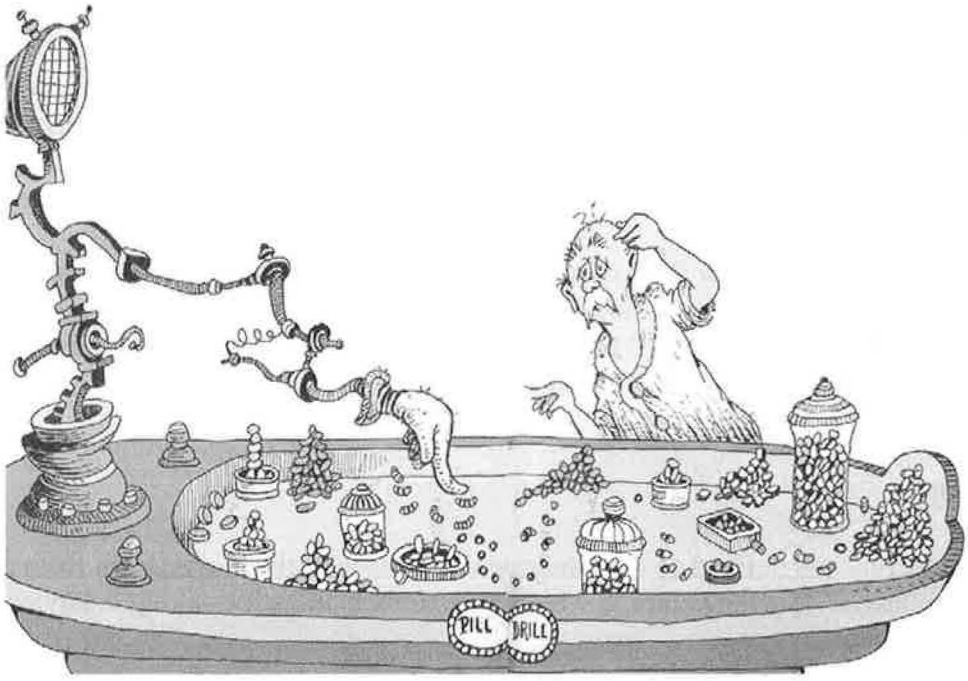
Medication Adherence in the Elderly: A Matter of Patient Safety and More



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MEDICATION ADHERENCE IN THE ELDERLY: A MATTER OF PATIENT SAFETY AND MORE

Patients typically take only half of the medications that are prescribed to them. Nonadherent patients incur more procedures, hospitalizations, emergency room and unscheduled office visits than adherent counterparts.[1]

In 2000, the Institute of Medicine incorporated the problem of medication adherence into its definition of adverse drug events.[2] Adverse events related to medication use, underuse and overuse are associated to an increased risk of toxicity, increased likelihood of accidents, development of drug resistance and an increased risk of treatment failure and relapses.[3]

Nonadherence is responsible for 27% of all adverse drug event-related hospitalizations[4] and for 20% of adverse drug events in the ambulatory care setting.[5] In the United States, nonadherence directly costs the health system $ 100 billion annually. Indirect costs are said to exceed $1.5 billion in lost patient earnings and $50 billions in lost productivity.[6]

DEFINITION

Medication adherence is defined as the intentional or non-intentional deviation from prescribed medication regimens.[7] It is the extent to which a person's medication-taking behavior coincides with provider advice.

The term adherence is a non-judgemental one; it is a statement of fact rather than of blame of the patient, prescriber or treatment.

In the medical literature, adherence assumes a collaborative process; compliance implies a more passive patient.

The term nonadherence may encompass medication under use, overuse, missed doses, failure to take at specified times, taking them at incorrect intervals and taking with other preparations. In the elderly, most deviations from medication taking are toward lower dosing and less frequent drug intake.[8]

MEASURES OF MEDICATION ADHERENCE

There are many ways of determining patient adherence. There are **direct measures** such as serum levels of drugs and tracers or medication taking observation such as that seen in TB clinics. **Indirect measures** include pill count, medication event monitors, patient interviews, therapeutic responses and pharmacy data bases.

Pill counts

Pill counts are commonly used to measure medication adherence in ambulatory care settings. Although useful in specific clinical situations, they are too time-consuming and cumbersome for

most busy outpatient practices. Pill counts overestimate adherence and do not account for medication "dumping".

MEMS

Originally felt to be the "gold standard" of medication adherence studies, medication event monitors, MEMS, feature micro chips that provide an objective measure of pill bottle opening. With this method which records time and date of each container opening, researchers have been able to learn much about medication taking behaviors and patterns. Electronic monitor devices are expensive and most often used in single drug, short randomized controlled trials. They are not efficient, however, when multiple medications are used, medications are moved or pocketed or when pill boxes or liquid or transdermal medication delivery forms are used.

Patient interviews

In younger patient populations, such as those with HTN[9] or HIV[10], patient interviews can provide good, rough measures of patient adherence. The predictive validity of patient responses improves when the **questioner is not the health care provider**.[11] Patient recall appears to limit the accuracy of responses to questions about adherence over a period longer than one week, a fact that is especially pertinent to older populations. Although patient interview data overestimates adherence, patients who admit to problems with medication taking may be more responsive to interventions than those who deny adherence problems.

Provider interviews

Clinicians **would do better to toss a coin than to try to predict adherence.**[12, 13] In a study conducted within the medical service and outpatient clinics of Baltimore City Hospitals,[14] copies of discharge orders listing medications were obtained daily for all patients discharged over a 4 week period. Within 24 hours of each discharge, the responsible intern and resident were asked to 1) predict whether or not patient would attend first follow-up visit and 2) predict the percentage of the amount of prescribed medication to be taken up to the first follow-up visit that the patient would actually take. At the end of the 187 patient study, researchers found that at best, the Hopkins house staff could only predict 35% of non-compliers. In addition, less than one half of physician predictions correctly discriminated between compliant and non compliant patients.

Experienced physicians seem to be more aware of the problem of medication adherence,[15] yet they do no better when asked to identify adherent patients among all medication takers.

Pharmacy records

Many pharmacoepidemiological studies now use automated data bases constituted by records of prescriptions written by clinicians and filled by patients to determine drug use. These data bases provide a reliable measure of medication taking that would be difficult or very expensive to obtain in other ways. The most widely used method of estimating medication adherence from pharmacy claims is the **medication possession ratio**. First developed by Sclar, the MPR is the sum of the days' supply of medication divided by the number of days' supply of the last refill. This calculation usually results in a ratio less than 1.0 if there are lapses in prescription refilling. Early refilling would lead to an MPR of more than 1.0; the MPR in such cases is often truncated at the maximum value of 1.0 indicating the potential for perfect compliance.[16]

Pharmacy-based assessments offer several advantages including avoiding a possible Hawthorne effect because patients are unaware they are being monitored. In order to be accurate, data must be complete and capture the amount of time in between refills. Over-the-counter preparations and drug samples are not accounted for in many pharmacy data bases. Another problem is misinterpretation of usage when dosing changes. Dose timing is also unaccounted for when adherence is measured by pharmacy records alone.[17]

Despite these problems, pharmacy-based measures of adherence have been associated with important intermediate outcomes in patients with chronic conditions such as variable as HIV, hypertension, schizophrenia[18] depression and rheumatoid arthritis.[19]

EPIDEMIOLOGY

In ancient Greece, Hippocrates' *Decorum* directed physicians' attention to the way patient were taking their prescriptions. He advised them to be alert to patients' attitudes to medical recommendations, "... refusing to accept their faults and refusing to admit that they have not been taking their medicine".

The modern history of provider concern with patient adherence begins in the late 19th century. Shortly after Koch determined that tuberculosis was communicable, officials enacted numerous policies to prevent its spread including coughing into handkerchiefs and isolation of actively infected persons. The introduction of antibiotics for tuberculosis in the 20th century increased clinician vigilance for, even though isoniazid and streptomycin offered a revolutionary chance for cure, many patients did not take their medications as prescribed. More importantly, not only did these patients spread infection but their erratic adherence produced drug resistance.

Newer antibiotics led to studies of adherence in patients other than those with tuberculosis. In one early study of streptococcal pharyngitis it was found that patients rarely completed ten- day courses of 4 times daily antibiotics. Problems of medication taking were seen both in public and private settings and led to the widespread recommendation for one time long acting penicillin that still stands today.

With the advent of more complex but effective treatments of chronic diseases, adherence has become a common problem among all cohorts. Today typical adherence rates are about 50%,[7] and range from 1-100% depending on duration of medication, condition treated and medication used. Data on adherence are often disease-specific or derived from clinical trials.

In the outpatient setting, a third of prescriptions written by providers are never filled and over half of those that are filled are used incorrectly. Patients who are nonadherent are likely to have fewer provider visits and are more adherent with number of doses than with timing. Good adherence to drug therapy is associated with decreased mortality but so is that to placebos used in many clinical drug trials.[20] This fascinating observation has lead to the conclusion that adherence may be a marker for healthy behaviors.

Among the elderly, who consume the largest proportion of prescriptions and over-the-counter preparations, adherence rates range between 25-75%. Among the young old, adherence rates are often better than in younger cohorts. In the older old, adherence rates are lower until caregiving is assumed by others.[21]

In one study of 315 consecutive hospitalized elders ages 65 to 99 admitted to a Massachusetts hospital, Col et al.[22] found that 11.4% admissions were due to nonadherence. Among this group of patients, 32 % had a history of nonadherence in the year preceding their admission. The most common form of nonadherence was underuse; 54% of all nonadherence was reported as being intentional. Among patients whose admission was related to nonadherence, side-effects and forgetfulness were reported as causes of nonadherence. The medication most often associated to non-adherence in this study was furosemide; the proportion of patients with a history of non-adherence was highest among cardiac admissions.

Community-based seniors are also nonadherent with medications. In 2001, Barat[8] reported on scores of agreement between general practioner medication lists and patients' actual consumption as determined by a home visit. In these patients of an average age of 75, there was 66% discordance between providers' lists and what was happening at home. Sixty-per cent of patients claimed they knew the purpose of their medications but took lower or less frequent doses anyway. Once again, drugs most often missed were diuretics. As in the Col study, living alone placed patients at risk for non-adherence.

Among insured elderly patients with moderate to severe glaucoma, Patel and Spaeth[23] found that the main reasons given by patients themselves for non adherence included forgetfulness, (39%), being away from the home and medication (26%) inconvenient timing and frequency (9%) and side effects (2%).

DETERMINANTS OF ADHERENCE

Because it is a complex, multidimensional problem with hundreds of components, the problem of adherence cannot be explained by one factor alone. In the elderly however, some determinants seem to be more important than others.

Dosing

Taking a **number of four or more prescriptions** a day,[8, 24, 25] is associated to nonadherence in the elderly. Polypharmacy may be unavoidable in patients with multiple chronic illnesses. As noted above and in other studies, in patents on multiple medications, nonadherence can be preparation-specific.[26] In general, patients take cancer medications most consistently and inhalers, the least.[27]

Frequency of dosing also affects adherence. In a large review of 76 smaller trials using the MEMS, Claxton et al.[27] found that adherence was inversely proportional to frequency of dose and that patients taking medication four times a day attained adherence of about 50% (range 31 to 71).

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[18,26,29,35,36,62]	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

A study of 105 Missouri veterans also monitored adherence to hypertensives using electronic pill devices. Researchers found that medication adherence improved from 59.0% on a three-time daily regimen to 83.6 % when veterans were changed to a once daily regimen.[28]

Frequency of dosing alone, however, does not explain patient nonadherence. In one very large osteoporosis study using data a broad pharmacy retail database of 211,319 mostly senior patients, , even when bisphosphonates were being given weekly, only 48% patients were adherent at least 80% of the time. Little is known about adherence to longer acting depo preparations and transdermal patches.

Dose timing, especially midday dosing, is especially onerous to employed and active seniors. **Frequent dose changes** also make nonadherence more likely.

In all patients **dose response** should be seen as a continuum. A threshold of eighty percent adherence may be good enough for depression or osteoporosis but not for anti-coagulation. Dose response is better in patients taking longer acting preparations. Adherence rates decrease with increasing medication regimen complexity.[27]

Providers

There is a greater likelihood of discrepancies between the way prescriptions are written and the way they are taken when the prescription writer is a cardiologist or when a patient has multiple providers.[29] Veterans are more likely to take their medications when they trust their providers.[30] "White coat adherence" is the medical provider's version of the "tooth brush effect."[31] The practice of improving medication-taking behavior five days before and after an appointment with a health care provider may explain why patients adherence improves when they see their provider more often.[32]

Side-effects

Adverse effects of medications are common causes of medication nonadherence in all patient populations.[33] In the elderly, adverse events such as hypotension increase with the number of drugs used.[34] Side-effects are common and may be explained by the fact that randomized trials rarely include patients with multiple co-morbidities or over the age of 75.[35, 36] Concern about common side-effects may explain why adherence to cardiovascular and psychiatric medications is poor.

Medication cost
Although medication adherence is an issue in all socio-economic groups, studies have shown than cost-related nonadherence is greatest among low income beneficiaries with high-out-of pocket-spending for medications and other living expenses.[37] In addition, there is an association between decreased access to public funding for medications and institutionalization.[38]

Several studies of prescription assistance programs have reported that increases in indigent patients' access to medications are associated with decreases in health care expenditures and costs to the patient.[38]

Prescription events increase as drug coverage generosity improves.[39] But medication expense alone does not explain the problem of medication adherence in the elderly and in patients with chronic conditions. Among the indigent, even when prescription drug plans remedy cost-related concerns, adherence is still poor.[21] Veterans who report medication underuse for reasons other than cost were also more likely to report cost-related underuse.[30]

Depression
Depression affects adherence in both young and elderly populations.[40, 41] Compared with nondepressed patients, depressed patients are two to three times more likely to be nonadherent with medical treatment.[30, 40, 42] The precise mechanism is unclear but, in older adults, depression appears to be associated to a greater sensitivity to unpleasant side effects from medications.[43] In general, depressed seniors tend to take more medications than non-depressed seniors.[34]

Cognitive impairment
Older adults and chronically ill adults often experience declines in the cognitive processes necessary for medication adherence. The incidence of cognitive deficits increases with age and may account for the prevalence of medication nonadherence in very old patients who have no active caregivers.

Our study of 301 indigent elderly showed a strong association between cognitive impairment as determined by ability to draw a clock and nonadherence when patients reported independence in activities of daily living.[21] Our data is consistent with findings in a study of Air Force retirees by Royall et al.[44] wherein measures of executive function like the clock drawing and Trail Making B also predicted ability to live independently. In our study and another MEMS-based single medication one carried out among 100 seniors living in San Antonio, mini-mental status examination, MMSE, scores alone did not predict nonadherence.[45]

Another retrospective chart review of Canadian elders participating in a self-medication program where adherence was determined by direct observation found that MMSE and ability to cook[25] were independent predictors of ability to take medications correctly.

In preliminary data from an NIA-funded study now underway, inability to complete a maze task was significantly related to medication adherence in unassisted elderly patients whose capacity to take donepezil was monitored with a Medication Event Monitoring System, MEMS device.[46]

Transportation
Car ownership was found to be an independent predictor of medication adherence in a study of 57 community dwelling elderly.[47] Among Parkland community-dwelling indigent seniors without caregivers, lack of transportation is also strongly associated to nonadherence.[21] Adherence is also more likely in patients able to attend clinic more often.

Health literacy
Patients' lack of understanding of medical illness and the medication taking process is often attached to the medication adherence problem. Among cognitively impaired elders, educational level of caregivers plays an often over-looked role as well.[21]

In the elderly, elaborate education, counseling and literacy interventions alone do not appear to improve long-term adherence rates or disease outcomes.[48]

Researchers at UCSF assessed whether health literacy was associated with non-adherence to warfarin as determined by time in therapeutic INR range among 179 anti-coagulated English or Spanish-speaking patients. They found that limited health literacy was not associated with self-reports of missing doses or therapeutic INR. Knowledge about the mechanisms of action of warfarin or side-effects did not affect adherence rates, either.[49]

Self-Reported Adherence And INR Control, Comparing Patients With Limited To Adequate Health Literacy[49]

	Limited Health Literacy (%)	Adequate Health Literacy (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Self-reported adherence				
Missed a dose within the last 3 d	6.5	17.1	0.6 [0.2 to 1.7]	0.5 [0.1 to 2.1]
Missed a dose within the last 2 wk	12.0	14.3	0.6 [0.3 to 1.4]	0.7 [0.3 to 2.2]
Did not miss a dose in >3 mo	61.1	51.4	1.5 [0.8 to 2.7]	0.9 [0.4 to 2.0]
Person-time in therapeutic INR range	45.0	43.2	1.2 [0.9 to 1.5]	1.0 [0.7 to 1.4]

** Adjusted for age, sec, race / ethnicity, education, years on warfarin and s-CASI score.*
INR: international normalized ratios; s-CASI: short form Cognitive Abilities Screening Instrument.

The role of caregivers
The presence of a caregiver who assists with purveyance of medications is strongly associated to better adherence among indigent minority patients with and without impairment in activities of daily living. In patients with caregivers, rates of adherence approach those of younger patients. Patients with caregivers between the ages of 65 and 85 take more medications than those who do not.[21]

Functional impairment
Self-reported functional integrity was not associated to better adherence in a patient population with high prevalence of cognitive impairment and caregiver involvement. Ability to draw a clock, which in many studies has been associated to ability to perform instrumental activities of daily living such as medication management, was.[21]

INTERVENTIONS

The heterogeneity of the elderly population and the diversity and complexity of the problem of medication adherence makes generalizations about interventions problematic.

In an updated Cochrane review of all adherence interventions tested in randomized controlled trials, R. B. Haynes[48] noted that improvements in medication taking attained with the interventions were small, often short-lived and inefficient. To be effective, he concluded, interventions must be simple, maintained for as long as treatment is needed and be based on a better understanding of patients complex needs.

In its action plan for improving the use of prescription medications, the National Quality Forum, NQF, also recommends a "comprehensive set of practices" that address specific practices to the needs of vulnerable populations.

In an attempt to determine which interventions would make more sense for our Parkland patient population, we examined adherence in 301 seniors attending the Parkland Primary Care Internal Medicine clinic and the Amelia Court Geriatrics Center. Patients' average age was 71.6 years with 28% patients over the age of 75; most were female and African-American. Average number of prescriptions was 5.23; average adherence rate was 45% Medication adherence among those being cared for in the interdisciplinary setting of Amelia Court was better than that seen in the Primary Care internal medicine clinic: 50% compared to 40%.

All patients were beneficiaries of the Parkland Plus pharmacy program. Using the system's database to determine patients' refill records, we found that determinants of nonadherence in our largely minority population were:

1) Number of medications
2) Years of education
3) Ability to draw a clock
4) Age
5) Presence of a caregiver who helps with medications

In addition, when we compared the 128 elderly patients with caregivers to those without caregivers, we found that in patients with caregivers, age no longer determined adherence. In patients without caregivers, transportation problems predicted adherence more than years of education.

SO WHICH INTERVENTIONS WILL WORK IN THE ELDERLY?

Interventions to improve adherence in the elderly should be simple, interdisciplinary, and patient and determinant specific. They should be directed at patients with **uncontrolled chronic disease processes**, those identified to be **at risk for nonadherence** or those with a **history of nonadherence.**

Provider interventions

History and physical

Realizing that 50% patients can be nonadherent with medications, before writing prescriptions, providers or their surrogates should ask the following medication **history** questions of patients or their caregivers.[50]

1) Has your provider changed the dose or stopped any of your medications recently?
2) Have you changed the dose or stopped any of your medications recently
3) Have any of your medications been causing you side effects
4) Your medication record reveals that you may have run out of some medications. Are you still taking any of these?
5) Have you spent any days in the hospital recently?
6) When you feel better, do you sometimes stop taking your medication
7) Sometimes if you feel worse when you take your medication, do you stop it?
8) Are the pills in the bottle the same as what is on the label?
9) Can you read the label to me?
10) Have you had to change your daily routine to take your medications? In your mode of transportation?

Elements of the **physical** exam of the elderly nonadherent patient should include a depression screen, and cognitive testing focused on executive function like clock-drawing or Trails B testing.

Before writing prescriptions

In **cognitively impaired** patients, identify caregivers and determine their individual needs, prescribe pill-boxes or other memory aids. Mobilize families to assist in supervision even if via telephone. Tie in medication taking activities to daily routines.

In patients with very **low or high levels of health literacy**, offer structured support for medical problem solving by providing drug-related information and asking patients to explain consequences of under taking, over taking medication and how they will cope with side -effects. Functionally illiterate patients will need special labeling; non-English speakers will need labeling in their language of choice.

In patients with **complex regimens**, simplify to fewest possible doses in a day.

In patient with **access issues**, enlist assistance of social workers to determine transportation options, eligibility for entitlements or manufacturers' or mail order programs.

If a **patient is nonadherent**, providers should tailor medication regimens to more realistic – perhaps not optimal – treatment regimens. Increasingly, standards of chronic disease management are being adapted to accommodate the unique preferences and needs of patient with dementia or functional impairment.[51]

Particular attention should be placed on those patients with a history of **partial adherence**. A closer look at these patients may reveal a change in function or caregiver situation, a concern about specific side-effects, worsening health or finances or perhaps substance abuse. In patients with **recalcitrant non-adherence**, treatment goals should be revisited and alternatives to care such as institutionalization, considered.

Health system interventions
Adherence is an important modifier of health system effectiveness and financial viability.

In a 2005 report on what it deems a global problem, the World Health Organization concludes that "the health outcomes predicted by treatment efficacy data will not be achieved unless adherence rates are used to inform" health care delivery systems and strategies.

Because they can easily access refill records, pharmacists and pharmacies are at the forefront of many medication adherence programs. In interdisciplinary **ambulatory care settings**, their vigilance may account for better recognition of nonadherence.[21] Nationally, several chain pharmacies have been using call centers to contact patients to remind them to refill medications or pick up medications that have been filled.[41] Medication safety initiatives in Massachusetts and Canada include adherence interventions as well.

To improve patient adherence in **hospital and outpatient settings**, adherence integrity measures are being incorporated into medication conciliation processes mandated by the National Patient Safety Goal standards being implemented by the Joint Commission of Accreditation of Health Organizations, JCAHO.

Designed to improve **medication affordability** for seniors, the federal Medicare Part D program is expected to cost tax payers 1.2 trillion dollar s over the next ten years. Fragmented and unwieldy in its early application, the effect of this new, publicly funded benefit on patient adherence and chronic disease outcomes is yet to be determined. To date, however, the problems of restricted formularies, formulary switching, variable co-pays seem to have limited the impact of its implementation.

On a more individual level, issues of adherence have been tied to calls for more **patient responsibility.** Beginning in the fall of 2006, for instance, some of West Virginia's Medicaid recipients will be asked to sign a "Member Agreement" promising to keep doctor appointments, receive health screenings, take medications as directed, and participate in health education. This new program provides for cuts in benefits such as unlimited medications, if patients do not meet standards. The expectation, yet "unproven and untested" is that Medicaid recipients will modify nonadherent behaviors, that health will improve and Medicaid costs diminish.[52]

CONCLUSION

The problem of medication adherence is an old, common and complex one. Technology and innovations like the electronic medical record and the "advanced medical home" [53] vest providers and the health care system with strategies for transformation.

Future interventions to improve adherence should include the chronically ill and frail. Studies evaluating their effectiveness should go beyond disease-specific measures and examine outcomes that are more geriatric-relevant such as institutionalization rates, change of functional level or caregiver burden.

Until then, research such as that outlined here challenges us to identify the problem, its often overlooked consequences and determinants. Patients do better when they take their medications. Prescription writing in the face of persistent evidence of nonadherence does them, and our overtaxed health care system, no good.

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