, and are paid, cannot be compliant for 2 weeks, who is? This makes me rethink some of my patients who swear they are compliant but with other data (such as protimes) suggesting otherwise. *Marjorie A. Bowman, MD, MPA*

Cancer chemoprevention is a developing field with novel pharmacological and nutritional interventions being tested to decrease the incidence of cancer. Chemopreventive approaches are directed at essentially normal, healthy subjects who are at risk of developing cancer in the future. Patient adherence to regular drug ingestion is necessary for the proper interpretation and validation of data obtained from such trials.[1,2] It is important to identify valid adherence parameters in short-term trials to be applied in prospective, randomized trials. Few studies have looked at adherence to regular drug ingestion in normal subjects in a chemoprevention trial.[3,4] We studied adherence to regular aspirin ingestion in normal, healthy subjects in a phase I colorectal chemoprevention trial.

Previously, adherence has been measured by patient self-reporting (SR), pill counts (PCs), and serum or urine drug levels.[5,6] Patient SR is too subjective, since patients tend to overestimate their compliance by as much as twofold to fourfold.[7] Pill counts can be misleading if unused bottles are misplaced or deliberately not returned. In a long-term, randomized trial investigating medication compliance of an antihypertensive drug, Rudd et al[8] reported PCs to be an unreliable measure of medication adherence. Ingestion of occasional extra pills can balance with days of missed pills, masking the efficacy of the drug being tested.[6] Pullar et al[1] further demonstrated the drawbacks of PCs after assessing adherence in three separate studies using PC and low-dose phenobarbital as a marker. Eighty-seven percent of the patients were poorly adherent based on level-dose ratios, although PCs assessed them as adherent. Measurements of serum and urine drug levels are often subject to individual differences in drug absorption, distribution, and metabolism.

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Furthermore, these measures do not provide an accurate record of subjects' prescription intake.[9]

The microelectronic monitoring system, Medication Event Monitoring System (MEMS, Aprex Corp, Fremont, Calif) offers an additional method of monitoring the patients' adherence by providing essential recordings of the subjects' behavior (a presumptive dose, date, time, and duration of opening for later retrieval on a microcomputer), when they are not being directly monitored, unlike PCs or drug assays. While MEMS does not prove that the drug actually entered the body, it provides data on the dates and particular time at which the subjects' pill container was opened and a dose presumably consumed. Additionally, this method can accurately identify errors in dosing intervals.[5]

In a phase I, short-term colorectal chemoprevention trial investigating regular drug intake (aspirin), we compared the differences in adherence reporting between patient SR and MEMS. We hypothesized that the MEMS data would provide a more accurate description of participants' behavior.

## SUBJECTS AND METHODS

### SUBJECT SELECTION

Sixty-four healthy subjects were selected for paid participation in the trial. Subjects were not permitted to take any medication, except birth control pills; smokers were not excluded from the study. The study was approved by the local Institutional Review Board. Written, informed consent was obtained from all participants.

### METHODS

#### Instruction to Subjects

At the time of enrollment, each subject was asked to take either a specific dose of aspirin or placebo once daily, at a chosen time, for a total of 14 days. The subjects were not randomized, and there was no blinding of the treatment. Placebo controls were included to assess variation of the biological end point. Each subject was given his or her initial dose on day 1 in the General Clinical Research Center (University of Michigan Medical Center), in which the subjects were outpatients on days 1 and 2 for pharmacokinetic studies and sigmoidoscopic rectal biopsies. Adherence was monitored from days 3 through 14 (total of 12 days). Specific instructions were given to take the drug at a chosen time ±2 hours every day. The subjects were informed that adherence was being monitored by MEMS and they were requested to remove the daily dose from the MEMS capped container immediately prior to administration.

Subjects were asked to report the number of doses of aspirin missed and the number of dosing interval errors on day 7 by telephone and in person on day 15. The MEMS containers were collected from the subjects, and the data were retrieved using MEMS Data Retrieval Software (Aprex Corp).

The MEMS prescription containers are normal-appearing medication bottles that contain a pressure-activated microprocessor in the cap. The microprocessor records each opening as a presumptive dose, listing the date, time, and duration of opening for later retrieval on a microcomputer. Internal circuitry permits the exclusion of multiple openings (ie, separated by 5 seconds or less, if the subject had difficulty in opening or closing the container). The MEMS cap has a capacity to store a total of 1800 events plus patient and drug information and has an 18-month battery life. The MEMS cap is typically accurate to within ±30 s/mo, and its accuracy does not vary over time (personal communication, Aprex Corp, August 1995). The MEMS data were retrieved by connecting the monitor to an IBM PC-compatible computer via a specially designed communicator module. The module was attached to the computer's serial port and plugged into the MEMS data retrieval port, which is recessed in the cap. These data were then stored in a relational data base (4th Dimension, ACI, US, Cupertino, Calif).

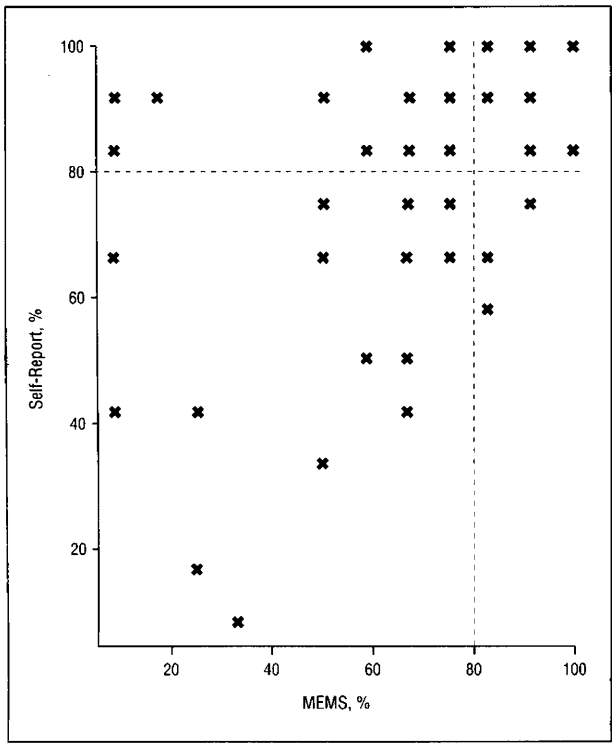
#### Statistical Considerations

The data were analyzed to compare the adherence rates for SR and MEMS. For the purpose of these analyses, patients were classified as *adherent* if the measure of adherence (SR, MEMS) suggested that 80% or greater of the aspirin doses were taken as prescribed. This rate was chosen because it is a rate frequently cited in the literature as achievable or acceptable.[10,11] *Dosing interval errors* were defined as the ingestion of aspirin beyond ±2 hours of the subject's chosen time of day to routinely take their dose. Doses were considered *missed* if the MEMS data did not report any recording of an opening on a given day. Missed doses were also counted if subjects disclosed that they had accidentally missed a dose. Both missed doses and dosing interval errors were compared between SR and MEMS. The Student paired *t* test was used to test the differences between the adherence rates measured by SR and MEMS. Gender differences were also analyzed.

## RESULTS

Of 64 subjects enrolled in the study, data on 58 subjects were available for analysis. Six subjects had incomplete data and were excluded from the final analysis. One of the subjects withdrew from the study because of medical complications. The other five subjects had unavailable and/or incomplete data. Of these 58 participants (30 male and 28 female), 47 were white, six were Asian, four were African American, and one was Latino.

There was a significant difference in adherence rates for all dosing errors (missed doses and dosing interval errors) between SR and MEMS ($P = .002$). Adherence rates due to missed doses as well as dosing interval errors between SR and MEMS were significantly different ($P = .004$ and $P = .006$, respectively). When 80% or greater of the aspirin doses were taken as prescribed,




*Comparison of self-reporting data with the Medication Event Monitoring System (MEMS, Aprex Corp, Fremont, Calif) data (N=58). Shaded areas indicate an adherence rate of 80% (x); points in the upper right plot sector (adherent), patients who are ≥80% adherent, as estimated by both self-reporting and MEMS; and points in the upper left sector, patients who are <80% adherent, based on MEMS analysis.*

subjects were classified as adherent. Using this criterion, we found that adherence rates for SR, MEMS, and a combination of SR and MEMS were 73%, 44%, and 35% (95% confidence interval, 23% to 97%), respectively. The adherence rates for SR and MEMS for each participant are shown in the **Figure**. Adherence rates by gender also showed no difference ($P$= .95). There were no gender differences in adherence rates for all dosing errors ($P$= .78).

## COMMENT

Despite our best efforts in identifying a highly motivated (financial incentives, prevention of cancer), educated (most subjects were college educated or higher) study population taking a widely used and recognized drug (aspirin) with careful instruction and known electronic monitoring on a simple dosing schedule (once daily), adherence was poor. Given our data from this and our previous report,[9] as well as those of others,[12] the definition of adherence and the method of adherence measurement are critical to understanding the efficacy of new medical treatments such as with aspirin in the prevention of colorectal cancer. Since there are no accepted "gold standards" for definitions of adherence or monitoring methods, researchers need to develop definitions that are relevant to the agent under study and use a combination of monitoring methods.

In the past, researchers have defined adherence using inexact measurement methods without reference to the clinical outcome.[13-15] Some researchers have used conventional measurement methods to determine the level of adherence associated with optimal clinical outcome. Sackett[16] defined a patient as adherent if 80% or more of the prescribed medication in an antihypertensive drug trial had been removed. The arbitrary definition was supported by a regression analysis that showed that it was only at an adherence of 80% or greater that diastolic blood pressure fell systematically. We chose the same definition, realizing that it may not be relevant to our ultimate outcome: prevention of colorectal cancer death. In fact, the epidemiological studies suggesting that aspirin reduces risk and mortality of colorectal cancer define regular aspirin use from three times a week, every other day, to daily.[17-22] So, the definition of adherence for aspirin use in colorectal cancer prevention with a single daily dose could be 50% as opposed to 80%. As highlighted in the Figure, if this definition was accepted, significantly more of the subjects were adequately adherent. However, this may significantly reduce the efficacy of aspirin. In the physician's health study,[23] subjects taking at least 95% of a single daily dose of aspirin have a statistically significant reduction in myocardial infarctions.[23] If subjects took 50% or less of the pills, the reduction in myocardial infarction was only 17%.[23]

We have tested the feasibility of using the MEMS in a short-term trial and have found it to be informative. Reliance on SR as the sole measure of adherence is insufficient. Information on dosing interval errors cannot be obtained from SRs. Such dosing interval errors may have therapeutic importance if treatment depends on a drug with a short half-life. Pill counts have been associated with important shortcomings as well.[1,6,8,9] Microelectronic monitoring provides information about dose errors and dosing interval errors. However, other researchers should not be seduced by the technology and rely only on electronic montoring. Patients can transfer drugs to another container prior to administration. The electronic monitor then suggests nonadherence when, in fact, the patient did take the medication at the appropriate time. Thus, microelectronic monitoring remains an insufficient tool with which to monitor adherence and must, therefore, be supplemented with other methods of adherence measurement, such as SR. For practicing physicians, an essential critical appraisal of all reports on new therapies should be the level of adherence, definitions, and monitoring methods used.

While our intent in measuring adherence in this trial was to ensure integrity of biochemical end-point data, the lessons learned from our experience are broadly applicable to medical therapeutics. Subjects missed doses, divided doses within a day rather than taking the dose once daily, and took extra doses beyond the treatment period. Adherence failure is likely to be a common cause of therapeutic failure. Methods to assess and intervene to improve adherence to home-based treatment regimens are warranted. For practicing physicians, this is not a new problem. The MEMS equipment is available to practicing physicians, but it is not designed to improve adherence. In addition, it is expensive ($100 per cap plus cost of computer hardware and

software) (personal communication, Aprex Corp, August 1995) and time-consuming to use. The single, most common source of nonadherence has been shown to be forgetfulness.[24] Based on the most frequently occurring problems associated with nonadherence, common stategies such as information and motivation have been used. However, it is unclear what strategies work best to enhance adherence.[24]

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